The Journal of Nutrition
Nutritional Epidemiology

Urinary Phytoestrogen Concentrations Are Not Associated with Incident Endometriosis in Premenopausal Women[1–3]

Sunni L Mumford,[4]* Jennifer Weck,[4] Kurunthachalam Kannan,[5] and Germaine M Buck Louis[4]

[4]Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD; and [5]Wadsworth Center, New York State Department of Health and Department of Environmental Health Sciences, University at Albany, Albany, NY

Abstract

Background: Phytoestrogens have been associated with subtle hormonal changes, but their effects on endometriosis are largely unknown.

Objective: We assessed the association between urinary concentrations of phytoestrogens and incident endometriosis.

Methods: We included an operative sample of 495 premenopausal women aged 18–44 y undergoing laparoscopies and laparotomies at 14 clinical sites between 2007 and 2009 and a general population sample of 131 women from the same geographic area who were matched on age and menstruation status. Endometriosis in the surgical sample was assessed by surgical visualization (clinical gold standard), whereas disease in the general population sample was assessed with the use of a pelvic MRI. Urine concentrations of genistein, daidzen, *O*-desmethylangolensin, equol, enterodiol, and enterolactone were measured at baseline. Poisson regression with robust error variance was used to estimate the risk of an endometriosis diagnosis for each sample after adjusting for age and body mass index (in kg/m^2). Separate models were run for each phytoestrogen.

Results: Overall geometric mean urine concentrations of phytoestrogens were as follows: genistein [88 nmol/L (95% CI: 72, 108 nmol/L)], daidzein [194 nmol/L (95% CI: 160, 236 nmol/L)], *O*-desmethylangolensin [4 nmol/L (95% CI: 3, 6 nmol/L)], equol [4 nmol/L (95% CI: 4, 6 nmol/L)], enterodiol [29 nmol/L (95% CI: 22, 38 nmol/L)], and enterolactone [355 nmol/L (95% CI: 395, 544 nmol/L)]. Geometric mean concentrations of phytoestrogens did not significantly differ by endometriosis status in either sample. Adjusted RRs for endometriosis ranged from 0.87 to 1.09 for the 6 phytoestrogens measured, with all CIs including a value ≥1. Phytoestrogens were not associated with the severity of endometriosis when restricting the analysis to women with moderate-to-severe disease per the revised American Society for Reproductive Medicine criteria. Furthermore, no associations were observed between self-reported high soy intake and endometriosis.

Conclusions: Despite endometriosis being an estrogen-dependent disease, we found no evidence that urinary phytoestrogens were associated with a higher risk of an endometriosis diagnosis in either a sample of premenopausal women or in a surgical sample. *J Nutr* 2017;147:227–34.

Keywords: phytoestrogens, endometriosis, genistein, daidzein, lignans

Introduction

Endometriosis is a hormone-responsive gynecologic disorder of unknown etiology (1). The etiology is considered to be multifactorial (2), and it has been hypothesized that dietary intake, among other factors, may influence the physio- and pathologic processes of the disease (3–5). Dietary factors that have been shown to influence steroidogenesis may be of particular interest (6–8). Phytoestrogens are plant-derived compounds with estrogenic activity and include both isoflavones (most commonly found in soy and soy products) and lignan metabolites (most commonly found in flax seeds, nuts, grains, and cruciferous vegetables). Although phytoestrogens have different dietary sources, all phytoestrogens are structurally similar to estrogen and can bind to both estrogen receptor (ER)[6]-α and ER-β. Phytoestrogens have been reported to exert both estrogenic and

[1] This article was presented in abstract form at the 97th Endocrine Society Annual Meeting, San Diego, CA, 5–8 March 2015, and 28th Society for Epidemiology Research and Society for Pediatric and Perinatal Epidemiology Annual Meeting, Denver, CO, 15–16 June 2015.

[2] Supported by the NIH, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and University of Utah.

[3] Author disclosures: SL Mumford, J Weck, K Kannan, and GMB Louis, no conflicts of interest.

*To whom correspondence should be addressed. E-mail: mumfords@mail.nih.gov.

[6] Abbreviations used: ENDO, Endometriosis, Natural History, Diagnosis, and Outcomes; ER, estrogen receptor; *ESR2*, estrogen receptor 2.

