Original Contribution

Plasma Enterolignan Concentrations and Colorectal Cancer Risk in a Nested Case-Control Study

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Enterolignans are biphenolic compounds that possess several biologic activities whereby they may influence carcinogenesis. The authors investigated the association between plasma enterolactone and enterodiol and colorectal cancer risk in a Dutch prospective study. Among more than 35,000 participants aged 20–59 years, 160 colorectal cancer cases were diagnosed after 7.5 years of follow-up (1987–2003). Cohort members who were frequency-matched to the cases on age, sex, and study center were selected as controls (n = 387). Plasma enterodiol and enterolactone were not associated with risk of colorectal cancer after adjustment for known colorectal cancer risk factors (highest quartile vs. lowest: for enterodiol, odds ratio = 1.11, 95% confidence interval: 0.56, 2.20 (p-trend = 0.75); for enterolactone, odds ratio = 1.70, 95% confidence interval: 0.88, 3.27 (p-trend = 0.15)). However, sex (p-interaction = 0.06) and body mass index (p-interaction < 0.01) modified the relation between plasma enterolactone and colorectal cancer risk; increased risks were observed among women and subjects with a high body mass index. The association between plasma enterodiol and colorectal cancer risk was modified by smoking status; risk was increased among current smokers (p-interaction < 0.01). These findings do not support the hypothesis that high plasma enterodiol or enterolactone concentrations are associated with reduced risk of colorectal cancer.

biological markers; colorectal neoplasms; lignans; prospective studies

Abbreviations: CI, confidence interval; OR, odds ratio.

Dietary patterns high in fruits and vegetables, high in whole grains, nuts, and seeds, and low in red and processed meats are associated with lower risk of colorectal cancer in humans (1, 2). Because lignans are present in many foods of plant origin (3), the beneficial effect might be partly related to lignans. Plant lignans are biphenolic compounds that are converted by intestinal bacteria to the enterolignans enterodiol and enterolactone (4–6). Most plant lignans are first converted to enterodiol and subsequently to enterolactone; matairesinol, one of the plant lignans, can be converted directly to enterolactone (5). The role of lignans in colorectal carcinogenesis has only been investigated in in vitro or animal-based studies. In a study with four colon cancer cell lines (LS174T, CaCo-2, HCT-15, and T-84), enterodiol and enterolactone, each at 100-μmol/liter concentrations, demonstrated estrogen-independent growth-inhibitory effects (7). At a concentration of 40 μmol/liter, enterodiol and enterolactone induced cell-cycle arrest of colon cancer cells (SW480) (8). Furthermore, enterodiol and enterolactone possess several biologic activities in vitro, potentially influencing carcinogenic processes such as antioxidant activity (9, 10), stimulation of sex...
plasma concentrations and colorectal adenomas in women (48) and men (49). Two recent studies 
indicated a protective effect of enterolignans on colorectal cancer risk, the latter study providing a 
long-term follow-up (27, 28).

To our knowledge, no epidemiologic studies to date have examined the associations between 
enterolignans and colorectal cancer. However, we recently observed an inverse association 
between plasma concentrations and colorectal adenoma risk in a case-control study (19). 

Materials and Methods

Study population and baseline data collection

We conducted a nested case-control study within the Monitoring Project on Cardiovascular Disease Risk Factors, a large survey of cardiovascular risk factors in the Netherlands (27). This survey was carried out between 1987 and 1991 among more than 35,000 men and women aged 20–59 years. They were examined by the municipal health services in three Dutch municipalities: Amsterdam, Doetinchem, and Maastricht. All participants gave written informed consent, and approval was obtained from the medical ethics committees of Leiden University and the Netherlands Organization for Applied Scientific Research.

Laboratory analyses

The concentrations of enterodiol and enterolactone in plasma were measured by liquid chromatography with tandem mass spectrometry using triply labeled isotopes (29). The samples were analyzed in 22 runs over an 8-week period. For both enterolignans, the within-run coefficient of variation was 3–6 percent and the between-run coefficient of variation was 10–14 percent. The limit of detection was 0.55 nmol/liter for enterolactone and 0.15 nmol/liter for enterodiol. Laboratory technicians were blinded to the status of the subjects. Cases and controls were randomly distributed over the runs.

