Lignan and isoflavone excretion in relation to uterine fibroids: a case-control study of young to middle-aged women in the United States[1–3]

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ABSTRACT

Background: Uterine fibroids are hormonally responsive; estradiol and progesterone stimulate their growth, and gonadotrophin-releasing hormone agonists shrink them. Phytoestrogens, including isoflavones and lignans, can act as weak estrogens or antiestrogens.

Objective: The objective of this case-control study was to evaluate the relation between uterine fibroid risk and phytoestrogen exposure.

Design: Two overnight urine collections (48 h apart) from 170 uterine fibroid cases and 173 controls were analyzed for isoflavonoids (ie, daidzein, genistein, equol, and *O*-desmethylangolensin) and lignans (enterodiol and enterolactone). Logistic regression was used to determine associations between the mean excretion of the 2 collections and the risk of uterine fibroids.

Results: Unadjusted isoflavone excretion did not differ significantly between cases and controls (2.33 ± 5.82 and 2.60 ± 5.90 nmol/mg Cr, respectively; $P = 0.68$), but cases excreted significantly less lignans than did controls (2.86 ± 3.45 and 4.57 ± 6.67 nmol/mg Cr, respectively; $P < 0.01$). The trend for a reduced risk of uterine fibroids with increasing quartiles of lignan excretion was significant (odds ratio for highest versus lowest quartile = 0.31; 95% CI: 0.17, 0.58; P for trend < 0.01). When adjusted for age, BMI, race, family history of uterine fibroids, and isoflavone excretion, this trend remained but was attenuated ($P = 0.07$).

Conclusions: Our findings suggest a modest inverse association between lignan excretion and uterine fibroid risk. Whether this relation represents an effect of lignans per se or of other constituents of lignan-containing foods on the development of uterine fibroids remains to be determined. No association was found between isoflavone excretion and uterine fibroids; however, the intake of soy foods, the primary source of isoflavones, was low in this population. *Am J Clin Nutr* 2006;84:587–93.

KEY WORDS Isoflavone, leiomyomata, lignan, phytoestrogen, uterine fibroid, women

INTRODUCTION

Uterine fibroids are common in women of reproductive age (1, 2), and, although benign, they are a major source of morbidity in a subset of women who have bleeding, pelvic pain, and other symptoms (3). Treatment options are limited; at present, hysterectomy is the only effective treatment for most symptomatic women diagnosed with these neoplasms. Uterine fibroids are hormonally responsive; they are not observed in prepubertal girls (3), and postmenopausal women are at a significantly lower risk of developing these benign tumors (4). Furthermore, estradiol and progesterone can stimulate growth of uterine fibroids (5, 6), and gonadotrophin-releasing hormone agonists shrink uterine fibroids (6–8).

Phytoestrogens, or plant estrogens, are structurally similar to mammalian estrogens (9, 10) and have received considerable attention for their potential health benefits in humans. They have weak estrogenic effects, and some evidence exists that they may also act as antiestrogens (10–13). Isoflavones and lignans are the 2 main classes of phytoestrogens. Isoflavones such as daidzein and genistein are found predominantly in soy foods (14), whereas lignans such as secoisolariciresinol and matairesinol are widespread in a variety of plant foods, with flaxseed and whole-grain foods being particularly rich sources (15–17). They are present in plants predominantly as glycosides, and, on ingestion, the sugar moieties of isoflavone and lignan glycosides are hydrolyzed to release the aglycones, which are absorbed or can be metabolized further by intestinal bacteria to additional metabolites. However, substantial interindividual differences exist in the production of certain metabolites; for example, it has been observed that only ≈30–50% of humans have the intestinal bacteria that can metabolize daidzein to equol (18), and wide ranges in the production of the mammalian lignans, enterodiol and enterolactone, from plant lignans such as secoisolariciresinol have been observed, even when study subjects consume the same amount of flaxseed (19, 20). Thus, interindividual differences in gut bacterial communities can result in interindividual differences in exposure to certain phytoestrogen metabolites. Given that some phytoestrogen metabolites may be more biologically active than their precursors

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(18), such differences may ultimately be associated with disease risk.

