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

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Renal cell carcinoma (RCC) of the renal parenchyma accounts for more than 80% of all kidney cancers, the majority of which are adenocarcinomas. Renal cell carcinoma incidence rates in the United States had been increasing in 1970-1990s, especially among black women and men; more recent data suggest a leveling off in this trend for most racial groups. Environmental factors including diet are believed to contribute significantly to the etiology of RCC.

The evidence that fish consumption, especially fatty fish, may be associated with lower risk of several cancers is not consistent. A recently published systematic review of prospective cohort studies on total fish intake (fatty and lean fish not separated) and risk for major cancers (RCC not included) did not support the hypothesis about the protective effect of fish consumption on cancer development. Epidemiological studies of RCC risk in relation to fish consumption are scarce and based on case-control design only; there was no significant association observed in any of these studies. However, all the previous studies have analyzed total fish consumption not taking into account that there are large differences between fatty fish and lean fish in the content of omega-3 fatty acids and vitamin D. Marine omega-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaneoic acid, which are present in significant amounts in fatty cold-water fish (up to 20-30 times higher content than in lean fish), have been reported to inhibit promotion and progression stages of carcinogenesis. Docosahexanoic acid is capable of significantly reducing the invasive profile of RCC. Moreover, fatty fish has 3 to 5 times higher content of vitamin D than lean fish. Lower serum vitamin D levels have been associated with

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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development and progression of 
RCC. To our knowledge, no previ-
ous study has investigated the associa-
tion between fatty fish and lean fish, 
specifically, and the risk for develop-
ment of RCC.

The population-based Swedish Mam-
mography Cohort provided an oppor-
tunity to evaluate prospectively the re-
lationship between long-term fatty fish 
and lean fish consumption (using up-
dated information on diet) and the in-
cidence of RCC in a population with a 
relatively high consumption of fatty 
fish.

**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 Upp-
sala and Vastmanland counties in 
central Sweden, together with an invi-
tation to a free-of-charge mammogra-
phy examination, received a mailed 
questionnaire on diet, intake of alco-
holic beverages, weight, height, and 
education.

Of the 90,303 women in the source 
population, 66,651 (74%) returned a 
completed questionnaire. After exclud-
ing from the baseline population 
women with erroneous or missing na-
tional registration number, those who 
reported implausible values for total en-
ergy intake, (ie, 3 SDs from the mean 
value for log-transformed energy in-
take), and those with a previous can-
cer diagnosis (except nonmelanoma 
skin cancer), the study cohort in-
cluded 61,433 women. In September 
1997, a second questionnaire was sent 
to 56,030 participants who were still 
alive (3332 died before the date of send-
outs) and residing in the study area 
(2071 moved out) to update dietary 
data, alcohol, and anthropometric mea-
sures and to collect information on 
other lifestyle factors (including cigare-
rette smoking) and medical history of 
diabetes mellitus (additional informa-
tion about history of diabetes was ob-
tained by computerized linkage of the 
study population with the national in-
patient register) and hypertension; 
39,227 women (70% response rate) an-
derned this questionnaire. After exclu-
sions according to the same criteria as 
at baseline, the subset cohort with up-
dated exposure information included 
36,664 women.

The response of these women to the 
questionnaire after reading an at-
tached information letter about our co-
hort study was treated as an informed 
consent of study participants. The in-
vestigation was approved by the re-
geonal ethical review board in Stock-
holm, 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 consump-
tion of each food item during the past 
year, filling in 1 of 8 predefined fre-
cency 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 
day, 3 servings per day; and in the 
1997 FFQ: 0 servings per month, 
1-3 servings 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 
include mainly cod, tuna, and sweet 
water fish; and other seafood included 
shrimp, lobster, and crayfish.

The baseline FFQ has been vali-
dated in a subsample of 129 women randomly chosen from the study popu-
lation. The Spearman correlation coeffi-
cients 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 ascer-
tained through computerized linkage 
of the study population with the na-
tional and regional cancer registers. The 
regional cancer registers receive notifi-
cation about newly diagnosed cases 
first from the pathology/cytology labo-
atory, followed by a clinical notifica-
tion. These registers have been esti-
mated to provide approximately 100% 
complete case ascertainment in Swe-
den. 96% of all kidney cancers in 
Sweden are cytologically or histologi-
cally confirmed. From the Swedish 
Death and Population registers at Sta-
tics Sweden, we obtained informa-
tion on the dates of death and migra-
tion from the study area, when appli-
cable.