Follow-up for cancer incidence

Follow-up for cancer incidence was based on computerized record linkage to national and regional cancer registries between 1987 and mid-2003. Information on diagnosis, tumor site classification, and morphology (according to the International Classification of Diseases for Oncology, Second Edition, classifications) was obtained.

Nested case-control design

We used a nested case-control study design, which represents a cost-efficient alternative to a traditional full-cohort analysis. According to this approach, all incident colorectal carcinomas (n = 161) were identified; of these, 101 were colon carcinomas and 60 were rectosigmoid junction or rectum carcinomas. In addition, a random sample of controls (n = 165) was selected from the full cohort at baseline, frequency-matched on age (5-year intervals), sex, and study center. One case was excluded because no control with the same matching criteria as the case was selected. We simultaneously selected a random sample of controls from this cohort for a nested case-control analysis on myocardial infarction. These controls did not have a history of myocardial infarction or heart surgery at baseline, and follow-up data on myocardial infarction were present. In these controls, plasma enterolignan concentrations were analyzed as well. From this sample, controls with the same matching factors as the colorectal cancer cases were selected (n = 222). We combined the two control groups for our data analysis. In total, 160 cases and 387 controls were used for data analysis. When data analysis was restricted to the case-control subset excluding the myocardial infarction controls, risk estimates did not change substantially (data not shown).
Data analysis

Concentrations of enterodiol and enterolactone were log-transformed prior to the analyses to improve normality. For continuous study characteristics, PROC GLM (SAS statistical software, version 9.1; SAS Institute, Inc., Cary, North Carolina) was used to compare mean values and to calculate a p value for trend between quartiles of enterolignan concentrations in the control group (n = 387), accounting for the matching factors, age, sex, and study center. For categorical variables, quartile differences were evaluated on the basis of Cochran-Mantel-Haenszel statistics. The relations of plasma enterodiol and enterolactone concentrations with colorectal cancer risk were analyzed by conditional logistic regression using odds ratios and 95 percent confidence intervals. The odds ratios were examined according to quartiles of enterodiol and enterolactone concentration, with cutoff points based on the distribution among controls. For all of the models, linear trends were tested using median concentrations of the quartiles. Risk estimates were computed in a crude model (adjusted for matching variables, which are controlled for automatically by design). Additionally, two different sets of covariates were used. Adjusted model 1 included lifestyle factors: body mass index (weight (kg)/height (m)²), smoking status (never, former, or current smoker), duration/intensity of smoking (pack-years), alcohol intake (g/day), physical activity at work (low vs. high), physical activity during leisure time (low vs. high), educational level (low (primary, technical, or professional school), medium (secondary school), or high (university degree)), and aspirin use (occasional; yes vs. no). Adjusted model 2 additionally included dietary intakes of energy, calcium, fiber, meat, fish, fruits, vegetables, tea, wine, and whole-grain bread. Fruits and vegetables, tea, wine, and whole-grain bread are sources of plant lignans. We included these sources of plant lignans in order to evaluate whether the observed effect for enterolignans could be attributed to other components. Furthermore, we conducted analyses using plasma enterolignan concentrations continuously using the interquartile ranges (1.50 nmol/liter for enterodiol and 14.61 nmol/liter for enterolactone) as increments and calculated a p value for trend based on the continuous variables.

In order to explore potential modification of the effects of enterolignans by cancer site (colon and rectosigmoid plus rectum), sex, body mass index (<25 vs. ≥25), and smoking status (never, former, or current), we performed stratified analyses in a reduced model. For the reduced model, we selected lifestyle and dietary covariates that significantly contributed to the reduced model (p < 0.05) based on the log likelihood ratio test, using the SCORE option in the software package. The reduced model was adjusted for matching factors and included the covariates body mass index, alcohol intake, current smoking status, and physical activity in leisure time. In the subgroup analyses for women, menopausal status and oral contraceptive use were considered as additional confounders. To test for statistical interactions with sex, body mass index, and smoking status, we calculated the p values for their product terms with enterolignans. In order to assess the effect of prediagnostic changes in exposure assessment, we also performed analyses excluding cases diagnosed during the first 2 years of follow-up.