It has been suggested that the consumption of phytoestrogens can alter a woman's hormonal milieu, but data from intervention studies are conflicting with respect to the effects of these compounds on circulating concentrations of hormones (21–30). Animal studies have shown that isoflavones and lignans can accumulate in the uterus (31, 32), but, to our knowledge, no studies have investigated the association between exposure to these phytoestrogens and the risk of uterine fibroids. However, a prospective study of Japanese women observed an inverse association between soy intake and the risk of premenopausal hysterectomy, which suggested a potentially protective effect of soy foods in relation to diagnoses (eg, uterine fibroids) that are the major clinical indications for hysterectomy (33). We therefore compared the urinary excretion of isoflavones and lignans in uterine fibroid patients and controls from a population-based case-control study.

SUBJECTS AND METHODS

Study participants

Participants in this phytoestrogen excretion study were drawn from a larger case-control study of risk factors for uterine fibroids (34), and they have been described in detail elsewhere (35). Briefly, participants in the main case-control study were members of Group Health Cooperative (GHC), a large mixed-model health care system in Washington State. Cases ($n = 647$) were women with a first diagnosis of uterine fibroids between September 1995 and June 1998. The presence of fibroids was confirmed by ultrasound or surgery; patients were not eligible to participate if the only confirmation was by clinical examination. For comparison, we enrolled an age-stratified random sample of 637 women with no history of uterine fibroids after they were identified from 2 overlapping GHC databases. Pilot studies showed that ≈20% of the women identified for this study as having uterine fibroids would have come to clinical attention in the absence of symptoms. Because of this finding and concerns that such cases may have lifestyle characteristics that are associated with propensity to seek medical care, we sought to include among our controls a sample of women who, had they developed uterine fibroids, would have had more opportunity than the average female member of GHC to have come to clinical attention in the absence of symptoms. Thus, we selected 80% of the controls from the general GHC membership file and 20% of the controls from among women whose outpatient visit record in the GHC database indicated a visit for a well-woman check-up. These latter controls were selected from among the group of women with well-woman check-ups in each calendar quarter during which cases were diagnosed. Studies have shown that a substantial proportion of women harbor asymptomatic uterine fibroids (2); inclusion of such women as controls could potentially weaken the ability of the study to identify associations with risk factors. We therefore invited a random sample of 407 controls to undergo a transvaginal ultrasound examination, which was intended to identify women with fibroids that were not clinically evident; 299 (73.5%) of these 407 controls participated in the procedure. Of these 299 controls who were examined by ultrasound, 139 (46%) were found to have fibroids. Because of limited funding, we did not attempt to recruit all controls into the transvaginal ultrasound protocol.

Between April 1997 and October 1999, a subset of 191 cases and 177 controls participated in an ancillary protocol in which 2 overnight urine samples (separated by 48 h) were collected. These represented 88% and 79% of the eligible cases and controls, respectively, who were approached for participation in the ancillary protocol. Asian and African American women were oversampled for the ancillary protocol. Of the controls, 90 women (50.8%) had completed the transvaginal ultrasound examination.

Written informed consent was obtained from all participants in both the parent and ancillary studies. The institutional review boards of the Fred Hutchinson Cancer Research Center and GHC approved all study procedures.

