Dietary Intake of Lignans and Risk of Esophageal and Gastric Adenocarcinoma: A Cohort Study in Sweden

Yulan Lin, Alicja Wolk, Niclas Häkansson, Jesper Lagergren, and Yunxia Lu

Abstract

High intake of phytoestrogen lignans has been found to be associated with decreased risk of esophageal adenocarcinoma in our previous population-based case–control study in Sweden. To further evaluate this possible association, we tested the hypothesis of an inverse association between dietary lignan intake and risk of esophageal and gastric adenocarcinoma using a prospective design. In a population-based cohort study in Sweden, 81,670 participants who were cancer-free at baseline were followed up during 1998 to 2009. All participants completed a 96-item food frequency questionnaire (FFQ), which was used to assess dietary exposure to lignans (secoisolariciresinol, matairesinol, lariciresinol, pinoresinol, medioresinol, and syringaresinol). All cases of esophageal, gastroesophageal junctional, and gastric adenocarcinoma were identified through linkage to the Swedish Cancer Register. Cox proportional hazard models were used to estimate HRs and 95% confidence intervals (CI), with adjustment for potential confounding factors. During an average follow-up of 9.9 years, a total of 211 cases were identified, including 83 cases of esophageal or junctional adenocarcinoma, and 128 cases of gastric adenocarcinoma. There was no statistically significant association between dietary intake of lignans and any of the studied adenocarcinomas. Compared with participants in the lowest quartile of lignan intake, the adjusted HR of the highest quartile was 0.96 (95% CI, 0.46–2.00; \( P_{\text{trend}} = 0.70 \)) for adenocarcinoma of the esophagus or gastroesophageal junction, and 0.89 (95% CI, 0.52–1.55; \( P_{\text{trend}} = 0.78 \)) for gastric adenocarcinoma. No clear support for a protective role of dietary intake of lignans in the development of esophageal or gastric adenocarcinoma was found.

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Introduction

Esophageal and gastric adenocarcinoma are characterized by a strong male predominance, with male-to-female ratio of 5:1 to 8:1 for esophageal adenocarcinoma and 2:1 for gastric adenocarcinoma, respectively (1–3). It has been speculated that female sex hormones, mainly estrogen, may contribute to the sex difference in the incidence among these patients (4). Phytoestrogens, a group of compounds that naturally occur in plant food, show estrogenic properties due to their similar structure to endogenous estrogens (5). Lignans, present in whole grain bread, berries, fruits, vegetables, flaxseed, and sesame seed, are the most abundant phytoestrogens in the Western diet (6). Recent experimental studies have observed anticarcinogenic effects of phytoestrogens on esophageal and gastric cancer cells (7, 8). We have recently tested this hypothesis in a Swedish population-based case–control study, which showed statistically significant inverse associations between lignan intake and risk of adenocarcinoma of the esophagus and gastroesophageal junction (9). However, evidence from prospective cohort studies is lacking. By analyzing 2 well-defined cohorts in Sweden, we tested the hypothesis of an inverse association between dietary intake of phytoestrogen lignans and esophageal and gastric adenocarcinoma using a prospective design.

Materials and Methods

Study population

This cohort study included 2 large population-based Swedish cohorts, the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM), which have been described in detail elsewhere (10). Briefly, the SMC was established between 1987 and 1990, when all women born between 1914 and 1948 residing in 2 counties in central Sweden (Västmanland and Upplands counties) received a mailed questionnaire. In the autumn of 1997, an expanded questionnaire with about 350 items about diet, other lifestyle factors, and medical history was mailed to all women who were still alive and residing in the study.
area. Among them, 39,227 women (70% of all eligible) completed the questionnaire. The COSM began in the autumn of 1997, when 48,850 men (49% of all eligible) born between 1918 and 1952 and residing in 2 counties in central Sweden (Västmanland and Örebro counties) answered a mailed questionnaire that was identical (except for some sex-specific questions) to the SMC questionnaire in 1997. Eligible participants for the current study were women and men who completed the 1997 questionnaire. We excluded participants with incorrect or missing personal identity numbers, those with implausibly low or high total energy intake (i.e., 3 SDs from the mean value) and those with cancer (except nonmelanoma skin cancer) diagnosed before enrollment or during the first year of follow-up. The final baseline population consisted of 81,670 participants (36,697 women and 44,973 men) of ages 45 to 83 years. The information on history of gastroesophageal reflux symptoms and ulcer disease was collected from the nationwide complete Swedish Patient Register, whereas the diabetes data were obtained by the combined information from the Swedish Patient Register, the Swedish National Diabetes Register, and the questionnaires.