RESULTS

Characteristics of the controls are presented in table 1. Lifestyle factors pointed in the direction of a healthy lifestyle among subjects with higher enterolignan concentrations: Body mass index decreased with increasing concentrations of plasma enterolignans. The highest percentiles of current smokers were observed in the lowest quartiles of plasma enterodiol and enterolactone. Alcohol intake increased with quartiles of plasma enterolactone. Educational level was higher with increasing enterolactone plasma concentration (p = 0.01) but not with enterodiol concentration. Physical activity at work and in leisure time and use of aspirin were not related to either plasma enterolignan. Additionally, the consumption of important dietary sources of plant lignans, such as fruits, vegetables, whole-grain products, tea, and wine, increased with increasing concentrations of plasma enterolignans. Meat consumption and fish consumption were not related to plasma enterolignans. Intakes of fiber and calcium increased with increasing concentrations of plasma enterolignans. In women, menopausal status and oral contraceptive use did not differ between quartiles (table 1).

No statistically significant associations between plasma enterodiol and enterolactone and risk of colorectal cancer were present in the highest quartiles versus the lowest quartiles or in the continuous model using the interquartile ranges (1.50 nmol/liter for enterodiol and 14.61 nmol/liter for enterolactone) as increments (table 2). In the model adjusted for lifestyle factors (adjusted model 1), the odds ratio for continuous enterodiol concentration was 1.03 (95 percent confidence interval (CI): 0.96, 1.11; p = 0.46), and for enterolactone it was 1.46 (95 percent CI: 0.86, 2.48; p = 0.16). In the model adjusted for lifestyle and dietary factors (adjusted model 2), the odds ratio for enterodiol was 1.03 (95 percent CI: 0.95, 1.11; p = 0.47), and for enterolactone it was 1.56 (95 percent CI: 0.89, 2.72; p = 0.12). Adjusted models 1 and 2 did not alter the crude risk estimates by more than 10 percent (table 2). In the third quartile of enterodiol concentration, odds ratios were significantly higher than those in the lowest quartile in both the crude model and the adjusted models. However, the odds ratios over the quartiles were not linear, as indicated by the p value for trend (table 2).