Phytoestrogen analysis

Urinary excretion of isoflavones (ie, daidzein, genistein, equol, and *O*-desmethylangolensin) and lignans (enterodiol and enterolactone) were measured on aliquots from all overnight urine samples using gas chromatography–mass spectrometry (GC-MS) in the selected-ion monitoring mode with deuterated internal standards (35, 36). We have described the method details previously (35). Intra-run CVs for duplicate quality-control urine aliquots were $< 5\%$ for all compounds. Inter-run CVs for daidzein, genistein, *O*-desmethylangolensin, equol, enterodiol, and enterolactone were 12.9%, 22.4%, 16.7%, 14.8%, 6.2%, and 8.2%, respectively. Urinary creatinine concentrations were measured on the basis of a kinetic modification of the Jaffe reaction by using the Roche Reagent for Creatinine on a Roche Cobas Mira Plus chemistry analyzer (Roche Diagnostic Systems, Nutley, NJ).

Participant interviews and dietary data

In-person interviews, conducted by using a structured questionnaire, were carried out as part of the main case-control study. Each woman was assigned a reference date (month and year), and all questions referred to events and behaviors before this reference date. For cases, the reference date was the date of the initial clinical diagnosis of a uterine fibroid. For controls selected from the general GHC membership file, the reference date was a date selected at random from among the clinical diagnosis dates of the cases identified up to the point at which the control was selected. For controls selected because they had participated in well-woman check-ups, the reference date was selected at random from the quarter in which each woman's check-up occurred. During the interview, information on demographic characteristics, prior medical conditions, menstrual history, pregnancy history, contraceptive methods, use of noncontraceptive hormones, exercise habits, use of cigarettes and alcoholic beverages, health care–seeking behavior, family history of uterine fibroids and other diseases, and other characteristics suspected of being related to the development of uterine fibroids was gathered.

In the evening on which each overnight urine collection began, participants were asked to complete a self-administered, structured questionnaire regarding their diet earlier in the day of the collection. Thus, each woman completed 2 such dietary questionnaires, corresponding to each of the days on which the overnight urine collections were begun. The questionnaire was formulated specifically for this study, and consisted of a list of 82

items within the following categories: vegetables, beans, fruit (not juices), foods made from soybeans, breads and cereals, meat, fish, poultry, beverages, and other foods. In addition to the listed foods, each woman was asked to list any dietary supplements, such as herbal products and protein, she had consumed that day.

Statistical analysis

Data from 21 cases and 4 controls were unavailable or excluded from analyses because of interview responses that were eventually determined to be indicative of a history of fibroids before the reference date ($n = 18$ and $n = 2$ for cases and controls, respectively) or missing dietary or other pertinent data ($n = 3$ and $n = 2$ for cases and controls, respectively), to give a final sample size of 170 cases and 173 controls. Student's t tests and chi-square tests were used to assess differences between cases and controls in participant characteristics. Data were analyzed by using SAS software (version 9.1; SAS Institute, Cary, NC), and a P value of ≤ 0.05 was considered significant.

Urinary phytoestrogen data were expressed per mg Cr, which is a commonly used method of adjusting phytoestrogen concentration for variability in urinary output (37–40), and the mean excretion over both nights was used for a more representative measure of usual phytoestrogen excretion. As in other observational studies in a US population, urinary phytoestrogen data were skewed. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% CIs to quantify the association between isoflavone and lignan excretion and uterine fibroids, which does not require the data to be normally distributed. Data on isoflavone and lignan excretion were analyzed both as continuous data and as quartiles of excretion, and the assignment of quartiles was based on excretion by controls. The following potential confounders were examined to ascertain whether they altered ORs by >10%: age, body mass index (BMI; in kg/m^2), race, smoking status, use of oral contraceptives, family history (maternal or sibling) of uterine fibroids, number of live births, income, and intake (yes or no) of soy foods on either day of the structured recalls. Soy foods listed on the recall included tofu, tempeh, miso, soy burgers, soy hot dogs, soy cheese, soy yogurt, soy ice cream or frozen yogurt, soymilk, and soybean sprouts. Examples of soy-containing foods that were consumed by study participants in addition to those listed on the recall included soy protein powder or shakes and soy nuts. None of these factors altered continuous ORs by >10%. BMI and race altered categorized ORs by >10% for all levels of lignan excretion. In addition, age, family history of uterine fibroids, and mean excretion of lignans over the 2 nights were significantly associated with the risk of uterine fibroids; therefore, data are presented, first, without adjustment and, second, after adjustment for age, BMI, race, family history of uterine fibroids, and mean excretion over the 2 nights of either lignans (for analyses concerning isoflavones) or isoflavones (for analyses concerning lignans).

