Long-term Fatty Fish Consumption and Renal Cell Carcinoma Incidence in Women

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Context The epidemiological evidence that fatty fish consumption may be associated with the lower risk of several cancers is not consistent and no studies of renal cell carcinoma (RCC) exist.

Objective To examine the association between fatty and lean fish consumption and risk of RCC in women.


Main Outcome Measure Incident renal cell carcinoma.

Results During a mean of 15.3 years (940,357 person-years) of follow-up between 1987 and 2004, 150 incident RCC cases were diagnosed. After adjustment for potential confounders, an inverse association of fatty fish consumption with the risk of RCC was found ($P$ for trend = .02), but no association was found with lean fish consumption. Compared with no consumption, the multivariate rate ratio (RR) was 0.56 (95% confidence interval [CI], 0.35-0.91) for women eating fatty fish once a week or more. Compared with women consistently reporting no fish consumption, the multivariate RR was 0.26 (95% CI, 0.10-0.67) for those women reporting consistent consumption of fatty fish at baseline and 1997 (based on a subset of 36,664 women who filled in the baseline and 1997 questionnaires, with 40 incident RCC cases during the 1998-2004 follow-up period).

Conclusion Our study suggests that consumption of fatty fish may reduce the occurrence of RCC in women.

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METHODS

Study Population

The Swedish Mammography Cohort is a population-based prospective cohort study established between March 1, 1987, and December 14, 1990, when all women who were born between 1914 and 1948 and residing in Uppsala and Västmanland counties in central Sweden, together with an invitation to a free-of-charge mammography examination, received a mailed questionnaire on diet, intake of alcoholic beverages, weight, height, and education.

Of the 90,303 women in the source population, 66,651 (74%) returned a completed questionnaire. After excluding from the baseline population women with erroneous or missing national registration number, those who reported implausible values for total energy intake, (ie, 3 SDs from the mean value for log-transformed energy intake), and those with a previous cancer diagnosis (except nonmelanoma skin cancer), the study cohort included 61,433 women. In September 1997, a second questionnaire was sent to 56,030 participants who were still alive (3,332 died before the date of send-outs) and residing in the study area (2,071 moved out) to update dietary data, alcohol, and anthropometric measures and to collect information on other lifestyle factors (including cigarette smoking) and medical history of diabetes mellitus (additional information about history of diabetes was obtained by computerized linkage of the study population with the national inpatient register) and hypertension; 39,227 women (70% response rate) answered this questionnaire. After exclusions according to the same criteria as at baseline, the subset cohort with updated exposure information included 36,664 women.

The response of these women to the questionnaire after reading an attached information letter about our cohort study was treated as an informed consent of study participants. The investigation was approved by the regional ethical review board in Stockholm, Sweden.

Assessment of Diet

At baseline, a 67-item food frequency questionnaire (FFQ) was used to assess dietary intake. An expanded 96-item FFQ was used to update information on dietary intake in 1997. In these FFQs, women reported their usual average frequency of consumption of each food item during the past year, filling in 1 of 8 predefined frequency categories (in the baseline FFQ: never or seldom, 1-3 servings per month, 1 serving per week, 2-3 servings per week, 4-6 servings per week, 1 serving per day, 2-3 servings per day, ≥4 servings per day; and in the 1997 FFQ: 0 servings per month, 1-3 servings per month, 1 serving per month, 1-2 servings per week, 3-4 servings per week, 5-6 servings per week, 1 serving per day, 2 servings per day, ≥3 servings per day); on both occasions, there were questions about consumption of the same types of fish. We considered fatty fish to include salmon, herring, sardines, and mackerel; lean fish included mainly cod, tuna, and sweet water fish; and other seafood included shrimp, lobster, and crayfish.

The baseline FFQ has been validated in a subsample of 129 women randomly chosen from the study population. The Spearman correlation coefficients between the FFQ and the mean of four 1-week weighted diet records was 0.5 for fatty fish, 0.4 for lean fish, and 0.6 for other seafood.