Manuscript received July 7, 2016. Initial review completed August 31, 2016. Revision accepted November 30, 2016.
First published online December 28, 2016; doi:10.3945/jn.116.238840.

antiestrogenic effects (9, 10) and as such may play an important role in endometriosis, although the effects of specific phytoestrogens could differ.

Phytoestrogens have been associated with subtle hormonal changes (11), a reduced risk of hormone-dependent cancers, including endometrial cancer (12–14), and endometriotic implant regression in animal models (15, 16). However, the effects on endometriosis are largely unknown. Available evidence is conflicting, with one small study among nulliparous infertile Japanese women finding that the phytoestrogen genistein was associated with a reduced risk of endometriosis, particularly among those with the estrogen receptor 2 (*ESR2*) *RsaI* gene polymorphism (17). In contrast, high intakes of soy products were associated with endometrial pathology among 3 women (18), and long-term supplementation of isoflavones was associated with endometrial hyperplasia among healthy postmenopausal women (19). Laboratory animal studies have also shown that at high doses certain phytoestrogens such as resveratrol have the potential benefit of reducing the proliferation of the human endometrium (20, 21). Understanding the role of various phytoestrogens in endometriosis may offer the potential for low-cost intervention strategies to improve this condition.

Therefore, we evaluated the association between specific urinary phytoestrogen concentrations, including both isoflavones and lignan metabolites and endometriosis, in the ENDO (Endometriosis Natural History, Diagnosis, and Outcomes) study, which included both an operative and general population sample to more completely capture endometriosis cases.

Methods

Design and study population. The ENDO surgical sample (n = 495) comprised women scheduled for laproscopy or laparotomy; the general population sample (n = 131) comprised a matched group of currently menstruating women similar in age and from the same geographic area. The population cohort was not seeking surgery but was at risk for endometriosis and diagnosis. The details of the study design and sampling framework have been described in detail elsewhere (22). In short, to be included women had to be currently menstruating, aged 18–44 y, and scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy regardless of clinical indication at 1 of 14 surgical centers located in Salt Lake City, Utah, or San Francisco, California, between 2007 and 2009. Women with a history of surgically confirmed endometriosis (prevalent disease) or who could not communicate in English or Spanish were excluded. Other exclusion criteria included currently pregnant or breastfeeding ≥6 mo, injectable hormones within the past 2 y, or a cancer diagnosis other than nonmelanoma skin cancer.

Institutional review board approval was obtained from all participating study sites. Women provided written informed consent before data collection, and all participants were modestly remunerated for time and travel.

Outcome assessment. Endometriosis was defined as consistent with the clinical gold standard of surgically visualized disease (1, 23) and assessed and staged surgically for the surgical sample and by pelvic MRI for the general population sample. Complete information on endometriosis status was available for 473 and 127 women in the operative and general population samples, respectively. Surgeons completed a standardized operative report immediately after surgery to capture the gynecologic postoperative diagnosis, including normal pelvis, endometriosis, uterine fibroids, pelvic adhesions, benign ovarian cysts, neoplasms, and congenital müllerian cysts. For women with endometriosis, surgeons indicated disease severity with the use of the revised American Society for Reproductive Medicine staging criteria (23). Disease stage was automatically calculated via the revised American Society for Reproductive Medicine weighted point score.

Measurement of phytoestrogens. Phytoestrogens were measured in urine at baseline for all participants for whom sufficient urine was available for analysis (n = 625) and included the isoflavones genistein, daidzein, O-desmethylangolensin, and equol, the latter 2 of which are daidzein metabolites, and the lignan metabolites enterodiol and enterolactone. Phytoestrogens were measured with the use of an HPLC electrospray tandem MS method (interassay CV <6% based on quality control data acquired during the analysis of the study samples) as described elsewhere (24). Urine samples were prepared with [$^2H_3$]daidzein and [$^2H_4$]genistein as internal standards and then mixed gently, followed by the addition of 300 μL β-glucuronidase/sulfatase buffer containing 2 μL enzymes in a 1-mL 1 M ammonium acetate solution. After enzymatic deconjugation, phytoestrogens were extracted with a methyl-tert-butyl ether/ethyl acetate mixture. The negative-ion multiple-reaction monitoring mode was used in the analysis of phytoestrogens. The analytes were quantified by an isotope dilution method. All machine-observed concentrations were retained in the analysis without any substitution or removal of concentrations below the limits of detection to avoid introducing biases (25–27). All analyses were subjected to standard quality assurance procedures, and all reported results were from runs found to be in control by standard statistical methods (24). Consistent with previously published methods for lipid standardization for lipophilic agents, we do not present creatinine-adjusted phytoestrogen concentrations, although we do compare results from regression models that did and did not adjust for creatinine concentrations (28).