Soy foods are the primary source of isoflavones (14), and an additional analysis was conducted based on soy food–consumption patterns. For women who did not consume soy foods, the isoflavone concentration in urine was rarely >10 nmol/mg Cr; therefore, in addition to the analyses in which excretion among soy consumers and nonconsumers was combined, an analysis was conducted with 10 nmol/mg Cr as the high cutoff, and approximate tertiles were assigned for those with isoflavone excretion < 10 nmol/mg Cr. Because lignans are widespread in a variety of foods (15–17), additional analyses based on consumption patterns of lignan-containing foods were not conducted. The primary analyses were based on comparisons of 170 cases and 173 controls, but analyses also were conducted by using cases and the subset of controls ($n = 90$) who had undergone a transvaginal ultrasound examination. In these analyses, we compared phytoestrogen excretion according to 3 subject types (ie, cases, controls with ultrasound-detected fibroids, and controls without ultrasound-detected fibroids) and estimated the association between phytoestrogen excretion and a woman's risk of having (cases and controls with ultrasound-detected fibroids) or not having (controls without ultrasound-detected fibroids) fibroids.

TABLE 1
Characteristics of uterine fibroid cases and controls

Characteristic	Cases ($n = 170$)	Controls ($n = 173$)	P[1]
Age (y)[2]	45.8 ± 6.3[3]	44.4 ± 6.7	0.05
Race/ethnicity [*n* (%)][4]			
White	119 (70)	141 (82)	<0.01
African American	28 (16)	6 (4)	
Other[5]	23 (14)	24 (14)	
Level of education [*n* (%)]			
High school only	26 (15)	23 (13)	0.29
> High school but no college graduation	52 (31)	42 (24)	
College graduation or more	92 (54)	108 (63)	
Annual income [*n* (%)][6]			
≤ $19 999	13 (8)	8 (5)	0.61
$20 000–34 999	29 (17)	26 (16)	
$35 000–69 999	78 (47)	79 (47)	
≥ $70 000	47 (28)	54 (32)	
Maternal or sibling history of uterine fibroids [*n* (%)]			
Yes	33 (19.4)	20 (11.6)	0.04
No	137 (80.6)	153 (88.4)	
BMI (kg/m^2)[2]	29.0 ± 7.4	26.3 ± 5.9	<0.01
Current smoker [*n* (%)][4]			
Yes	17 (10.0)	18 (10.5)	0.87
No	153 (90.0)	153 (89.5)	
Live births (*n*)[7]	1.5 (0–5)	1.3 (0–4)	0.37
Duration of prior oral contraceptive use (mo)[8]	64.8 (0–286)	56.1 (0–303)	0.25
Consumed soy foods [*n* (%)]			
Yes	28 (16.5)	43 (24.9)	0.06
No	142 (83.5)	130 (75.1)	

[1] Calculated by Student's t test or chi-square analysis.
[2] $n = 170$ for controls.
[3] $\bar{x} \pm SD$ *(all such values).*
[4] $n = 171$ for controls.
[5] Predominantly Asian.
[6] $n = 167$ each for cases and controls.
[7] $n = 169$ and $n = 172$ for cases and controls, respectively. *n*; range in parentheses (all such values).
[8] $n = 168$ for cases.