Ascertainment of Cases and Follow-up

Incident cases of RCC were ascertained through computerized linkage of the study population with the national and regional cancer registers. The regional cancer registers receive notification about newly diagnosed cases first from the pathology/cytology laboratory, followed by a clinical notification. These registers have been estimated to provide approximately 100% complete case ascertainment in Sweden. 96% of all kidney cancers in Sweden are cytologically or histologically confirmed. From the Swedish Death and Population registers at Statistics Sweden, we obtained information on the dates of death and migration from the study area, when applicable.

Statistical Analysis

Person-time was accrued for each participant from the date of entry into the cohort to the date of diagnosis of RCC, death, migration, or December 31, 2004, whichever came first. We grouped participants into categories according to intake of fatty fish and lean fish. In the main analyses, we used fish consumption data in 2 ways: (1) baseline information only for the entire period of follow-up, as well as (2) updated average consumption to better represent long-term average intake and reduce random within-person variation. Specifically, for the updated consumption we used the baseline data for the 1987-1997 follow-up period, and an average of the baseline and 1997 data for the 1998-2004 follow-up period, using midpoints of frequency categories for both questionnaires. In sensitivity analyses of internal consistency of results over time, we analyzed baseline exposure data for the first period of follow-up (1987-1997) only, and the subset of 1997 data separately for the second period of follow-up (1998-2004).

Furthermore, we analyzed RCC incidence in relation to consistently reported long-term consumption patterns (ie, the same at baseline and 1997). We grouped women into the ref-
ference category of consistent no consumption if they reported never or seldom consumption at baseline FFQ and 0 consumption at 1997 FFQ, and in the category of consistent consumption if they reported 1 to 3 servings per month or more at both FFQs; all other women were grouped into the no consistent category (ie, those women who changed from no consumption at baseline to ≥1-3 servings per month at 1997 FFQ or vice versa from ≥1-3 servings per month at baseline to no consumption at 1997 FFQ).

We used Cox proportional hazards regression models (PROC PHREG in SAS version 9.1 software; SAS Institute Inc, Cary, NC) to estimate rate ratios (RRs) with 95% confidence intervals (CIs). Age in months and year of entry into the cohort were used as stratification variables in the Cox proportional hazards regression model. In all multivariate analyses, we controlled for age, education, body mass index (calculated as weight in kilograms divided by height in meters squared), and intakes of total energy, alcohol, total meat, fruits, and vegetables. In additional analyses, we further adjusted for smoking, diabetes, and hypertension. Cox proportional hazards regression assumption was tested for fatty and lean fish variables in relation to risk of RCC using the likelihood ratio test, comparing nested models with and without interaction terms for fish intake and follow-up time. There was no evidence of violation of the proportional hazards regression assumption. To test for linear trend across categories, we modeled fish intake as a single continuous variable using the median value within categories. All reported P values were from 2-sided statistical tests and P<.05 was considered statistically significant.

**RESULTS**

During a mean (SD) of 15.3 (2.8) years and 940 357 person-years of follow-up between 1987 and 2004, there were 150 incident RCC cases diagnosed in the cohort. The mean (SD) age at diagnosis was 67.2 (9.4) years. On average, women consuming fatty fish more frequently had a higher energy intake and consumed more alcohol, meat, fruit, and vegetables as well as lean fish; they also had slightly higher prevalence of hypertension (TABLE 1).

In both age-adjusted and multivariate analyses, fatty fish consumption of 1 or more servings per week was associated with a statistically significant 44% decreased risk of RCC; the results were consistent for both types of analyses (based only on the baseline [1987-1990] exposure data for the whole follow-up period and on updated consumption taking into account changes in fish consumption between baseline and 1997) (TABLE 2). We did not observe any statistically significant association with lean fish or other seafood (RR, 0.71; 95% CI, 0.34-1.47) for 1 or more servings of seafood per week vs no consumption. Exclusion of the first 2 years of follow-up from analyses did not change our results.