In the reduced model, the continuous risk estimates were 1.02 (95 percent CI: 0.95, 1.10) for enterodiol and 1.41 (95 percent CI: 0.84, 2.35) for enterolactone (table 3). When results were stratified for cancer site, no consistent associations were observed between enterolignan concentrations and cancer risk (table 3). When stratifying according to sex, there was an increased risk for women with increasing concentrations of enterolactone (odds ratio (OR) = 2.63, 95 percent CI: 1.09, 6.33); this was not observed for enterodiol concentrations or in men. For enterolactone, the odds ratios among men and women were almost significantly different (p for interaction = 0.06). In women, menopausal status and oral contraceptive use were not considered confounders because they did not significantly change the risk estimates...
<table>
<thead>
<tr>
<th>Quartile concentration (nmol/liter) and cutpoint [median]</th>
<th>Enterodiol</th>
<th>Enterolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>Quartile concentration (nmol/liter)</td>
<td>&lt;0.45 [0.26]</td>
<td>0.45–0.89 [0.66]</td>
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<tr>
<td>Lifestyle factors</td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>49.6 (0.8)</td>
<td>50.2 (0.8)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2 (0.4)</td>
<td>25.0 (0.4)</td>
</tr>
<tr>
<td>Alcohol consumption (g/day)</td>
<td>11.5 (1.4)</td>
<td>13.2 (1.4)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Former smoker</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Current smoker</td>
<td>53</td>
<td>48</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>16.3 (1.6)</td>
<td>15.7 (1.5)</td>
</tr>
<tr>
<td>Physical activity at work (% high)</td>
<td>34</td>
<td>30</td>
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<tr>
<td>Physical activity during leisure time (% high)</td>
<td>45</td>
<td>53</td>
</tr>
<tr>
<td>Education (%)</td>
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<td></td>
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<tr>
<td>Low (primary school)</td>
<td>74</td>
<td>72</td>
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<tr>
<td>Medium (secondary school)</td>
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<td>15</td>
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<tr>
<td>High (university degree)</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Use of aspirin (% yes)</td>
<td>27</td>
<td>30</td>
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<tr>
<td>Dietary factors</td>
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<tr>
<td>Energy (kJ/day)</td>
<td>6,496 (215)</td>
<td>7,285 (211)</td>
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<tr>
<td>Fiber (g/day)</td>
<td>14.7 (0.6)</td>
<td>17.4 (0.6)</td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
<td>850 (43)</td>
<td>944 (42)</td>
</tr>
<tr>
<td>Meat (g/day)</td>
<td>86 (4)</td>
<td>87 (4)</td>
</tr>
<tr>
<td>Fish (g/day)</td>
<td>11.5 (1.3)</td>
<td>10.7 (1.3)</td>
</tr>
<tr>
<td>Fruits (g/day)</td>
<td>88 (7)</td>
<td>92 (7)</td>
</tr>
<tr>
<td>Vegetables (g/day)</td>
<td>122 (6)</td>
<td>127 (6)</td>
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<tr>
<td>Tea (g/day)</td>
<td>184 (34)</td>
<td>275 (33)</td>
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<tr>
<td>Wine (g/day)</td>
<td>7.6 (5.5)</td>
<td>20.9 (5.4)</td>
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<tr>
<td>Whole-grain bread (g/day)</td>
<td>45.6 (9.3)</td>
<td>78.1 (9.2)</td>
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<tr>
<td>Ever use of oral contraceptives (%)</td>
<td>57</td>
<td>70</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>57</td>
<td>43</td>
</tr>
</tbody>
</table>

* Controls (n = 387) were randomly selected from the source population. Matching factors were age, sex, and study center. Continuous variables are expressed as mean values and standard errors with p values for trend; categorical variables are expressed as percentages with p values for differences, estimated using Cochran-Mantel-Haenszel statistics.
† Numbers in parentheses, standard error.
‡ Weight (kg)/height (m²).
TABLE 2. Odds ratios for colorectal cancer according to plasma enterolignan concentration in multivariate analysis (quartiles and log-transformed continuous variables), Monitoring Project on Cardiovascular Disease Risk Factors, the Netherlands, 1987–2003

<table>
<thead>
<tr>
<th></th>
<th>Quartiles (Q)*</th>
<th>Continuous variables†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1†</td>
<td>Q2</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>OR</td>
</tr>
<tr>
<td>Enterodiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>No. of controls</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Crude model#</td>
<td>1.00</td>
<td>1.24</td>
</tr>
<tr>
<td>Adjusted model 1**</td>
<td>1.00</td>
<td>1.37</td>
</tr>
<tr>
<td>Adjusted model 2††</td>
<td>1.00</td>
<td>1.29</td>
</tr>
<tr>
<td>Enterolactone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>No. of controls</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>Crude model#</td>
<td>1.00</td>
<td>1.16</td>
</tr>
<tr>
<td>Adjusted model 1**</td>
<td>1.00</td>
<td>1.15</td>
</tr>
<tr>
<td>Adjusted model 2††</td>
<td>1.00</td>
<td>1.23</td>
</tr>
</tbody>
</table>

