Short Communication

Fatty Fish Consumption Lowers the Risk of Endometrial Cancer: A Nationwide Case-Control Study in Sweden[1]

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Abstract

The consumption of fatty fish, which contains large amounts of omega-3 fatty acids, may lower the risk of hormone-responsive cancers. Our aim was to study the association of fish consumption and endometrial cancer risk in Sweden, a country with a wide range of high fatty fish consumption. Using data from a large, nationwide case-control study (709 cases and 2888 controls), we analyzed consumption of both fatty (*e.g.*, salmon and herring) and lean (*e.g.*, cod and flounder) fish in relation to endometrial cancer risk, adjusting estimates for a wide range of potentially confounding variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed from unconditional logistic regression models fit by maximum likelihood methods. Consumption of fatty fish was inversely associated with endometrial cancer risk. The multivariate OR for women in the highest quartile level (median, 2.0 servings per week), compared to women with in the lowest (median, 0.2 servings per week), was 0.6 (95% CI, 0.5–0.8; *P* for trend, 0.0002). The corresponding OR for women in the highest quartile level of lean fish (median, 2.5 servings per week), compared to women in the lowest (median, 0.6 servings per week), was 1.0 (95% CI, 0.8–1.3; *P*-value for trend, 0.72). Total fish consumption was inversely associated with risk, although weakly. Our results suggest that the consumption of fatty fish, but not other types of fish, may decrease the risk of endometrial cancer.

Introduction

A recent cross-sectional study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in 16 regions of Europe showed significantly increased (3- to 4-fold) plasma levels of EPA,[3] an omega-3 fatty acid, in people from Sweden and Denmark with high consumption levels of fatty fish (1). EPA competes with arachidonic acid as substrate for cyclooxygenases, and, therefore, high concentrations of EPA can lead to important changes in relative concentrations of tumor growth-enhancing prostaglandins (2, 3). In Sweden, for example, a recent cohort study of 6272 men found that high fish consumption was associated with a significant reduction in prostate cancer incidence and mortality (4).

Although omega-3 fatty acids contained in fatty fish have been shown to retard the growth of hormone-responsive tumors *in vitro* and in animal experiments (2, 3), evidence from studies of hormone-responsive cancers conducted among human populations remains sparse. Regarding endometrial cancer, five case-control studies (5–9) and one prospective cohort study (10) of total fish consumption have found mixed results. However, none of these studies have specifically examined the consumption of fatty fish or omega-3 fatty acids in relation to risk. Null results are not surprising in populations with a low range of total fish consumption, especially if the percentage of fatty fish is also low. Therefore, we examined the association between the consumption of fatty fish, lean fish, and endometrial cancer in a nationwide case-control study of women in Sweden, a country with a relatively wide range of fatty fish consumption (11).

Materials and Methods

The methods of this population-based case-control study have been described elsewhere (12). In brief, the study was conducted among postmenopausal women ages 50–74 years, born in Sweden and residing in Sweden from 1994 through 1995. Eligible as case patients (n = 1055) were women with an incident, primary, endometrial cancer, identified through six regional cancer registries in Sweden. Control women (n = 4216) were randomly selected from a continuously updated population register. Participation rates were 75% among case patients (789 of 1055 eligible) and 79.9% among the control women (3368 of 4216 eligible). Histological specimens for case women were reviewed by the study pathologist (Anders Lindgren) who, blinded to any characteristics of the subjects, reclassified 80 cases as endometrial atypical hyperplasia, which we excluded from the analysis.

Data were obtained through mailed questionnaires. Participants were asked how often per day, per week, or per month, on average, 1 year prior to the interview, they had consumed different types of fish and 32 other foods, using nine predefined frequency categories that ranged from "never/seldom" to "three or more times per day." The questionnaire also covered hormone replacement therapy (12), reproductive and medical histories, anthropometrical measures, and lifestyle factors such as physical activity, smoking, and multivitamin use.

Among control subjects, 480 (14.3%) of 3368 failed to return the mailed questionnaire but agreed to a telephone interview including most questionnaire items (except family history of cancer, diet, alcohol consumption, and medical history). These controls were excluded from the present analysis. An additional 36 controls (1.2%), and 9 cases (1.3%), failed to

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[3] The abbreviations used are: EPA, eicosapentanoic acid; OR, odds ratio; CI, confidence interval.

Table 1 Baseline characteristics of the study subjects

Characteristics	Cases/Controls	Cases	Controls
Fatty fish (median servings/wk)	680/2776	0.6	0.9
Other Fish (median servings/wk)	683/2796	1.1	1.1
Age (medians in yr)	709/2877	66	64
Body mass index (median kg/m^2)	709/2868	26.6	24.9
Leisure time physical activity (% low)	704/2869	21.0	17.8
Smoking (% >1 yr)	709/2887	34.0	42.8
Alcohol (mean g/day)	704/2859	1.9	2.1
Parity (mean no. of children)	709/2886	1.9	2.1
Age at menarche (% <12 yr)	643/2608	23.0	21.5
Diabetes (%)	709/2874	11.7	5.7
Oral contraceptive use (%)	692/2765	20.4	32.1
Hormone replacement therapy use potency %[a]			
Low	705/2856	19.9	11.1
Medium	680/2801	13.4	5.0
Medium with continuous progestins	675/2779	5.0	7.1
Medium with cyclic progestins	675/2782	11.6	9.3

[a] See Ref. 12 for details.

