Plasma Enterolignans Are Associated with Lower Colorectal Adenoma Risk

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Abstract

Lignans are biphenolic compounds that occur in foods of plant origin such as whole grains, seeds, fruits and vegetables, and beverages, such as coffee and tea. Plant lignans are converted by intestinal bacteria into the enterolignans, enterodiol and enterolactone. Enterolignans possess several biological activities, whereby they may influence carcinogenesis. We studied the associations between plasma enterolignans and the risk of colorectal adenomas in a Dutch case-control study. Colorectal adenomas are considered to be precursors of colorectal cancer. Cases (n = 532) with at least one histologically confirmed colorectal adenoma and controls (n = 503) with no history of any type of adenoma were included. Plasma enterodiol and enterolactone concentrations were measured by liquid chromatography with tandem mass spectrometry. Associations were stronger for incident than for prevalent cases. When only incident cases (n = 262) were included, high compared to low plasma concentrations of enterodiol were associated with a reduction in colorectal adenoma risk after adjustment for confounding variables. Enterodiol odds ratios (95% confidence intervals) were 1.00, 0.69 (0.42–1.13), 0.60 (0.37–0.99), and 0.53 (0.32–0.88) with a significant trend (P = 0.01) through the quartiles. Although enterolactone plasma concentrations were 10-fold higher, enterolactone’s reduction in risk was not statistically significant (P for trend = 0.09). Use of oral antibiotic therapy could decrease the plasma concentrations of enterolactone.Exclusion of antibiotic users resulted in similar odds ratios for both enterolignans, but the association for enterolactone became somewhat stronger (P = 0.05 versus P = 0.09). We observed a substantial reduction in colorectal adenoma risk among subjects with high plasma concentrations of enterolignans, in particular, enterodiol. These findings could be important in the prevention of colorectal adenomas. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1132–6)

Introduction

Lignans are biphenolic compounds that occur in foods of plant origin such as whole grains, seeds, especially flaxseed, fruits and vegetables, and beverages such as coffee and tea (1). Following consumption, plant lignans are converted by intestinal bacteria into the enterolignans, enterodiol and enterolactone (2-4).

No epidemiologic studies on the relation between lignan exposure and risk of colon cancer have been published. Associations between other cancers and urinary or plasma enterolignans are inconsistent. Inverse associations for breast cancer were reported in four case-control studies and one prospective study (5-9), whereas no associations were found in three prospective studies (10-14). No associations were observed in a case-control study. Colorectal adenomas are considered to be precursors of colorectal cancer. Cases (n = 532) with at least one histologically confirmed colorectal adenoma and controls (n = 503) with no history of any type of adenoma were included. Plasma enterodiol and enterolactone concentrations were measured by liquid chromatography with tandem mass spectrometry. Associations were stronger for incident than for prevalent cases. When only incident cases (n = 262) were included, high compared to low plasma concentrations of enterodiol were associated with a reduction in colorectal adenoma risk after adjustment for confounding variables. Enterodiol odds ratios (95% confidence intervals) were 1.00, 0.69 (0.42–1.13), 0.60 (0.37–0.99), and 0.53 (0.32–0.88) with a significant trend (P = 0.01) through the quartiles. Although enterolactone plasma concentrations were 10-fold higher, enterolactone’s reduction in risk was not statistically significant (P for trend = 0.09). Use of oral antibiotic therapy could decrease the plasma concentrations of enterolactone. Exclusion of antibiotic users resulted in similar odds ratios for both enterolignans, but the association for enterolactone became somewhat stronger (P = 0.05 versus P = 0.09). We observed a substantial reduction in colorectal adenoma risk among subjects with high plasma concentrations of enterolignans, in particular, enterodiol. These findings could be important in the prevention of colorectal adenomas. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1132–6)