RESULTS

Cases were slightly older, were more likely to be African American and to have a family history of uterine fibroids, had a higher BMI, and were less likely to consume soy foods than were controls (**Table 1**). The cases and controls did not

TABLE 2
Risk of uterine fibroids associated with urinary isoflavone and lignan excretion[1]

	Cases	Controls	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)[2]
	n	*n*		
Isoflavone excretion				
Per nmol/mg Cr[3]	168	172	0.99 (0.96, 1.03)	1.01 (0.97, 1.05)
Per nmol/mg Cr[4]	200	58	1.00 (0.95, 1.06)	1.00 (0.94, 1.06)
Quartiles (nmol/mg Cr)				
≤ 0.395[5]	48	43	1.00	1.00
0.396–0.702	30	43	0.63 (0.34, 1.16)	0.65 (0.33, 1.26)
0.703–1.898[5]	45	43	0.94 (0.52, 1.69)	0.86 (0.46, 1.62)
≥ 1.899[6]	45	43	0.94 (0.52, 1.69)	1.14 (0.59, 2.18)
P for trend			0.89	0.58
Lignan excretion				
Per nmol/mg Cr[7]	170	173	0.92 (0.87, 0.98)	0.95 (0.90, 1.01)
Per nmol/mg Cr[4]	202	58	0.90 (0.84, 0.97)	0.96 (0.88, 1.04)
Quartiles (nmol/mg Cr)				
≤ 1.359[8]	75	43	1.00	1.00
1.360–2.576[9]	33	43	0.44 (0.24, 0.79)	0.60 (0.32, 1.15)
2.577–5.459[6]	38	43	0.51 (0.29, 0.90)	0.71 (0.37, 1.37)
≥ 5.460	24	44	0.31 (0.17, 0.58)	0.47 (0.23, 0.98)
P for trend			<0.01	0.07

[1] Odds ratios and 95% CIs were determined by using unconditional logistic regression.
[2] Adjusted for age (continuous), BMI (continuous), race [white, African American, other (predominantly Asian)], family history of uterine fibroids (yes or no), and mean lignan or isoflavone excretion (continuous).
[3] $n = 168$ controls for adjusted analyses.
[4] Cases include all cases plus controls with ultrasound-detected uterine fibroids ($n = 199$ for adjusted analyses); controls include women without ultrasound-detected uterine fibroids.
[5] $n = 42$ controls for adjusted analyses.
[6] $n = 41$ controls for adjusted analyses.
[7] $n = 168$ cases and 168 controls for adjusted analyses.
[8] $n = 74$ cases and 41 controls for adjusted analyses.
[9] $n = 37$ cases and 42 controls for adjusted analyses.

differ significantly by current smoker status, levels of education and income, number of live births, and prior use of oral contraceptives.

The mean unadjusted excretion of isoflavones (sum of daidzein, genistein, equol, and *O*-desmethylangolensin) did not differ significantly between cases and controls: 2.33 ± 5.82 (range: 0.11–50.80) compared with 2.60 ± 5.90 (0.16–43.53) nmol/mg Cr, respectively ($P = 0.68$). Cases had significantly less ($P < 0.01$) mean lignan excretion (sum of enterodiol and enterolactone) than did controls: 2.86 ± 3.45 (range: 0.03–20.54) compared with 4.57 ± 6.67 (0.06–60.29) nmol/mg Cr, respectively. In logistic regression analyses of continuous data, total urinary isoflavone excretion (**Table 2**) and excretion of the individual isoflavones (data not shown) were not associated with risk of uterine fibroids. Total urinary lignan excretion (Table 2) and excretion of the individual metabolites (data not shown) were associated with a significantly lower risk of uterine fibroids, but these relations weakened slightly and were no longer significant in adjusted analyses (Table 2).

Trends across quartiles of total isoflavone excretion were not significant, whether data were unadjusted or adjusted (Table 2); findings for individual isoflavones did not differ significantly (data not shown). When analyses were conducted with 10 nmol/mg Cr as the highest level of excretion ($n = 5$ and $n = 9$ for cases and controls, respectively), these findings did not change (data not shown). For unadjusted lignan excretion, the trend for a lower risk of uterine fibroids was significant across quartiles of lignan excretion (Table 2). In adjusted analyses, this trend was still evident but no longer significant (Table 2). Such trends were seen across quartiles of enterolactone, but not enterodiol, excretion; the adjusted OR (including adjustment for either continuous enterodiol or enterolactone excretion) for the highest versus the lowest quartile of enterolactone excretion was 0.50 (95% CI: 0.23, 1.07; *P* for trend = 0.07) and for the highest versus the lowest quartile of enterodiol excretion was 1.29 (0.61, 2.70; *P* for trend = 0.43).