* Quartile cutpoints are given in table 1.
† Log-transformed continuous concentrations of enterolignans were used in this model; the increments were based on the interquartile ranges (1.50 nmol/liter for enterodiol and 14.61 nmol/liter for enterolactone).
‡ Reference category.
§ p values for trend were based on median concentrations in quartiles.
¶ OR, odds ratio; CI, confidence interval.
# Adjusted for the matching factors by design.
** Additionally adjusted for lifestyle factors: body mass index, alcohol consumption, smoking status (never, former, or current smoker), duration of smoking, physical activity during leisure time and at work, aspirin use, and educational level.
†† Additionally adjusted for lifestyle factors (adjusted model 1) and dietary factors: intakes of energy, fiber, calcium, meat, fish, fruits, vegetables, tea, wine, and whole-grain bread.
When analyzing the data for women by menopausal status, an increased risk was observed for enterolactone in postmenopausal women (n = 33; OR = 5.12, 95% CI: 1.25, 21.0), whereas no association was observed in premenopausal women (n = 38; OR = 1.37, 95% CI: 0.34, 5.56). However, the p value for interaction was not significant (p = 0.29). This was not observed for enterodiol.

When stratifying for body mass index, we observed an increased risk for subjects with a high body mass index (>21) with increasing concentrations of enterolactone (OR = 2.44, 95% CI: 1.17, 5.08). For enterodiol, the odds ratio was 1.09 (95% CI: 0.99, 1.20) in subjects with a high body mass index; the p value for interaction was <0.01 for enterolactone and 0.02 for enterodiol. In never smokers, plasma enterodiol was inversely associated with colorectal cancer risk (p = 0.05); in current smokers, the relation between enterodiol and cancer risk was positively associated (p = 0.02); and in former smokers, no association was observed (for interaction with smoking status, p < 0.01). These estimates were not consistent with plasma enterolactone concentrations, where no associations with colorectal cancer risk were observed (table 3).

The mean time period from blood collection to diagnosis was 7.5 years, with a range of 5 months to 15 years. The associations of enterodiol and enterolactone with colorectal cancer were not substantially altered when subjects diagnosed within 2 years of follow-up (n = 14) were excluded (data not shown). Neither were any consistent associations observed between plasma enterodiol and enterolactone concentrations and colorectal cancer risk according to years of follow-up: In the strata 0–7.5 years of follow-up and >7.5–15 years of follow-up, the odds ratios for enterodiol were 1.02 (95% CI: 0.93, 1.12) and 1.04 (95% CI: 0.94, 1.15), respectively, and for enterolactone, the odds ratios were 1.61 (95% CI: 0.80, 3.27) and 1.25 (95% CI: 0.65, 2.40), respectively (data not shown in table).

**DISCUSSION**

To our knowledge, this is the first study that has evaluated the relation between plasma enterolignans and colorectal cancer risk using a prospective design. The results of this analysis, a case-control study nested within a cohort of more than 35,000 subjects, do not support the hypothesis that high plasma enterodiol or enterolactone concentrations are associated with reduced risk of colorectal cancer. In our study,
plasma enterolignan concentrations were similar to concentrations in other epidemiologic studies.

In epidemiologic studies, associations between other cancers and urinary or plasma enterolignan concentrations are inconsistent. Inverse associations for breast cancer were reported in four case-control studies and one prospective study (30–34), whereas no associations were found in five prospective studies (35–39). No associations were observed between plasma enterolactone and prostate cancer in three nested case-control studies (40–42). In contrast, Hernandez et al. (43) reported a positive association between plasma enterodiol concentrations and premalignant lesions of the cervix.

Recently, we reported results from a case-control study in which we observed an inverse association between plasma concentrations of enterolignans and colorectal adenoma risk (19). In the present study, we were not able to confirm the inverse association between plasma enterolignans and colorectal cancer risk. Colorectal adenomas are widely accepted as precursors of colorectal cancer in humans. However, only a few adenomas develop into carcinomas. Enterolignans might decrease or delay the development of colorectal adenomas, but once adenomas are formed, enterolignans may no longer influence their further development to cancer. Colorectal carcinogenesis has been demonstrated to involve the accumulation of genetic alterations, in which individual dietary factors, such as lignans, may play a small but not crucial role. Therefore, the possible protective role of enterolignans in the development of colorectal adenomas might no longer be observed when evaluating the development of colorectal cancer, which involves multiple factors and takes several years or even decades. Another reason could be that we lacked statistical power to see any association. With the size of this study, we would be able to demonstrate an odds ratio of less than 0.47 (80 percent power; two-sided) in the highest quartile versus the lowest. For individual dietary factors, like enterolignans, this is a very large effect.