Table 2 ORs of endometrial cancer according to fish consumption

	Fish consumption quartiles				*P*-trend[a]
	1	2	3	4	
Fatty fish (*e.g.*, salmon, herring, mackerel)					
Median consumption/wk	0.2	0.6	1.0	2.0	
No. of cases/controls	175/630	182/671	187/816	136/659	
Age adjusted OR[b] (95% CI)	1.0, referent	1.0 (0.8–1.2)	0.8 (0.6–1.0)[c]	0.7 (0.5–0.9)[d]	0.0007
Multivariate OR (95% CI)[e]	1.0, referent	1.0 (0.8–1.3)	0.8 (0.6–1.09)[c]	0.6 (0.5–0.8)[f]	0.0002
Lean fish (*e.g.*, cod, flounder, shellfish)					
Median consumption/week	0.6	0.9	1.1	2.5	
No. of cases/controls	215/833	102/413	216/968	150/582	
Age adjusted OR (95% CI)	1.0, referent	1.0 (0.7–1.2)	0.9 (0.7–1.1)	1.0 (0.8–1.2)	0.54
Multivariate OR (95% CI)[e]	1.0, referent	1.0 (0.7–1.3)	0.9 (0.7–1.2)	1.0 (0.8–1.3)	0.72
Total fish					
Median consumption/week	0.9	1.7	2.4	3.5	
No. of cases/controls	167/624	172/690	158/717	166/689	
Age adjusted OR (95% CI)	1.0, referent	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.9 (0.7–1.1)	0.14
Multivariate OR (95% CI)[e]	1.0, referent	1.0 (0.8–1.2)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.05

[a] All *P* are from two-sided tests.
[b] OR, odds ratio.
[c] $P < 0.05$.
[d] $P < 0.01$.
[e] Multivariate models adjusted for age, body mass index, smoking, leisure time physical activity, consumption of alcohol, multivitamin use, and prevalence of diabetes.
[f] $P < 0.001$.

respond to questions regarding fish consumption. This left 698 cases and 2720 controls available for analysis. ORs were computed from unconditional logistic regression models fit by maximum likelihood methods. For tests of trend, median values of each category of categorized variables were fitted in risk models as successive integers (13). Multivariate models adjusted for age (as a continuous variable), body mass index (in quartiles defined among controls), smoking (ever >1 year, never), leisure time physical activity 1 year prior to the interview (never, <1 h/week, 1–2 h/week, >2 h/week), consumption of alcohol (in quartiles), multivitamin use (never, sometimes, frequent), and history of diabetes (yes or no).

Results

Baseline characteristics of the study subjects are shown in Table 1. Cases consumed less fatty fish than controls, although consumption of other fish did not vary according to case-control status; were less likely to smoke than controls; had a lower mean number of children; and had a lower prevalence of oral contraceptive use. Cases also had a higher median body mass index, a higher prevalence of diabetes, and a higher prevalence of hormone replacement use.

Fatty fish consumption was inversely associated with endometrial cancer in models that adjusted estimates for age and for the potentially confounding factors listed in Table 2. The OR of invasive endometrial cancer for women in the highest quartile level of fatty fish (median, 2.0 servings per week) compared to women with in the lowest (median, 0.2 servings per week) was 0.6 (95% CI, 0.5–0.8; *P* for trend, 0.0002). The corresponding OR for women in the highest quartile level of lean fish (median, 2.5 servings per week) compared with women in the lowest (median, 0.6 servings per week) was 1.0 (95% CI, 0.8–1.3; *P* for trend, 0.72). Total fish consumption was only weakly associated with endometrial cancer. The corresponding OR for women in the highest quartile level of total fish compared with women in the lowest was 0.8 (95% CI,

0.6–1.0; *P* for trend, 0.05). Age-adjusted results were similar to those with multivariate-adjustment, which were essentially unchanged after additional adjustment for height (in quintiles defined among controls), leisure time physical activity between ages 18 and 30 (never, <1 h/week, 1–2 h/week, >2 h/week), consumption of high fiber grains, dairy products, fruit, *brassica* and non-*brassica* vegetables (in quintiles), parity (as a continuous variable), duration of hormone replacement therapy (as a continuous variable), age at menarche (<12 years, 12–14 years, >14 years), age at menopause and age at first birth (in quartiles), history of hypertension (yes, no), and quintiles of total food consumption (estimated by totaling all of the food items in the food frequency questionnaire).

Discussion

We found that consumption of fatty fish was inversely associated with endometrial cancer risk. In contrast, we observed no association when we modeled the consumption of lean fish. Even in this population with a relatively high consumption of fatty fish, total fish consumption was only weakly associated with endometrial cancer risk, which underscores the need for separate analyses according to the type of fish consumed.

Total fish consumption was inversely associated with endometrial cancer in two previous case-control studies (5, 9). The specific type of fish examined in these studies was not considered, however, which makes comparisons with our findings difficult. Two previous case-control studies found no association with total fish consumption (6, 7), whereas a case-control study (8) and a prospective cohort study (10) found that high total fish consumption increased the risk. However, the prospective cohort study excluded canned tuna from their total fish measure, which might have been one of the most important sources of omega-3 fatty acids in the population of women from the Midwestern United States.

Our data were limited by the likelihood of nondifferential measurement error with respect to fish consumption. Nondifferential misclassification would tend to attenuate true associations and can stem from measurement error in the assessment of diet because of inaccurate recall of past diet (14), or because of changes in diet over time (14). Finally, although we adjusted our estimates for a wide range of potentially confounding variables, uncontrolled confounding from dietary (or other) factors cannot be excluded.

We conclude that high fatty fish consumption may reduce endometrial cancer risk. Fatty fish are a good source of omega-3 fatty acids, which, possibly acting through inhibition of arachidonic acid-derived eicosanoid biosynthesis, may reduce concentrations of tumor growth-enhancing prostaglandins (2, 3). Given the scarcity of studies of fish consumption and endometrial cancer risk, additional investigations are warranted.

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