Materials and Methods

Study Population. A retrospective case-control study (the POLIEP study) was conducted in the Netherlands between June 1997 and October 2002. The study, which was designed to investigate gene-environment interactions and the risk of colorectal adenomas, has been described in detail elsewhere (30, 31). In brief, participants were recruited among patients undergoing endoscopies, later referred to as the index endoscopy, in 10 outpatient clinics in the Netherlands. We defined cases as those with at least one histologically confirmed colorectal adenoma ever in their life. In controls, diagnosis of any type of adenomas was negative at the index endoscopy, and they had no history of any type of adenomas (based on medical records). Ninety percent of the cases and 87% of the controls underwent a full colonoscopy (i.e., full colonoscopy or sigmoidoscopy combined with X-ray). Other subjects did not have full visualization of the colon, i.e., they had a sigmoidoscopy without X-ray or a colonoscopy in...
which the cecum was not reached. Response rates varied from 35% to 91% in different outpatient clinics, the overall response was 54%. Eligible subjects were Dutch-speaking persons of European origin aged between 18 and 75 years at the time of the index endoscopy. They did not suffer from inflammatory bowel disease and did not have a history of colorectal cancer, (partial) bowel resection, or serious disabling morbidity. Furthermore, they had no hereditary colorectal cancer syndromes (i.e., familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer). Of 1,477 eligible participants, we excluded 92 subjects because plasma samples were not available. We additionally excluded 350 subjects whose blood was drawn the same day as their index endoscopy or from whom the date of blood sampling was missing. As patients are not allowed to eat solid foods for 24 hours prior to endoscopy and they receive medication to clean the colon, intestinal bacteria are (partially) washed away and plasma enterolignan concentrations no longer reflect long-term exposure to enterolignans in these patients. Data analyses included 1,035 participants: 532 cases and 503 controls. The medical ethical committees of all participating hospitals and of Wageningen University approved the study protocol and all participants provided written informed consent.

Data Collection. Cases and controls were asked to complete self-administered questionnaires on diet, medical history, and lifestyle, relating to their habits in the year preceding their index endoscopy. Dietary intake was assessed with a standardized and validated semiquantitative food frequency questionnaire that was originally developed for the Dutch cohort of the European Prospective Investigation into Cancer and Nutrition (32, 33). Information on demographic and lifestyle factors, like smoking habits, physical activity level (34), and family history, was obtained from a self-administered questionnaire.

Collection of Plasma Samples. For cases and controls, nonfasting venous blood samples were taken into vacuum tubes containing EDTA. Samples were taken, on average, 4 months after admission to the hospital for endoscopy. Samples were transported to our laboratory at Wageningen University in a foam fridge containing cooling materials at 4°C. Within 48 hours, samples were centrifuged at 1,187 g for 10 minutes at 4°C, and then kept at −80°C until analysis.

Assay of Plasma Samples. The concentrations of enterodiol and enterolactone in plasma were measured by liquid chromatography with tandem mass spectrometry using triply 13C-labeled isotopes (35). The samples were analyzed in 20 runs over a 12-week period. The between-run coefficient of variation of the quality control plasma samples was 10% for enterolactone and 14% for enterodiol. The limit of detection was 0.55 nmol/L for enterolactone and 0.15 nmol/L for enterodiol. Seven percent of the subjects had concentrations below the detection limit of enterodiol. Only 3% had concentrations below the detection limit of enterolactone. Lab technicians were blinded to the status of the subjects.

Data Analysis. To assess the association between plasma enterolignans and colorectal adenomas, we used logistic regression models. First, we calculated odds ratios (OR) and 95% confidence intervals per quartile of enterolignan concentrations in plasma. Quartiles of plasma enterodiol and plasma enterolactone were based on the distribution among controls. The quartile with the lowest enterolignan concentration (Q1) was used as a reference. A multivariate logistic regression model was used to account for the effect of several potential confounding factors, i.e., age, sex, body mass index, physical activity, smoking, alcohol intake, regular use of nonsteroidal anti-inflammatory drugs (≥12 times a year), family history of colorectal cancer, indication for endoscopy, use of oral contraceptives, and use of hormone replacement therapy (FULL model). Variables were dropped from the model when they did not change the ORs by >10% (backwards modeling). “Time interval between endoscopy and blood sampling,” and “outpatient clinic” were included as covariates, but because they did not change the ORs by >10%, they were not included in the FULL model. Because age and sex distributions differed between cases and controls, and are related to the development of colorectal adenomas, these variables remained in the model at all times.