To evaluate how robust our risk estimates were, we performed sensitivity analyses using baseline data for the first period of follow-up (1987-1997) of 61 433 women, covering 551 113 person-years with 79 incident RCC cases, and a separate analysis using 1997 exposure data for the second period of follow-up (1998-2004), covering 249 850 person-years with 40 incident RCC cases that occurred in the subset of 36 664 women (for 31 cases diagnosed after 1997, there were no updated exposures available). Compared with no consumption, eating fatty fish 1 to 3 times per month or more (median frequency, 1-3 servings per month) often was associated with a multivariate RR of 0.69 (95% CI, 0.42-1.14) for the first period. Corresponding value for the second period of follow-up had an RR of 0.39 (95% CI, 0.19-0.82); however, median frequency of consumption category was 1 to 2 servings per week. Further adjustments of the second period data for smoking gave an RR of 0.39 (95% CI, 0.18-0.82) and adjustment for smoking, diabetes, and hypertension gave an RR of 0.37 (95% CI, 0.18-0.80). Lean fish consumption was not statistically significantly associated with RCC risk in any of the follow-up periods.

In the analysis of the subset of 36 664 women with available information on fatty fish consumption at baseline and 1997 and then followed up during

**Table 1.** Age-Standardized Characteristics of 61 433 Women in the Swedish Mammography Cohort by Fatty Fish Consumption at Baseline (1987-1990)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0</th>
<th>1-3 per mo</th>
<th>≥1 per wk (1 per wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women at baseline†</td>
<td>15 594</td>
<td>31 620</td>
<td>14 219</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>54.8 (10.2)</td>
<td>52.9 (9.5)</td>
<td>54.4 (9.6)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>24.7 (4.0)</td>
<td>24.6 (3.8)</td>
<td>25.2 (4.0)</td>
</tr>
<tr>
<td>Postsecondary education, %‡</td>
<td>10.7</td>
<td>13.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Hypertension, %‡</td>
<td>20.3</td>
<td>21.7</td>
<td>23.0</td>
</tr>
<tr>
<td>Diabetes mellitus, %‡</td>
<td>4.2</td>
<td>3.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Ever smoking, %‡</td>
<td>47.7</td>
<td>45.6</td>
<td>46.8</td>
</tr>
<tr>
<td>Dietary intake, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy, kcal/d</td>
<td>1490 (460)</td>
<td>1583 (444)</td>
<td>1687 (492)</td>
</tr>
<tr>
<td>Alcohol, g/d</td>
<td>1.9 (3.2)</td>
<td>2.7 (3.5)</td>
<td>2.9 (3.8)</td>
</tr>
<tr>
<td>Meat, g/d</td>
<td>73.8 (45.8)</td>
<td>82.9 (38.2)</td>
<td>93.1 (48.7)</td>
</tr>
<tr>
<td>Fruits, servings/d</td>
<td>1.6 (1.2)</td>
<td>1.7 (1.2)</td>
<td>2.0 (1.3)</td>
</tr>
<tr>
<td>Vegetables, servings/d</td>
<td>1.5 (1.2)</td>
<td>1.7 (1.1)</td>
<td>2.1 (1.5)</td>
</tr>
<tr>
<td>Lean fish, servings/wk</td>
<td>1.0 (0.1)</td>
<td>1.1 (0.1)</td>
<td>1.3 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

†The 1997 subset of 36 634 women was distributed into the 3 fatty fish consumption categories as follows: 4416, 9039, and 23149 (median frequency in the ≥1 per week group was 1-2 servings per week).

‡Information (self-reported) from the 1997 questionnaire. Additional information about history of diabetes was obtained by computerized linkage of the study population with the national inpatient register.
1998-2004, we observed that those women who consistently reported long-term consumption of fatty fish of 1 to 3 servings per month or more at baseline (1987-1990) and 10 years later had a statistically significant 74% lower risk of RCC compared with those women who consistently reported no consumption of fatty fish at both time periods. Further adjustment for smoking or for smoking, hypertension, and history of diabetes did not change the results (Table 3).

**COMMENT**

In this large population-based cohort with data on long-term diet, we found that women who consumed 1 or more servings of fatty fish per week had a statistically significant 44% decreased risk of RCC compared with women who did not consume any fish. Women who reported consistent long-term consumption of fatty fish at baseline and 10 years later had a statistically significant 74% lower risk. In contrast, consumption of lean fish or other seafood was not associated with the risk of RCC. Per capita consumption of fatty fish in Sweden has been increasing since the baseline time in our cohort (late 1980s through early 2000s); consumption of salmon, the main fatty fish, almost doubled and consumption of canned herring and other fatty fish increased by about 50% during the follow-up period. Thus, the observed strong inverse associations may reflect greater true frequency of consumption of fatty fish during the 2 study periods than was reported on the baseline and 1997 FFQ and which is apparent in our tables.