Covariate assessment. Women completed questionnaires upon enrollment regarding demographic characteristics, reproductive history, multivitamin use, and lifestyle habits (including smoking status, alcohol intake, and caffeinated beverage consumption). Women were also asked about their use of vitamins and supplements in the past 3 mo, including supplements containing soy components. BMI (in kg/m^2) was calculated with the use of a portable stadiometer, and body weight was measured with the use of calibrated electronic scales. Physical activity was assessed via the International Physical Activity Questionnaire and categorized into low, moderate, and high categories per standard protocol (29).

Statistical analysis. Participant characteristics were compared between quartiles of urinary total phytoestrogens for both the operative and general population samples. Differences were assessed with the use of ANOVA and chi-square tests as appropriate. The distributions of individual phytoestrogens for each sample were compared overall by endometriosis diagnosis and severity. Geometric means and 95% CIs are presented unadjusted as well as adjusted for age and BMI. Multivariable RR estimation by Poisson regression with robust error variance was used to determine the RR of being diagnosed with endometriosis by concentration of individual phytoestrogens (assessed as quartiles and as a continuous variable). These models estimate the RR comparing quartiles with the first quartile as the reference group, as well as the RR per log-unit increase in phytoestrogens. Separate models were run for each phytoestrogen, with each model adjusted for age and BMI. Additional adjustment for race, site, supplement use, use of soy products, physical activity, creatinine, caffeine consumption, and the sum of the remaining individual phytoestrogens did not appreciably alter the results. Potential effect modification by age and BMI was assessed with the use of interaction terms. All analyses were performed with the use of SAS version 9.4 (SAS Institute).

Results

In the operative sample we observed that women in the lowest quartile of urinary total phytoestrogen concentrations tended to be older, have a higher BMI, be more likely to have less than a high school education, be a current smoker, and consume more caffeinated beverages than women in higher quartiles (**Table 1**). Women in the operative sample in the highest quartile were more likely to report that they had consumed a soy product >1 time/wk during the past 3 mo than women in the lowest

quartile; correspondingly, women in the operative sample who had consumed soy products had higher geometric mean urine phytoestrogen concentrations (5760 nmol/L; 95% CI: 3310, 10,000 nmol/L) than those who consumed no soy products (1250 nmol/L; 95% CI: 1080, 1440 nmol/L). Similar results were observed among women in the general population sample (consumed soy products: 3670 nmol/L; 95% CI: 1590, 8480 nmol/L; did not consume soy products: 1490 nmol/L; 95% CI: 1130, 1960 nmol/L). In the general population sample, women in the highest quartile of urinary total phytoestrogens were more likely to report having consumed a multivitamin >1 time/wk in the past 3 mo than women in the lower quartiles, and no associations were observed between total phytoestrogens and age, BMI, educational status, or smoking. No associations were observed between urinary total phytoestrogens and age at menarche, race, marital status, income, physical activity, or alcohol consumption in either sample.

Geometric mean concentrations of phytoestrogens were not significantly different by endometriosis status or stage in either sample (**Table 2**), although we did observe significantly lower equol concentrations among those with endometriosis stage III/IV than those with stage I/II. Adjusted RRs for endometriosis ranged from 0.87 to 1.09 for the 6 phytoestrogens measured, with all CIs including a value ≥1 (**Table 3**). Similar null results were observed when evaluating urinary phytoestrogens by quartile (Table 3). Given that many biomarker assessments

TABLE 1 Sociodemographic description of ENDO study participants by sample and quartile of total phytoestrogen concentrations[1]