After performing analyses for all subjects, cases were grouped into incident and prevalent cases. Incident cases (n = 262) were defined as those with a histologically confirmed colorectal adenoma or colorectal cancer at the index endoscopy, but no history of any type of polyps. Prevalent cases (n = 254) were defined as those with or without an adenoma at the index endoscopy, but with a history of at least one histologically confirmed colorectal adenoma. When data on prevalence of former polyps were missing, cases (n = 16) were excluded from these analyses. Because use of oral antibiotic therapy could decrease urinary and serum concentrations of enterolactone for 3 to 12 months (36, 37), additional analyses were done with incident cases excluding subjects using antibiotic therapy within the same calendar year as the blood sampling.

Finally, we calculated ORs and 95% confidence intervals for enterodiol and enterolactone using concentrations on a continuous scale. As increments, we used the difference between the median concentrations of the lowest and the highest quartile. For enterodiol, this increment was 4.9 nmol/L, and for enterolactone it was 39.1 nmol/L. In these analyses, concentrations were log-transformed because the distributions were skewed. Before log-transformation, we assigned a standard value (detection limit divided by two) to values of enterodiol and enterolactone that were below the detection limit. Tests for linear trend, representing potential dose-response effects, were done by fitting of a continuous variable. If P ≤ 0.05 (two-sided), the effect was considered significant. All statistical analyses were done using SAS statistical analysis package (version 9.1; SAS Institute, Inc., Cary, NC).

Results

Compared with controls, cases were more likely to be male, older, and have a slightly higher body mass index (Table 1). Furthermore, cases consumed more alcohol, and were more likely to smoke. The use of oral contraceptives, for women only, was higher among controls than among cases. The major indications for endoscopy among cases were complaints (44%), including bowel complaints, rectal bleeding and defecation problems, and screening (47%). For controls, these numbers were 80% for complaints and 10% for screening. Plasma enterodiol and enterolactone concentrations did not differ between cases and controls. Indication for endoscopy was different for prevalent and incident cases. Prevalent cases underwent endoscopy because of screening (83%) and incident cases underwent endoscopy because of complaints (76%, data not shown).

For total cases and controls, the adjusted OR estimates for the continuous model (FINAL model) showed no significant associations (Table 2). Only in the highest quartile of plasma enterolactone was the OR estimate significant. When analyses were done for incident cases only, the OR estimates showed that higher concentrations of enterodiol and enterolactone were associated with a reduction in risk of colorectal adenomas in a dose-dependent manner. This was particularly clear for enterodiol; the adjusted OR in the highest quartile was 0.53 (95% confidence intervals, 0.32-0.88; P = 0.01). In prevalent cases, no association was observed between either of the enterolignans and colorectal adenomas. ORs did not change...
substantially when we excluded subjects who did not have full visualization of the colon in incident and prevalent cases (data not shown).

Use of antibiotics, as expected, reduced enterolactone concentration in plasma substantially, but not the enterodiol concentration. The median concentration of enterolactone was 13.6 nmol/L in subjects using antibiotic therapy, whereas the concentration in the other subjects was 6.9 nmol/L. The concentration of enterodiol was 1.5 nmol/L in subjects using antibiotic therapy, and 1.2 nmol/L in the other subjects.