Of the 90 controls in the ancillary protocol who had undergone a transvaginal ultrasound examination, 32 (35.6%) were found to have ≥1 uterine fibroids. Mean adjusted lignan excretion (nmol/mg Cr) among cases ($n = 168$ for adjusted analyses), controls with ultrasound-detected fibroids ($n = 31$ for adjusted analyses), and controls without ultrasound-detected fibroids ($n = 58$) was 2.2 (95% CI: 1.5, 2.8), 2.6 (1.3, 3.9), and 3.0 (1.9, 4.1), respectively. The corresponding mean isoflavone excretion (nmol/mg Cr) was 3.5 (95% CI: 2.5, 4.5), 2.3 (0.3, 4.3), and 3.2 (1.5, 4.9), respectively. Associations with continuous lignan and isoflavone excretion did not differ significantly from those observed without adjustment for the results of the ultrasound examinations (Table 2). Analyses by quartile of isoflavone or lignan excretion were not conducted because of the low number of controls.

DISCUSSION

Uterine fibroids are clinically apparent in ≈25% of women (41) but can be found in the uteri of up to 77% of women (1, 2). Despite this high prevalence, relatively little is known about the causes of uterine fibroids, although several lines of evidence suggest that uterine fibroids are hormonally sensitive (42). Phytoestrogens and their metabolites have been shown to act as both estrogens and antiestrogens (10–13), and an attractive hypothesis for the biological effects of phytoestrogens is that it occurs via the modulation of endocrine function. To our knowledge, this is the first study to evaluate the relation between phytoestrogens and uterine fibroids. Our findings suggest a modest inverse association between urinary lignan excretion and uterine fibroids. In contrast, we did not observe a relation between urinary isoflavone excretion and uterine fibroids. However, soy consumption was low in this population (35); therefore, we are unable to exclude an association between isoflavones and uterine fibroids on the basis of these findings.

Lignans, including secoisolariciresinol, matairesinol, pinoresinol, and lariciresinol, are widespread in a variety of plant foods such as flaxseed, whole-grain foods, fruit, and vegetables (15–17) and are metabolized to enterodiol and enterolactone by intestinal bacteria. The assessment of dietary intake data to characterize lignan intakes is hampered by the fact that many current databases contain information on secoisolariciresinol and matairesinol but not on other important contributors to total lignan intakes, such as lariciresinol and pinoresinol (17, 43). Furthermore, wide ranges in urinary excretion of enterodiol and enterolactone have been observed in humans following various habitual diets and also in relation to a flaxseed challenge (19, 20, 44–47), and these wide ranges are likely due to interindividual differences in gut bacterial communities. Thus, urinary excretion of the lignan metabolites is a useful biomarker of individual exposure to these compounds because it takes into account interindividual differences in bacterial metabolism of dietary lignans. To our knowledge, no prior studies directly assessed the relation between urinary lignan excretion and the risk of uterine fibroids. In a case-control study of Italian women (48), those with uterine fibroids consumed green vegetables and fruit (which may be important sources of lignans) less frequently than did controls, which is somewhat in agreement with our finding that urinary lignan excretion is associated with a lower risk of uterine fibroids. Because lignans are widespread in a variety of foods that are generally perceived to be healthy, it is difficult to ascertain whether the relation between urinary lignan excretion and risk of uterine fibroids observed in our study represents an effect of lignans per se or whether lignan excretion is a marker of other dietary constituents that may modulate fibroid risk. However, given that the dietary instrument developed for this study was not designed to assess overall dietary quality or pattern, and given the well-known measurement issues that are associated with currently available dietary assessment tools (49), we did not attempt to assess other dietary constituents in relation to uterine fibroids.