	Operative sample[2]						General sample[3]					
Characteristics	Overall	Q1	Q2	Q3	Q4	*P*	Overall	Q1	Q2	Q3	Q4	*P*
n	494	123	124	124	123		131	32	33	33	33	
Age, y	33 ± 7	34 ± 7	33 ± 7	31 ± 7	33 ± 7	0.03	32 ± 8	32 ± 7	34 ± 6	32 ± 9	31 ± 8	0.42
BMI, kg/m^2	28 ± 8	30 ± 8	29 ± 8	27 ± 7	27 ± 7	0.03	27 ± 7	28 ± 6	27 ± 6	27 ± 8	26 ± 7	0.69
Age at menarche, y	13 ± 2	13 ± 2	13 ± 2	13 ± 2	13 ± 2	0.61	13 ± 2	13 ± 2	13 ± 1	12 ± 1	13 ± 2	0.66
Self-identified race/ethnicity						0.18						0.14
Hispanic	68 (14)	15 (12)	11 (9)	23 (19)	19 (15)		14 (11)	4 (13)	2 (6)	6 (18)	2 (6)	
Non-Hispanic white	369 (75)	98 (80)	102 (82)	84 (68)	85 (69)		106 (82)	25 (78)	29 (88)	24 (73)	28 (85)	
Non-Hispanic black	8 (2)	0 (0)	2 (2)	2 (2)	4 (3)		2 (2)	0 (0)	0 (0)	2 (6)	0 (0)	
Asian, Pacific Islander, or American Indian	29 (6)	5 (4)	4 (3)	9 (7)	11 (9)		5 (4)	3 (9)	0 (0)	0 (0)	2 (6)	
Other or multiracial	20 (4)	5 (4)	5 (4)	6 (5)	4 (3)		4 (3)	0 (0)	2 (6)	1 (3)	1 (3)	
Married or living as married	370 (76)	93 (76)	103 (83)	87 (71)	87 (73)	0.11	78 (60)	20 (63)	24 (73)	17 (52)	17 (52)	0.23
Education						0.002						0.29
≤High school or equivalent	98 (20)	37 (30)	24 (19)	19 (16)	18 (15)		13 (10)	6 (19)	4 (12)	1 (3)	2 (6)	
Some college or vocational school	197 (40)	47 (38)	50 (40)	60 (49)	40 (33)		58 (44)	14 (44)	16 (48)	16 (48)	12 (36)	
≥College graduate	195 (40)	39 (32)	50 (40)	43 (35)	63 (52)		60 (46)	12 (38)	13 (39)	16 (48)	19 (58)	
Household income						0.51						0.86
Below poverty line	55 (11)	13 (11)	11 (9)	19 (15)	12 (10)		16 (12)	6 (19)	2 (6)	4 (12)	4 (12)	
Within 180% of poverty line	58 (12)	19 (16)	13 (11)	12 (10)	14 (12)		17 (13)	4 (13)	4 (13)	5 (15)	4 (12)	
Above poverty line	373 (76)	89 (74)	99 (80)	92 (75)	93 (78)		92 (75)	22 (69)	26 (81)	24 (73)	25 (76)	
Multi- or prenatal vitamins taken >1 time/wk in past 3 mo	240 (49)	61 (50)	58 (47)	61 (49)	60 (49)	0.97	66 (50)	17 (53)	18 (55)	10 (30)	21 (64)	0.05
Soy products taken >1 time/wk in past 3 mo	31 (6)	4 (3)	2 (2)	6 (5)	19 (15)	<0.0001	13 (10)	3 (9)	2 (6)	1 (3)	7 (21)	0.07
Physical activity						0.81						0.13
Low	78 (18)	21 (20)	17 (15)	19 (17)	21 (19)		20 (16)	2 (7)	9 (30)	6 (18)	3 (10)	
Moderate	161 (37)	42 (40)	43 (38)	40 (37)	36 (32)		53 (43)	17 (59)	11 (37)	11 (33)	14 (45)	
High	198 (45)	41 (39)	53 (47)	50 (46)	54 (49)		50 (41)	10 (34)	10 (33)	16 (48)	14 (45)	
Smoking status						0.005						0.68
Nonsmoker	429 (87)	96 (78)	107 (86)	114 (92)	112 (91)		117 (89)	30 (94)	30 (91)	29 (88)	28 (85)	
Current (≥1 cigarette/d)	65 (13)	27 (22)	17 (14)	10 (8)	11 (9)		14 (11)	2 (6)	3 (9)	4 (12)	5 (15)	
Alcohol						0.30						0.84
None	384 (78)	95 (77)	98 (79)	102 (82)	89 (72)		100 (76)	24 (75)	27 (82)	25 (76)	24 (73)	
≥1 drink/wk	110 (22)	28 (23)	26 (21)	22 (18)	34 (28)		31 (24)	8 (25)	6 (18)	8 (24)	9 (27)	
Mean number of caffeinated beverages consumed/d						0.04						0.97
0	96 (19)	13 (11)	32 (28)	22 (18)	29 (25)		44 (34)	10 (31)	11 (34)	10 (31)	13 (39)	
1	138 (28)	40 (34)	28 (25)	35 (29)	35 (31)		43 (33)	11 (34)	12 (38)	10 (31)	10 (30)	
≥2	229 (46)	63 (54)	54 (47)	62 (52)	50 (44)		42 (33)	11 (34)	9 (28)	12 (38)	10 (30)	