**Statistical Analysis**
Person-time was accrued for each par-
ticipant 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 par-
ticipants into categories according to in-
take of fatty fish and lean fish. In the 
main analyses, we used fish consump-
tion data in 2 ways: (1) baseline infor-
mation only for the entire period of fol-
low-up, as well as (2) updated average 

take of fatty fish and lean fish. In the 
main analyses, we used fish consump-
tion data in 2 ways: (1) baseline infor-
mation only for the entire period of fol-
low-up, as well as (2) updated average 
consumption to better represent long-
term average intake and reduce ran-
don within-person variation. Specifi-
cally, 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 mid-
points 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 fol-

Furthermore, we analyzed RCC in-
cidence in relation to consistently re-
ported long-term consumption pat-
terns (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 \( \geq 1 \)–3 servings per month at 1997 FFQ or vice versa from \( \geq 1 \)–3 servings per month at baseline to no consumption at 1997 FFQ).

We used Cox proportional hazards regression models\(^{18}\) (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 at risk 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

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**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>( \geq 1 ) per wk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of women at baseline</strong></td>
<td>15 594</td>
<td>31 620</td>
<td>14 219</td>
</tr>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>54.8 (10.2)</td>
<td>52.9 (9.5)</td>
<td>54.4 (9.6)</td>
</tr>
<tr>
<td><strong>BMI, mean (SD)</strong></td>
<td>24.7 (4.0)</td>
<td>24.6 (3.8)</td>
<td>25.2 (4.0)</td>
</tr>
<tr>
<td><strong>Postsecondary education, %</strong></td>
<td>10.7</td>
<td>13.3</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Hypertension, %</strong></td>
<td>20.3</td>
<td>21.7</td>
<td>23.0</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, %</strong></td>
<td>4.2</td>
<td>3.3</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Ever smoking, %</strong></td>
<td>47.7</td>
<td>45.6</td>
<td>46.8</td>
</tr>
<tr>
<td><strong>Dietary intake, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Energy, kcal/d</strong></td>
<td>1490 (460)</td>
<td>1583 (444)</td>
<td>1687 (492)</td>
</tr>
<tr>
<td><strong>Alcohol, g/d</strong></td>
<td>1.9 (3.2)</td>
<td>2.7 (3.5)</td>
<td>2.9 (3.8)</td>
</tr>
<tr>
<td><strong>Meat, g/d</strong></td>
<td>73.8 (45.8)</td>
<td>82.9 (38.2)</td>
<td>93.1 (48.7)</td>
</tr>
<tr>
<td><strong>Fruits, servings/d</strong></td>
<td>1.6 (1.2)</td>
<td>1.7 (1.2)</td>
<td>2.0 (1.3)</td>
</tr>
<tr>
<td><strong>Vegetables, servings/d</strong></td>
<td>1.5 (1.2)</td>
<td>1.7 (1.1)</td>
<td>2.1 (1.5)</td>
</tr>
<tr>
<td><strong>Lean fish, servings/wk</strong></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, *2006 American Medical Association. All rights reserved.*

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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 per wk</td>
</tr>
<tr>
<td></td>
<td>Person-years</td>
<td>235,955</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 ≥1-3 per mo</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>0.46 (0.18-1.21)</td>
<td>0.28 (0.11-0.72)</td>
<td>.009</td>
</tr>
</tbody>
</table>

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 in 1997 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...
(3-4 fold) blood concentrations of eicosapentaenoic acid in study participants from Sweden and Denmark who consumed fatty fish. Our study based on a subgroup of 116 women from the cohort showed that fatty fish consumption is the main determinant of serum vitamin D concentrations during the winter season (A.W., unpublished data, 2006).

Several molecular mechanisms whereby marine fatty acids, eicosapentaenoic acid, and docosahexaenoic acid may affect carcinogenesis have been proposed, as we recently reviewed in more detail.11 The most known mechanism is ascribed to suppression of arachidonic acid–derived eicosanoid biosynthesis leading to altered immune response of cancer cells and modulation of inflammation, cell proliferation, apoptosis, and angiogenesis. It was recently observed in vitro that docosahexaenoic acid is capable of significantly reducing the invasive profile of RCC,13 and shark liver oil (rich in eicosapentaenoic acid and docosahexaenoic acid) suppressed neovascular response in mice grafted with human kidney cancer.21 Human RCC tissues express transcription factor peroxisome proliferator–activated receptor γ (PPAR-γ) and the synthetic PPAR agonist inhibits the growth of the RCC cells.22 Docosahexaenoic acid is a naturally occurring PPAR-γ agonist.23 Furthermore, eicosapentaenoic acid and docosahexaenoic acid might increase production of free radicals and reactive oxygen species, improve insulin sensitivity, and modulate cancer cell membrane characteristics, leading to a decreased ability to metastasize.11

