Public Health Nutrition: 12(5), 609–613 doi:10.1017/S1368980008003182

Fish intake and the risk of fatal prostate cancer: findings from a cohort study in Japan

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Submitted 13 June 2007: Accepted 2 May 2008: First published online 29 July 2008

Abstract

Objective: We investigated the relationship between the intake of fish and the risk of death from prostate cancer.

Design: Data were derived from a prospective cohort study in Japan. Fish consumption obtained from a baseline questionnaire was classified into the two categories of 'low intake' and 'high intake'. The Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% confidence intervals.

Subjects: Data for 5589 men aged 30–79 years were analysed.

Results: A total of twenty-one prostate cancer deaths were observed during 75 072 person-years of follow-up. Mean age at baseline study of these twenty-one subjects was 67·7 years, ranging from 47 and 79 years old. Results showed a consistent inverse association of this cancer between the high *v.* low intake groups. The multivariate model adjusted for potential confounding factors and some other food items showed a HR of 0·12 (95% CI 0·05, 0·32) for the high intake group of fish consumption.

Conclusions: These results support the hypothesis that a high intake of fish may decrease the risk of prostate cancer death. Given the paucity of studies examining the association between prostate cancer and fish consumption, particularly in Asian populations, these findings require confirmation in additional cohort studies.

Keywords
Cohort study
Fish intake
Mortality
Prostate cancer

Both the incidence of and mortality from prostate cancer vary substantially, from high in the USA and certain Western countries to considerably low in Asian countries such as China, Singapore and Japan[1]. Recently, however, these rates appear to have increased in Japan[2,3]. Among risk factors for prostate cancer, advanced age and family history appear to be strong determinants[4]. There is evidence that the incidence is increased notably in Japanese migrants living in Hawaii and is far higher than that among Japanese men living in Japan[5,6]. Environmental factors such as dietary habits may therefore play an important role in the causation of prostate cancer.

A review article[7] recently summarized the results from cohort and case–control studies examining the association between fish intake and risk of prostate cancer incidence or mortality, but could not provide conclusive evidence of this association. However, none of the studies quoted showed an increased risk of prostate cancer with high intake of fish, and some have suggested that a high intake of fish reduces the risk of prostate cancer[8,9]. Others have reported that *n*-3 fatty acids, which are found mainly in fish, may reduce the risk of prostate cancer[10,11]. These studies have been conducted mainly in American and Western countries, however, and the few studies conducted in Japan have yielded inconsistent findings[12,13].

Thus we conducted a prospective study in Japan to investigate whether a high intake of fish is protective against the risk of prostate cancer mortality.

Methods

Study population

Study subjects were the participants of the Miyako Study, a cohort study conducted in four areas of Fukuoka Prefecture, Japan. Details of the present cohort study have

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been described previously[14]. Briefly, the baseline survey was conducted from 1986 to 1989 via invitations to all inhabitants aged 30 to 79 years living in A town, B village, and selected districts of C city and D town (15 417 subjects in total) to participate in a self-administered questionnaire survey. Response rate was 86·1 %, equivalent to 13 270 subjects (5927 men and 7343 women), who constituted the cohort. Baseline characteristics were obtained through the self-administered questionnaire, which included questions on health-related factors including smoking, alcohol, diet, disease history and others.

These 13 270 subjects were then followed for vital status, updated annually through the collaboration of the respective municipal office, until the end of 1999 in one of the study areas and the end of 2003 in the other three. For deaths during the study period, the underlying cause of death was ascertained from death certificates and coded according to the International Classification of Diseases and Injuries, 9th revision (ICD-9). In the present analyses, prostate cancer was defined as code 185 in the ICD-9.

The research protocol of the study was approved by the Ethics Committee of Medical Care and Research of the University of Occupational and Environmental Health, Kitakyushu, Japan.

Exposure assessment

The usual intake of food during the year preceding the start of the study was assessed with the self-administered questionnaire, which included an item on fish intake. Fish intake was assessed at the five levels of 'twice or more per day', 'once a day', '2–4 times per week', '2–4 times per month' and 'seldom or never'. For the present analysis, consumption levels were converted into two groups by combining the '2–4 times per month' and 'seldom or never' groups into a new 'low intake' group; and the 'twice or more per day', 'once a day' and '2–4 times per week' groups into a 'high intake' group.

Exclusion

Among 5927 men at baseline, we excluded forty-eight subjects with any cancer diagnosed before the study baseline and 290 subjects with missing information on fish consumption, leaving 5589 men for analysis.