Therefore, in an additional analysis, we included only incident cases and controls who did not use antibiotics within

Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 532)</th>
<th>Controls (n = 503)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>59.6 ± 9.6</td>
<td>52.8 ± 13.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female (%)</td>
<td>47</td>
<td>62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of colorectal cancer (% yes)</td>
<td>24</td>
<td>21</td>
<td>0.30</td>
</tr>
<tr>
<td>Indication for endoscopy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complaints</td>
<td>44</td>
<td>80</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Screening</td>
<td>47</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Lifestyle characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking, ever (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity (% low)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular nonsteroidal anti-inflammatory drug use (≥12 times/y; % yes)</td>
<td>27</td>
<td>32</td>
<td>0.12</td>
</tr>
<tr>
<td>Antibiotics within the same calendar year of blood sampling (%)</td>
<td>21</td>
<td>25</td>
<td>0.12</td>
</tr>
<tr>
<td>Oral contraceptive use (% ever)</td>
<td>68</td>
<td>77</td>
<td>0.01</td>
</tr>
<tr>
<td>Hormone replacement therapy (% yes)</td>
<td>20</td>
<td>15</td>
<td>0.16</td>
</tr>
<tr>
<td>Plasma concentrations of enterolignans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterodiol (nmol/L)</td>
<td>1.3 (0.6-3.1)</td>
<td>1.5 (0.7-3.1)</td>
<td>0.38</td>
</tr>
<tr>
<td>Enterolactone (nmol/L)</td>
<td>11.2 (4.4-25.4)</td>
<td>11.6 (4.6-26.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Total enterolignans (nmol/L)</td>
<td>13.5 (6.2-29.4)</td>
<td>14.4 (6.0-28.7)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Values are medians (25th percentile-75th percentile).

Among women only (n = 250 cases and n = 312 controls).

Table 2. Adjusted ORs and 95% confidence intervals for plasma enterodiol and enterolactone concentrations in relation to colorectal adenomas

<table>
<thead>
<tr>
<th>Enterodiol concentration (nmol/L); cutoff (median)</th>
<th>Q1 (0.7)</th>
<th>Q2 (0.7-1.5)</th>
<th>Q3 (1.5-3.1)</th>
<th>Q4 (&gt;3.1)</th>
<th>P for trend*</th>
<th>Continuous model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases-controls (n)</td>
<td>149/126</td>
<td>142/126</td>
<td>107/126</td>
<td>134/125</td>
<td>532/503</td>
<td></td>
</tr>
<tr>
<td>FULL: age, sex</td>
<td>1.0</td>
<td>0.90 (0.63-1.29)</td>
<td>0.69 (0.47-1.00)</td>
<td>0.83 (0.58-1.19)</td>
<td>0.20</td>
<td>0.90 (0.77-1.06)</td>
</tr>
<tr>
<td>FINAL: age, sex, indication for endoscopy</td>
<td>1.0</td>
<td>0.88 (0.60-1.29)</td>
<td>0.61 (0.41-0.91)</td>
<td>0.75 (0.51-1.11)</td>
<td>0.09</td>
<td>0.86 (0.73-1.03)</td>
</tr>
<tr>
<td>Incident cases-controls (n)</td>
<td>81/126</td>
<td>68/126</td>
<td>58/126</td>
<td>55/125</td>
<td>262/503</td>
<td></td>
</tr>
<tr>
<td>FULL: age, sex</td>
<td>1.0</td>
<td>0.80 (0.53-1.23)</td>
<td>0.67 (0.43-1.03)</td>
<td>0.64 (0.41-0.99)</td>
<td>0.03</td>
<td>0.81 (0.66-0.98)</td>
</tr>
<tr>
<td>FINAL: age, sex, antibiotic use</td>
<td>1.0</td>
<td>0.65 (0.39-1.11)</td>
<td>0.62 (0.37-1.05)</td>
<td>0.48 (0.28-0.84)</td>
<td>0.01</td>
<td>0.75 (0.60-0.94)</td>
</tr>
<tr>
<td>Prevalent cases-controls (n)</td>
<td>65/126</td>
<td>71/126</td>
<td>47/126</td>
<td>71/125</td>
<td>254/503</td>
<td></td>
</tr>
<tr>
<td>FINAL: age, sex, family history of colorectal cancer, indication for endoscopy</td>
<td>1.0</td>
<td>1.04 (0.67-1.61)</td>
<td>0.68 (0.42-1.10)</td>
<td>1.02 (0.66-1.59)</td>
<td>0.90</td>
<td>0.99 (0.81-1.20)</td>
</tr>
</tbody>
</table>