Although plasma enterolignan concentrations were not associated with a reduced risk of colorectal cancer in the entire study population, results from some subgroup analyses are noteworthy. High plasma concentrations of enterolactone were associated with an increased risk of colorectal cancer in women, especially in postmenopausal women. Previously, Jacobs et al. (44) observed sex differences in colorectal adenoma recurrence in response to fiber intake, which is positively correlated with plasma enterolactone \((r = 0.30, p < 0.001)\) (45). Although no underlying mechanism has yet been established, the interaction with sex and menopausal status suggests that an estrogen-related hormonal mechanism might be involved.

Evidence is accumulating for a possible protective effect of estrogens. At all ages, women are less likely than men to develop colon cancer (25), and postmenopausal hormone replacement therapy has been shown to reduce colon cancer risk for women even further, by up to 25 percent (26). It has been suggested that enterolignans have antiestrogenic effects: They bind to estrogen receptors (46, 47), but their efficacy is lower, resulting in blocking of the effect of estradiol. This could become of crucial importance in postmenopausal women, who have low endogenous levels of estradiol.

Furthermore, we observed an increased risk for subjects with high body mass index. Body weight and body mass index have been found to be positively related to risk of colon cancer in men, whereas weaker associations or no associations have been reported for women (48). Because of the small numbers in our study, we could not further address the combined effects of body mass index, sex, and menopausal status.

The increased risk observed in women and in subjects with high body mass index could be the result of slower intestinal motility. The prevalence of constipation, which indicates slower intestinal motility, is higher in women than in men (49, 50). Constipation appears to be positively associated with serum enterolactone and is an important independent determinant of enterolactone concentration (51). Constipation may lead to more complete metabolism and absorption of lignans. Thus, higher enterolactone concentrations might be associated with slower intestinal motility. This could result in prolonged exposure to toxins in the colon, thus increasing the risk of colorectal cancer (52, 53). Unfortunately, we had no data available on defecation patterns or constipation in this study.

In this study, the association between plasma enterodiol and colorectal cancer risk was modified by smoking status. We observed an increased risk among current smokers and an inverse risk among never smokers. Although we did not observe similar modification with plasma enterolactone, it is interesting to note that this modification is consistent with observations on fruit and vegetable intake and smoking status in a large European cohort study, the European Prospective Investigation into Cancer and Nutrition (H. B. B., unpublished data). Fruits and vegetables are important sources of plant lignans, and plasma enterolignans might be markers of fruit and vegetable intake.

An important strength of our study was its prospective design. Plasma samples were obtained up to 15 years prior to the diagnosis of colorectal cancer, making the presence of cancer at the time of blood donation unlikely. Moreover, results remained unchanged when cancers arising in the first 2 years of follow-up were excluded. Furthermore, our study design ensured identical collection and handling of blood samples from case and control subjects. The main limitation of our study was the lack of information on antibiotic use during the year prior to blood sampling. Use of antibiotics reduces plasma enterolactone concentrations, and this effect is sustained for several months (54). Nevertheless, we have no reason to assume that use of antibiotics prior to the study differed between cases and controls. Finally, information on family history of colorectal cancer was not available. Although some hereditary forms of colorectal cancer exist, such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer, they constitute no more than 10 percent of total colorectal cancer occurrence; most colorectal cancer cases occur sporadically via the polyp-cancer sequence (55).

In summary, the findings of this nested case-control study do not support the hypothesis that high plasma enterodiol or enterolactone concentrations are associated with reduced
risk of colorectal cancer. Further studies are needed to examine the risk associations in subgroup analysis according to sex, body mass index, and smoking status. Additionally, studies are needed to identify determinants of plasma enterolignan concentration in order to evaluate their use as biomarkers of exposure.

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Conflict of interest: none declared.

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