Our results support the hypothesis that frequent consumption of fatty fish may lower the risk of RCC possibly due to increased intake of fish oil rich in eicosapentaenoic acid and docosahexaenoic acid as well as vitamin D. Results from a cross-sectional study in 16 regions in Europe (the European Prospective Investigation into Cancer and Nutrition) showed greatly increased

Table 2. Rate Ratios of Renal Cell Carcinoma by Fatty Fish and Lean Fish Consumption in the Swedish Mammography Cohort of 61,433 Women in the Follow-up Period 1987-2004*

<table>
<thead>
<tr>
<th>Servings at Baseline (Median Frequency Category)†</th>
<th>Fatty Fish Consumption</th>
<th>Lean Fish Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-3 per mo</td>
<td>1-3 per mo</td>
</tr>
<tr>
<td>No. of cases</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>Person-years</td>
<td>107,845</td>
<td>98,507</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>0.67 (0.46-0.97)</td>
</tr>
<tr>
<td>Multivariate‡</td>
<td>1.00</td>
<td>0.69 (0.47-1.01)</td>
</tr>
</tbody>
</table>

Table 3. Rate Ratios of Renal Cell Carcinoma by Long-term Fatty Fish Consumption (at Baseline and in 1997) in a Subset of 36,664 Women From the Swedish Mammography Cohort in the Follow-up Period 1998-2004

<table>
<thead>
<tr>
<th>Consumption at Baseline and in 1997*</th>
<th>Consistent No Consumption</th>
<th>No Consistent</th>
<th>Consistent Consumption</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>7</td>
<td>12</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.00</td>
<td>0.39 (0.15-1.00)</td>
<td>0.22 (0.09-0.52)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)†</td>
<td>1.00</td>
<td>0.46 (0.18-1.21)</td>
<td>0.29 (0.12-0.73)</td>
<td>.01</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)‡</td>
<td>1.00</td>
<td>0.46 (0.18-1.21)</td>
<td>0.28 (0.11-0.72)</td>
<td>.009</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)§</td>
<td>1.00</td>
<td>0.43 (0.16-1.14)</td>
<td>0.26 (0.10-0.67)</td>
<td>.007</td>
</tr>
</tbody>
</table>

Abbreviations: RR, rate ratio; CI, confidence interval.

*Consistent no consumption group includes women reporting never or seldom consumption at baseline and 0 consumption in 1997; consistent consumption of 1 to 3 servings per month or more group includes women who reported 1 to 3 servings per month or more at baseline and in 1997 (median frequency of consumption categories reported by this group were 1-3 servings per month on baseline and 1-2 servings per week at 1997 questionnaires); no consistent consumption group includes all other women (ie, those who changed from never or seldom consumption at baseline to >=1-3 servings per month in 1997, and vice versa from >=1-3 servings per month at baseline to 0 consumption in 1997).

†Stratified by age in months and adjusted for education (< high school, high school graduate, or > high school), body mass index (calculated as weight in kilograms divided by height in meters squared; <23.0, 23.0-24.9, 25.0-29.9, or ≥30.0), and intakes of total energy (continuous), alcohol (quartiles), total meat (quartiles), fruits (quartiles), and vegetables (quartiles); fatty fish and lean fish were mutually adjusted.

‡Baseline consumption analysis used only 1987-1990 exposure data for the whole follow-up period between 1987-2004. Updated consumption analysis was based on the baseline data for the 1987-1997 follow-up period and an average of baseline and 1997 data (using midpoints of frequency categories) for the 1998-2004 follow-up; if 1997 data were not available, baseline data were used even for the 1998-2004 follow-up period.

§Also adjusted for smoking (never, past, or current smoker), history of diabetes (yes or no), and hypertension (yes or no).
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REFERENCES