Isoflavones are found predominantly in soy foods (14) and are consumed in higher amounts by Asian than by Western populations (11, 50, 51). As such, studies in Asian populations, who commonly consume soy (52, 53), would be better able to address potential relations between isoflavones and the risk of uterine fibroids. No studies have directly investigated the prevalence of uterine fibroids in Asian women living in their country of birth, but, in a study of premenopausal women living in the United States, Asian women had a rate of new diagnoses of uterine fibroids similar to that in white and Hispanic women (54). It is possible that these Asian women were consuming a more Westernized diet that is low in soy and isoflavones. In a prospective cohort study of Japanese women, the association between soy intakes and the risk of premenopausal hysterectomy was inverse (33), which suggested that consumption of soy foods may protect against conditions, such as uterine fibroids, that frequently lead to hysterectomy (33). Prenatal exposure to the exogenous estrogen diethylstilbestrol has been associated with a greater risk of uterine fibroids (55), which suggests that early life exposure to potential endocrine disruptors such as phytoestrogens also may be important. In addition, interindividual differences in phytoestrogen metabolism in humans could contribute to interindividual variations in the effects of phytoestrogens on uterine fibroid risk, given that some metabolites appear to be more biologically active than others (18).

A potential limitation of this study is that not all controls were screened for asymptomatic uterine fibroids. Thus, in our primary analyses, some women in the control group would have had undetected uterine fibroids, and associations with phytoestrogen excretion may have been attenuated. In subanalyses involving cases and the ≈50% of controls who had undergone transvaginal ultrasound examinations, we found that controls with ultrasound-detected fibroids had lignan excretion that was intermediate between that of cases and of controls without ultrasound-detected fibroids, whereas controls with ultrasound-detected fibroids had isoflavone excretion that was lower than that of both cases and controls without ultrasound-detected fibroids. Notably, when comparisons were made between women with fibroids (ie, women with either clinically recognized or ultrasound-detected fibroids) and women without fibroids (ie, women with neither clinically recognized or ultrasound-detected fibroids), associations with lignan and isoflavone excretion did not differ significantly from those observed without taking into account the results of the ultrasound examinations. Thus, little empiric evidence exists that the results from our primary analyses were meaningfully attenuated by the inclusion as controls of women with asymptomatic fibroids. Another limitation of this study is that urine samples were collected from cases after diagnosis. If changes toward a "healthier" lifestyle were made by patients after diagnosis, it is possible that urinary excretion of phytoestrogens that we measured may be higher than that which would have been measured before diagnosis. If so, the inverse association we observed with lignan excretion may in fact be more pronounced. However, we are not aware of general medical recommendations that fibroid patients should adopt particularly healthy diets to address this health problem (in contrast, for example, with the recommendations that exist for a patient who has received a diagnosis of coronary heart disease). In addition, although the cases comprised women with a first diagnosis of uterine fibroids, some of these women may have had asymptomatic fibroids before diagnosis. Depending on the length of time between the development of uterine fibroids and the manifestation of clinical symptoms, the measurement of urinary phytoestrogen excretion at—or even before—diagnosis may not capture exposure to these compounds before the development of uterine fibroids.

In conclusion, our findings suggest a modest inverse association between urinary excretion of the mammalian lignans enterodiol and enterolactone and the development of uterine fibroids. If

these findings are confirmed in prospective studies in which enterolactone and enterodiol excretion is measured before the diagnosis—or even the development—of uterine fibroids, lignan consumption may be a viable dietary strategy for reducing the risk of uterine fibroids. Given that soy intakes were low in this population, further studies are needed to ascertain the relation between consumption of isoflavone phytoestrogens and uterine fibroids.

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