Statistical analysis

Baseline characteristics of all study subjects were compared according to fish intake using the χ^2 test for categorical variables and ANOVA for continuous variables. We counted the number of person-years of follow-up for each subject from baseline until the date of death, the date of migration from the study area or the end of follow-up, whichever came first. We used Cox proportional hazards regression analysis to estimate the hazard ratios (HR) and their 95 % confidence intervals of prostate cancer mortality according to category of fish consumption, with the 'low intake' group considered the referent group. Patterns in Schoenfeld residuals with time were considered to identify possible violation of the proportional hazards model and found to be valid in our analysis[15].

In addition to age, the following variables were considered as potential confounders and included in the proportional hazards model (all missing data were considered an additional category, termed the 'unknown' category, and included in the analyses): smoking (never smoker, ex-smoker and current smoker); alcohol (never drinker, ex-drinker and current drinker); employment status (employed, self-employed and unemployed); history of diabetes (yes or no); living with spouse (yes or no); and study area (town A, village B, city C and town D). In the additional model, we adjusted for the confounding factors above and also adjusted for intake of other food items, including vegetables, fruit and meat. The intake of these food items was categorized into two groups, namely 'daily intake' and 'not daily intake'.

All P values and confidence intervals presented were based on two-sided tests. All statistical analyses were performed using the STATA statistical software package version 9·0 (Stata Corporation, College Station, TX, USA).

Results

During 75 072 person-years of follow-up in 5589 men (average follow-up 13·4 years), twenty-one deaths due to prostate cancer were recorded. Mean age at study baseline of these twenty-one subjects was 67·7 years, ranging from 47 and 79 years old. Among them, fifteen subjects (71 %) died from prostate cancer at the age 75 years or more. The mean follow-up period for these prostate cancer cases was 10·6 years. Distribution of some baseline characteristics differed somewhat between the case (n 21) and non-case subjects (n 5568). For example, proportions of current smokers as well as current drinkers were lower among case than non-case subjects (42·9 % and 66·7 % *v.* 50·5 % and 80·3 %, respectively). Furthermore, unemployment rate was 33·3 % *v.* 10·9 %; a history of diabetes was 14·2 % *v.* 6.5 %; and living with a spouse was 52·4 % *v.* 74·3 %. Moreover, case subjects reported more frequent consumption of vegetables and fruit than non-case subjects (33·3 % and 52·4 % *v.* 29·0 % and 42·1 %, respectively), but less frequent consumption of meat (3·1 % *v.* 7·6 %).

Table 1 shows the baseline characteristics of subjects by level of fish intake. Subjects with a high intake tended to be older ($P < 0·01$). Distribution of smoking and alcohol habits differed between the two fish intake levels ($P < 0·01$). Subjects who had a high intake of fish consumed more vegetables and fruits as well as meat ($P < 0·01$). The proportion of subjects living with a spouse was higher in the high intake group ($P < 0·01$), but no difference was seen for a history of diabetes ($P = 0·90$).

https://doi.org/10.1017/S1368980008003182 Published online by Cambridge University Press

Multivariate-adjusted HR and 95% CI for prostate cancer mortality by fish intake are shown in Table 2. Results showed a consistent inverse association in the high compared with low intake group, with a multivariate-adjusted HR of 0·11 (95% CI 0·04, 0·28). Further adjustment for intake of other food items, including vegetables, fruit and meat, did not substantially alter the estimated HR. This model showed a multivariate-adjusted HR of 0·12 (95% CI 0·05, 0·32) for the group with high fish intake.

Discussion

In our prospective study in a Japanese population, we found that a high intake of fish may be inversely associated with the risk of prostate cancer death. This association had also been examined by several previous studies. In the large Health Professionals' Follow-up Study in the USA, a significant inverse association was seen between fish intake and metastatic prostate cancer incidence, but the association was not significant for all prostate cancers or for advanced prostate cancer[8]. Further, a cohort study in Sweden showed a significant inverse association between prostate cancer incidence and mortality[9], and a case–control study in Poland found a significant inverse association with the consumption of smoked and fried fish[16]. In contrast, cohort studies in Hawaii[17] and The Netherlands[18] showed no preventive effect of fish consumption on the risk of prostate cancer incidence, while the few studies in Japan have been inconsistent: the Life Span Cohort Study in Hiroshima and Nagasaki found that subjects who consumed fish almost daily had a significantly increased risk of prostate cancer incidence[12], whereas a case–control study of 140 patients in Ibaraki and Hokkaido prefectures showed a protective effect of high fish consumption[13].