Enterolactone concentration (nmol/L); cutoff (median) <4.6 (1.6) 4.6-11.6 (7.8) 11.6-26.3 (17.3) >26.3 (40.6) Δ39.1

Total cases-controls (n) 137/126 132/126 133/125 130/126 532/503

FULL: age, sex 1.0 0.89 (0.62-1.28) 0.89 (0.62-1.28) 0.79 (0.55-1.14) 0.46 0.88 (0.62-1.24)

FINAL: age, sex, indication for endoscopy 1.0 0.81 (0.55-1.20) 0.74 (0.50-1.10) 0.66 (0.44-0.98) 0.12 0.75 (0.52-1.08)

Incident cases-controls (n) 78/126 70/126 54/125 60/126 262/503

FULL: age, sex 1.0 0.87 (0.57-1.32) 0.66 (0.43-1.03) 0.67 (0.43-1.04) 0.11 0.72 (0.48-1.08)

FINAL: age, sex, antibiotic use 1.0 0.72 (0.44-1.18) 0.61 (0.37-1.02) 0.63 (0.38-1.06) 0.09 0.64 (0.40-1.04)

Prevalent cases-controls (n) 55/126 57/126 77/125 65/126 254/503

FULL: age, sex 1.0 0.95 (0.59-1.52) 1.30 (0.83-2.04) 0.95 (0.60-1.51) 0.68 1.09 (0.72-1.66)

FINAL: age, sex, family history of colorectal cancer, indication for endoscopy 1.0 0.91 (0.41-2.01) 1.39 (0.64-3.06) 0.98 (0.45-2.13) 0.79 1.10 (0.53-2.29)

*Log-transformed continuous variables were used in this model. The increments are based on the difference of the median concentrations in quartile 1 and quartile 4.

The increment for enterodiol is 4.9 nmol/L; the increment for enterolactone is 39.1 nmol/L. Tests for linear trend were done by fitting of a continuous variable.

FULL model: adjusted for age, sex, alcohol, nonsteroidal anti-inflammatory drug use, body mass index, physical activity, smoking, family history of colorectal cancer, antibiotic use, and indication for endoscopy.
the same calendar year as the blood was drawn. In this analysis, 161 cases and 306 controls were included. For both enterolignans the age- and sex-adjusted ORs were similar to the FINAL model of incident cases, in which we adjusted for age, sex, and use of antibiotic therapy. Enterodiol ORs in the quartiles (from lowest to highest) were 1.00, 0.62 (0.36-1.07), 0.51 (0.29-0.89), and 0.48 (0.27-0.85). The OR on a continuous scale was 0.74 (0.57-0.96) with a significant trend (P = 0.02). Enterolactone ORs in the quartiles were 1.00, 0.75 (0.43-1.31), 0.64 (0.36-1.14), and 0.60 (0.34-1.06). The OR on a continuous scale was 0.56 (0.33-0.99) with a significant trend (P = 0.05) as well (data not shown).

**Discussion**

Our study shows that increased plasma concentrations of enterodiol and enterolactone are associated with a consider-
able reduction in colorectal adenoma risk in a dose-dependent manner. This inverse association was observed in incident cases only, and not in prevalent cases. No other epidemiologic studies on the relation between lignan exposure and risk of colorectal ademomas or colorectal cancer have been published before. However, consumption of lignan-containing products, such as cereals, nuts and grains, fruits, vegetables, and tea has been associated with lower risks of colorectal cancer (reviewed in ref. 38).