**Assessment and classification of lignan intake**

Dietary intake of lignans was assessed with the food frequency questionnaire (FFQ) about the habitual intake of 96 food items. Of these, 65 items (68%) were used to assess lignan intake, as the lignan content for the remaining items, was negligible. The participants were asked to report their average frequency of consumption for most food items using 8 predefined frequency categories. Energy content of each food item was obtained from the Swedish National Food Administration database (11). Total lignan intake was estimated using published content values of the 6 most prevalent dietary precursors of enterolactone: secoisolariciresinol (SECO), matairesinol (MAT), lariciresinol (LAR), pinoresinol (PIN), medioresinol (MED), and syringaresinol (SYR); refs. 12–19. Dietary intake of lignans was computed by multiplying the frequency of food items by the nutrient contents of the age and sex-specific servings (11). A recent validation study from our group comparing dietary assessment of lignans using the current version of the FFQ and serum concentrations of biomarker enterolactone indicated an acceptable correlation (r = 0.22; P = 0.01; ref. 20).

**Case ascertainment and follow-up**

All newly diagnosed cases of esophageal and gastric adenocarcinoma were identified through linkage to the Swedish Cancer Register, which was established in 1958 and is estimated to be almost 100% complete (21). Determination of date of death was accomplished by linkage to the Swedish Causes of Death Register and the Swedish Register of the Total Population. Cases of esophageal or gastric adenocarcinoma were defined as the first diagnosed malignant neoplasm detected since entry into the cohort. Each participant was followed from January 1, 1998 until the date of diagnosis of adenocarcinoma of the esophagus or stomach, any other cancer, death, or the end of the study period (December 31, 2009), whichever came first. To avoid detection bias, we excluded all persons-years during the first year of follow-up and all participants diagnosed with any cancer during the first year of follow-up. Because of the similar etiology and pattern of incidence, gastroesophageal junctional adenocarcinoma was combined with esophageal adenocarcinoma, whereas gastric adenocarcinoma was analyzed separately.

**Statistical analysis**

The exposure to dietary lignans was expressed in nutrient density by dividing the estimated intake of lignans (µg/d) by the total energy intake (MJ/d), according to a Multivariate Nutrient Density Model (22). HRs and 95% confidence intervals (CIs) were computed using Cox proportional hazard models. The proportional hazards assumption was tested for all potential confounders that were included in the final model, and all variables conformed to the assumption of proportionality. The exposure to lignans was categorized into 4 levels based on the quartile value of intake density assessed in the cohort. We also conducted a sensitive analysis using standard multivariate model and residual model, which indicated that the results of multivariate nutrient density model were similar to that of the 2 other models.

Possible confounding or effect modification by the following known risk factors were considered in the analyses: age (categorized into 3 groups: <60, 60–70, or >70 years), sex, education (<9, 9–12, or ≥13 years), body mass index (BMI; <25, 25–29.9, or ≥30 kg/m²), tobacco smoking status (nonsmoker, past smoker, or current smoker), alcohol drinking (quartile of total alcohol intake per week), energy intake (total energy intake per day), gastroesophageal reflux symptoms (yes or no), gastric ulcer (yes or no), duodenal ulcer (yes or no), and diabetes (yes or no). The basic model included adjustment for age, sex, and energy intake, whereas the full model adjusted for all variables listed earlier. To test for linear trend across lignan intake categories, we used the median lignan intake in different groups of quartiles, and then treated these values as a continuous variable in the model. Sex-stratified analyses were also conducted, but we displayed only the results for men and women combined and for men separately, as the number of female cases were too few to analyze separately. All P values presented are 2-sided and P < 0.05 was considered statistically significant. In the previous population-based case–control study, we detected the reduced risk of 35% and 65% for esophageal and gastroesophageal junctional adenocarcinoma, respectively, in the highest quartile of lignan intake compared with the lowest quartile (9). Therefore, we made an assumption of reduced risk of 50%, for both adenocarcinoma of esophagus and gastroesophageal junction, and gastric noncardia adenocarcinoma during the 10-year follow-up. The estimated statistical power for the test of esophageal and gastroesophageal junctional adenocarcinoma was
64%, and the corresponding power for gastric noncardia adenocarcinoma was 85%. The SAS Statistical Package (version 9.0, SAS Institute) was used for all analyses. The study was approved by the Regional Ethics Committee at the Karolinska Institutet (Stockholm, Sweden).