The protective effect of fish against fatal prostate cancer in our study might be explained by several potential mechanisms. First, it may be related to long-chain *n*-3 fatty acids[7,19,20], including EPA, docosapentaenoic acid (DPA) and DHA, which are particularly abundant in fish. A nested case–control study in Japan identified a trend to an increase in serum levels of EPA, DPA and DHA with an increasing intake frequency of fish in both men and women[21]. These fatty acids have been shown to inhibit the biological activity of eicosanoids and androgens, which are known to have a stimulating effect on prostate cancer cell growth[22]. Second, fish is also a source of Se[23], an essential trace mineral, which behaves both as an antioxidant and an anti-inflammatory agent[24]. Experimental and epidemiological evidence supports the anticarcinogenic role of Se and reported inverse associations with prostate cancer[25,26]. Third, fish may contain alternative or additional vitamin D, vitamin E and retinol, which have been associated with a decreased risk of prostate cancer[27]. These potential factors may act together to cause the protective effect against prostate cancer among those with a high intake of fish.

Although the number of deaths from prostate cancer was relatively low, the strength of the present study is its prospective design. Information on potentially confounding

Table 1 Baseline characteristics* of subjects according to level of fish intake: male participants of the Miyako Study cohort, Fukuoka Prefecture, Japan

Characteristic	Low intake	High intake	*P* value†
Number of subjects	1154	4435	
Age (years)			
Mean	51·4	53·2	<0·01
SD	13·1	13·3	
Smoking (%)			
Never smokers	18·4	18·3	<0·01
Ex-smokers	25·3	27·7	
Current smokers	51·1	50·4	
Unknown	5·2	3·6	
Alcohol (%)			
Never drinkers	17·2	12·0	<0·01
Ex-drinkers	3·6	3·4	
Current drinkers	75·4	81·7	
Unknown	3·8	2·9	
Employment status (%)			
Employed	40·5	45·8	<0·01
Self-employed	21·3	26·6	
Unemployed	13·8	10·3	
Unknown	24·4	17·3	
Daily intake of vegetables (%)	19·4	31·6	<0·01
Daily intake of fruit (%)	33·2	44·4	<0·01
Daily intake of meat (%)	4·4	8·3	<0·01
History of diabetes (%)	6·5	6·6	0·90
Living with spouse (%)	70·3	77·9	<0·01

*Information was obtained through self-report from the baseline questionnaire.
†*P* value based on the χ^2 test for categorical variables and ANOVA for continuous variables.

Table 2 Hazard ratios (HR) of prostate cancer deaths by level of fish intake: male participants of the Miyako Study cohort, Fukuoka Prefecture, Japan

	Low intake	High intake
No. of prostate cancer deaths	15	6
Person-years of follow-up	15 027	60 045
Crude HR (95% CI)	1·00 (referent)	0·10 (0·03, 0·25)
Age-adjusted HR (95% CI)	1·00 (referent)	0·10 (0·03, 0·29)
Multivariate-adjusted HR* (95% CI)	1·00 (referent)	0·11 (0·04, 0·28)
Multivariate-adjusted HR† (95% CI)	1·00 (referent)	0·12 (0·05, 0·32)

*Multivariate HR adjusted for age, smoking habit, alcohol habit, history of diabetes, employment status, living with spouse and study area.
†Multivariate HR adjusted for confounding factors in HR* and additionally adjusted for other food items, including vegetable, fruit and meat intakes.

https://doi.org/10.1017/S1368980008003182 Published online by Cambridge University Press

variables and fish intake was collected before the subsequent diagnosis of any cancer, reducing the potential for the information bias inherent in case–control studies. An additional strength was the likely consistency of the findings, which did not change after adjustment for other food items.

Several limitations warrant mention. First, results were derived from the assessment of exposure at baseline only, although fish consumption may have changed over time. However, this problem is common to all large cohort studies. Second, the type and amount of fish consumed were not described, even though only fish high in *n*-3 fatty acids are likely to lower the risk of prostate cancer[19]. Third, we did not assess the family history of prostate cancer, which is also reported to be an important risk factor[4].

In conclusion, these results support the hypothesis that a high intake of fish may decrease the risk of prostate cancer death. Given the paucity of studies examining this association, especially in Asian men, these findings require confirmation in further cohort studies.

Acknowledgements

Source of funding: The study was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas C-1 (12218216) and C-2 (12218237) from the Ministry of Education, Science and Culture of Japan. The authors gratefully acknowledge the public health authorities in the municipal offices and public health staff of Miyako Health Center and Munakata Health Center for their valuable cooperation.

Conflict of interest: None declared.

Authorship responsibilities: T.-M.P. conceived the study hypothesis, performed data analyses and wrote the manuscript. T.K., R.I. and S.M. contributed to data analyses and writing of the manuscript. Y.F., N.T., T.M., I.O. and T.Y. were principal investigators responsible for data management of the Miyako Study. All authors contributed to discussion of content and writing of the manuscript.

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https://doi.org/10.1017/S1368980008003182 Published online by Cambridge University Press