Despite accumulating evidence from experimental data based on cell cultures and animal models on the potential role of eicosapentaenoic acid and docosahexaenoic acid in carcinogenesis, support from observational epidemiological data is very inconsistent. A recent systematic review of 20 prospective cohort studies of the effect of omega-3 fatty acids and total fish intake (fatty and lean not separated) on the risk of 11 different types of cancers (RCC was not included due to lack of prospective data) revealed that there was a high degree of heterogeneity between results precluding pooling of data; the source of heterogeneity was not explained.9 The conclusion was that at present the accumulated evidence did not support a significant association between omega-3 fatty acids intake and overall cancer incidence. However, for most types of cancer, data were not sufficient to exclude an association with confidence.

Fatty fish is also a rich source of vitamin D.14 It was observed that serum vitamin D levels in patients with RCC were significantly lower than in non-cancer controls; patients with rapid-growth type of tumors (T3 and T4) had significantly lower levels of vitamin D3 than patients with slow-growth type RCC (T1 and T2).14 This result suggests that low serum levels of vitamin D3 may influence development and progression of RCC. Vitamin D3 exerts its biological activity by binding to the vitamin D receptors, which are present in kidney cells.23 Vitamin D receptor genotype may play an important role in determining the risk of developing more aggressive RCC.20

The main strengths of our study include its population-based prospective design, the availability of dietary exposure information collected from participants at 2 time points, and the practically complete follow-up of the study population through linkage with computerized registers. The prospective study design precluded potentially biased recall of dietary intake and the completeness of follow-up of the cohort minimized the concern that our findings have been affected by differential loss to follow-up. By using repeated measurement of diet, we could obtain a better estimate of long-term fish consumption and reduce measurement error.

Our study also has several limitations. Because diet was assessed with a self-administered FFQ, some misclassification of specific types of fish is inevitable and random misclassification would tend to attenuate any true association. Information on cigarette smoking, hypertension, and diabetes was first obtained in the second questionnaire; nevertheless, in a subanalysis using data from this questionnaire, the association between fatty fish consumption and risk of RCC persisted after adjustment for these 3 factors. Because of the observational nature of our study, we cannot rule out the possibility that an unmeasured risk factor for RCC, which is correlated with fatty fish consumption, has had some effects on our results. Another limitation is that we did not perform analyses of eicosapentaenoic acid, docosahexaenoic acid, and vitamin D intakes directly and our explanation of the observed results is based on speculations only. To better address the issue, a prospective study based on blood measurements of long-chain omega-3 fatty acids in blood (or preferably in adipose tissue) and of vitamin D would be needed; however, blood samples are not available in the Swedish Mammography Cohort.

In conclusion, findings from this population-based prospective study with repeated measurement of diet indicate that frequent consumption of fatty fish may be inversely associated with risk of RCC. Our results, however, require confirmation because this is the first epidemiological study addressing this issue.

Author Contributions: Dr Wolk, principal investigator of the Swedish Mammography Cohort, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wolk, Larsson, Johansson, Ekman. Acquisition of data: Wolk. Analysis and interpretation of data: Wolk, Larsson, Johansson, Ekman. Drafting of the manuscript: Wolk. Critical revision of the manuscript for important intellectual content: Wolk, Larsson, Johansson, Ekman. Statistical analysis: Wolk, Larsson. Obtained funding: Wolk. Administrative, technical, or material support: Wolk. Study supervision: Wolk, Johansson, Ekman. Financial Disclosures: None reported. Funding/Support: This study was supported by grants from the Swedish Cancer Foundation, the Swedish Research Council/Longitudinal Studies, and Västmanland County Research Fund Against Cancer. Role of the Sponsors: The funding sources had no role in the design and conduct of the study, in the collection, management, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.
FATTY FISH CONSUMPTION AND RENAL CELL CARCINOMA

REFERENCES


The artist brings something into the world that didn’t exist before, and . . . he does it without destroying something else.
—John Updike (1932- )