Results

Characteristics of study participants

The study included 81,670 study participants, of whom 36,697 were women (44.9%) and 44,973 were men (55.1%). Sex-specific baseline characteristics of these participants divided into quartiles of dietary lignan intake in energy density are shown in Table 1. Compared with women and men with low intake of lignans, those with higher intake were more likely to have a postsecondary education, have history of diabetes and ulcer, and less likely to smoke, drink alcohol, and have reflux. The BMI was similar between groups. During the average of 9.9 years of follow-up, 83 cases (69 male and 14 female) of esophageal or gastroesophageal junctional adenocarcinoma and 128 cases (72 male and 56 female) of gastric adenocarcinoma were identified.

Lignan intake and esophageal and gastric adenocarcinoma

The HRs between higher dietary lignan intake and risk of esophageal or gastric adenocarcinoma indicated slight inverse point risk estimates, but no statistically significantly decreased risks were identified, and no dose–response trends were observed (Table 2). In the entire cohort (men and women combined), the adjusted HR of adenocarcinoma of esophagus or gastroesophageal junction in the highest quartile of lignan intake was 0.96 (95% CI, 0.46–2.00), and no dose–response trend was identified ($P_{\text{trend}} = 0.70$). The corresponding HR for gastric adenocarcinoma was 0.89 (95% CI, 0.52–1.55), and no dose–response effect was found ($P_{\text{trend}} = 0.78$). Similar results were observed when only men were analyzed (Table 2).

Discussion

This study found no clear decreased risk of esophageal or gastric adenocarcinoma among persons consuming higher amounts of lignan.

Strengths of the study include the prospective and population-based design, the detailed exposure information, the availability of several possible confounders, and the reliable identification of esophageal and gastric adenocarcinoma cases. However, the study also carries limitations. Information was missing on some potentially important confounders, that is, Helicobacter pylori infection, the main risk factor of gastric adenocarcinoma (23), and use of antibiotics, which might reduce serum concentrations of enterolactone (24). Moreover, some level of dietary measurement error from using the FFQ was unavoidable, but our recently completed validation study indicated that the FFQ was a reasonably useful tool to assess dietary intake of lignans (20). The observed correlation coefficient between dietary lignan intake assessed by the FFQ and serum concentration of biomarker enterolactone was 0.22 ($P = 0.01$). Reasons for the limited

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dietary lignan intake density (µg/MJ$^*$) among 36,697 women$^b$</th>
<th>Dietary lignan intake density (µg/MJ$^*$) among 44,973 men$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quartile 1 (≤167.5)</td>
<td>Quartile 2 (167.5–203.4)</td>
</tr>
<tr>
<td>Number of individuals</td>
<td>9,179</td>
<td>9,174</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.6</td>
<td>62.0</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>25.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Overweight, %</td>
<td>44.4</td>
<td>43.6</td>
</tr>
<tr>
<td>Postsecondary education, %</td>
<td>14.1</td>
<td>18.1</td>
</tr>
<tr>
<td>Alcohol drinking, g/wk</td>
<td>31.5</td>
<td>31.6</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Current smoker, %</td>
<td>25.9</td>
</tr>
<tr>
<td>Past smoker, %</td>
<td>20.8</td>
<td>21.9</td>
</tr>
<tr>
<td>Nonsmoker, %</td>
<td>53.3</td>
<td>55.0</td>
</tr>
<tr>
<td>Reflux, %</td>
<td>6.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Ulcer, %</td>
<td>3.9</td>
<td>3.2</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>3.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

$^a$MJ = megajoule.

$^b$Dietary lignan intake density was calculated by dividing the estimated lignan intake (µg/d) by the total energy intake (MJ/d).
The measurement errors should also be encouraged.

Biomarker enterolactone with additional effort to eliminate the existing measurement errors in both FFQ and misclassification of the enterolactone exposure. Because the misclassification of the exposure in a prospective cohort study design tends to be nondifferential, that is, similar in cases and noncases, it might lead to attenuation of possible effects, and this may explain the lack of statistically significant associations in the present study.

In the current cohort study, we found inverse point risk estimates of esophageal and gastroesophageal junctional adenocarcinoma among those with higher dietary lignan intake compared with the lowest category, however, they were not statistically significant. Although, this cohort study did not provide strong evidence for any inverse association, which was found in our previous case–control study (9), the results from these 2 studies were partly consistent. A reason for the nonsignificant association in the present cohort study might be mainly ascribed to the lack of statistically significant associations in the present study.