In our study, inverse associations between enteroligian concentrations and colorectal adenomas were observed in incident cases, whereas no associations were observed in prevalent cases. This might be due to the time interval between the exposure assessment and the diagnosis of the first colorectal ademomas, which was different for incident and prevalent cases. For both incident and prevalent cases, the exposure to plasma enterolignans was measured shortly after the index endoscopy, whereas the time of first diagnosis of colorectal adenomas was earlier in prevalent than in incident cases. Prevalent cases were diagnosed prior to the index endoscopy (they have a history of colorectal adenomas); incident cases were first diagnosed at the index endoscopy itself. When the time interval becomes longer, the association between plasma enterolignans and colorectal adenomas might be weakened. Several factors, such as diet, disease status, and medication might have influenced the enterolignan plasma concentrations. The presence of adenomas usually does not provide any symptoms, reducing the possibility that people may have changed their dietary habits or that the tumor may influence plasma levels. However, due to perceived risks and/or to intestinal complaints, prevalent cases might have changed their diet (information bias). This might have changed the intake of plant lignans, and as a result, their enterolignan plasma concentrations. Therefore, the inverse association between plasma enterolignans, which we observed in incident cases, might have been diluted in prevalent cases.

Other factors that might have influenced plasma concentra-
tions of enterolignans, such as use of antibiotics, and time between endoscopy and blood sampling, were similar in incident and prevalent cases. Family history of colorectal cancer was equally distributed among prevalent and incident cases. Thus, for prevalent cases, the blood sample may reflect an improper exposure time window to study the relation between the formation of first colorectal adenomas and plasma enterolignans.

An advantage of our study is that we used plasma enterolignans, rather than dietary recall or records to measure the exposure to lignans. The concentration of enterolignans in plasma is not dependent on memory, and takes into account metabolism by the colonic flora and bioavailability as well. Enterolignans will accumulate in plasma when consumed twice or thrice a day (39). Thus, steady state plasma concentrations of enterodiol and enterolactone are likely to be achieved because plant lignans are present in many foods and beverages. Therefore, plasma enterolignans are expected to be suitable biomarkers of lignan exposure over a period of up to 2 years (40) and may be used to evaluate the effects of lignans. Because blood samples were collected after the index endoscopy, misclassification of exposure due to changes in diet or lifestyle might be a concern (information bias). However, as we do not expect incident cases and controls to be aware of risk factors for colorectal adenomas, there is no reason to believe that this misclassification is differential. Furthermore, both control and incident cases underwent endoscopy primarily for complaints (controls, 80%; incident cases, 76%). Hence, if they would change their diet because of these complaints in this short period, this would have similar in controls and incident cases.

Another important issue in case-control studies concerns selection bias. The response rate was rather low and varied widely by clinic. However, selection procedures were identical for incident cases and controls, reducing the possibility for differential selection bias. Unfortunately, we do not have data on the plasma concentrations of patients not participating in the study to further evaluate the possible selection bias due to nonresponse.

In this study, use of antibiotics within the same calendar year decreased plasma enterolactone and not enterodiol concentrations. Our results suggest that enterolactone concentrations are more affected by antibiotic use than enterodiol concentrations. When these antibiotics users were excluded from the analysis, the inverse association between plasma enterolactone and risk of colorectal adenomas became significant, although the ORs changed only slightly.

Enterodiol was similarly associated with colorectal adenomas as enterolactone in this study, although concentrations of enterodiol were 5- to 10-fold lower. This suggests that in the human body, enterodiol might be more active than enterolactone. Enterodiol had a higher antioxidant capacity than enterolactone in vitro (19, 20). On the other hand, enterolactone was two times more effective than enterolactone to inhibit the growth of colon tumor cells (21). Therefore, more work is needed to sort out whether real biological differences exist.

In summary, our study shows for the first time that both plasma enterolignans are associated with a lower risk of first colorectal adenomas. Although colorectal adenomas are considered to be precursors of colorectal cancer, only ~5% of colorectal adenomas are estimated to become malignant, which takes 5 to 10 years (41). To further investigate the role of enterolignans on the development of colorectal cancer, more prospective studies or recurrence trials are needed.

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**References**


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