Table 2. HR and 95% CI for the association between dietary intake of lignans and risk of esophageal and gastric adenocarcinoma in a cohort of 81,670 Swedish men and women

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Quartile 1 (≤163.3)</th>
<th>Quartile 2 (163.3–201.0)</th>
<th>Quartile 3 (201.0–243.9)</th>
<th>Quartile 4 (≥243.9)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and women combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of person-year</td>
<td>202,356</td>
<td>202,099</td>
<td>202,079</td>
<td>201,999</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma of esophagus and gastroesophageal junction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%)</td>
<td>24 (29)</td>
<td>21 (25)</td>
<td>19 (23)</td>
<td>19 (23)</td>
<td></td>
</tr>
<tr>
<td>HR^a</td>
<td>1.00</td>
<td>0.96 (0.53–1.73)</td>
<td>0.91 (0.50–1.66)</td>
<td>0.98 (0.54–1.81)</td>
<td>0.92</td>
</tr>
<tr>
<td>HR^b</td>
<td>1.00</td>
<td>0.65 (0.30–1.41)</td>
<td>0.89 (0.43–1.82)</td>
<td>0.96 (0.46–2.00)</td>
<td>0.70</td>
</tr>
<tr>
<td>Gastric adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%)</td>
<td>40 (31)</td>
<td>28 (22)</td>
<td>33 (26)</td>
<td>27 (21)</td>
<td></td>
</tr>
<tr>
<td>HR^a</td>
<td>1.00</td>
<td>0.72 (0.44–1.17)</td>
<td>0.88 (0.56–1.41)</td>
<td>0.78 (0.48–1.28)</td>
<td>0.46</td>
</tr>
<tr>
<td>HR^b</td>
<td>1.00</td>
<td>0.84 (0.49–1.42)</td>
<td>1.00 (0.60–1.66)</td>
<td>0.89 (0.52–1.55)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

| Men only | | | | |
| No. of person-year | 106,970 | 107,923 | 107,856 | 107,866 |
| Adenocarcinoma of esophagus and gastroesophageal junction | | | | |
| Number (%) | 18 (28) | 17 (25) | 16 (23) | 18 (26) |
| HR^a | 1.00 | 0.98 (0.50–1.89) | 0.96 (0.49–1.89) | 1.20 (0.62–2.33) | 0.59 |
| HR^b | 1.00 | 0.90 (0.43–1.90) | 0.96 (0.45–2.03) | 1.05 (0.49–2.24) | 0.88 |

| Men only Gastric adenocarcinoma | | | | |
| Number (%) | 24 (33) | 15 (21) | 17 (24) | 16 (22) |
| HR^a | 1.00 | 0.64 (0.32–1.22) | 0.76 (0.41–1.42) | 0.81 (0.43–1.55) | 0.57 |
| HR^b | 1.00 | 0.74 (0.36–1.51) | 0.97 (0.49–1.92) | 0.83 (0.40–1.76) | 0.74 |

^aMJ = megajoule.
^bAdjusted for sex, age (<60, 60–70, >70 years), and energy intake (continuous value).
^cAdjusted for sex, age (<60, 60–70, >70 years), education (<9, 9–12, ≥13 years), energy intake (continuous value), BMI (<25.0, 25.0–29.9, ≥30.0 kg/m²), alcohol intake (categories in quartiles), smoking status (nonsmoker, past smoker, current smoker), reflux (yes, no), waist-hip-ratio (categories in quartiles), and diabetes (yes/no).
^dAdjusted for sex, age (<60, 60–70, >70 years), education (<9, 9–12, ≥13 years), energy intake (continuous value), BMI (<25.0, 25.0–29.9, ≥30.0 kg/m²), alcohol intake (categories in quartiles), smoking status (nonsmoker, past smoker, current smoker), gastric ulcer (yes, no), duodenal ulcer (yes, no), and diabetes (yes/no).
^eAdjustment for sex was not included.
limited number of cases. More prospective studies with larger sample size are warranted for further investigation. To the best of our knowledge, there is no published cohort study that has examined the association between dietary intake of lignans and risk of esophageal or gastric adenocarcinoma. Because of the risk of exposure misclassification and the limited statistical power, further prospective studies with blood enterolactone concentration measurement or larger numbers of cases are warranted before we can exclude a possible protective role of lignans in the development of esophageal and gastric adenocarcinoma.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval, of the article.

References


Authors’ Contributions

Conception and design: A. Wolk, J. Lagergren, Y. Lu
Development of methodology: A. Wolk, Y. Lu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Wolk, N. Hakansson, J. Lagergren, Y. Lu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Lin, A. Wolk, J. Lagergren, Y. Lu
Writing, review, and/or revision of the manuscript: Y. Lin, A. Wolk, N. Hakansson, J. Lagergren, Y. Lu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Lin, A. Wolk, N. Hakansson, Y. Lu
Study supervision: A. Wolk, J. Lagergren, Y. Lu

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