[1] Values are means ± SDs or *n* (%). The respective operative sample concentration ranges for quartiles 1–4 were 7–435, 436–1310, 1320–3670, and 3670–184,000 nmol/L; the respective general population sample concentration ranges were 51–574, 575–1280, 1290–4490, and 4500–62,600 nmol/L. ENDO, Endometriosis, Natural History, Diagnosis, and Outcomes; Q, quartile.

[2] Missing information on age (*n* = 1), BMI (*n* = 4), age at menarche (*n* = 1), marital status (*n* = 5), educational status (*n* = 4), income (*n* = 8), physical activity (*n* = 57), and caffeinated beverage consumption (*n* = 31).

[3] Missing information on income (*n* = 1), physical activity (*n* = 8), and caffeinated beverage consumption (*n* = 2).

TABLE 2 Phytoestrogen concentrations of ENDO study participants and endometriosis status and severity[1]

	Operative sample				General sample		
	Overall	Endometriosis stage I/II	Endometriosis stage III/IV	No endometriosis	Overall	Endometriosis	No endometriosis
n	494	134	55	283	131	14	113
Isoflavones, nmol/L							
Genistein							
Unadjusted	88 (72, 108)	93 (63, 137)	94 (58, 152)	84 (64, 111)	112 (79, 158)	86 (28, 271)	116 (79, 170)
Adjusted[2]	88 (72, 108)	90 (61, 133)	96 (53, 175)	86 (65, 112)	113 (80, 160)	87 (30, 257)	116 (79, 170)
Daidzein							
Unadjusted	194 (160, 236)	219 (154, 310)	149 (84, 266)	194 (148, 253)	229 (159, 332)	182 (59, 561)	244 (163, 365)
Adjusted	195 (160, 237)	212 (146, 310)	151 (85, 270)	198 (152, 256)	228 (158, 331)	188 (61, 578)	243 (164, 361)
O-DMA							
Unadjusted	4 (3, 6)	5 (2, 9)	3 (1, 9)	5 (3, 7)	7 (4, 14)	4 (0, 39)	8 (4, 16)
Adjusted	5 (3, 6)	4 (2, 8)	3 (1, 8)	5 (3, 8)	7 (4, 13)	4 (1, 30)	8 (4, 16)
Equol							
Unadjusted	4 (4, 6)	6 (4, 9)*	3 (1, 5)*	4 (3, 6)	6 (4, 9)	6 (2, 21)	6 (4, 10)
Adjusted	5 (4, 6)	6 (4, 10)	3 (1, 5)	4 (3, 6)	6 (4, 9)	6 (2, 21)	6 (4, 10)
Total							
Unadjusted	397 (332, 475)	432 (309, 606)	332 (199, 553)	393 (308, 501)	467 (334, 654)	320 (108, 948)	500 (347, 722)
Adjusted	398 (332, 476)	421 (296, 597)	335 (196, 573)	399 (314, 508)	463 (330, 649)	330 (118, 924)	498 (347, 716)
Lignan metabolites, nmol/L							
Enterodiol							
Unadjusted	29 (22, 38)	31 (18, 52)	36 (16, 83)	27 (19, 38)	28 (16, 49)	36 (6, 205)	28 (16, 52)
Adjusted	28 (21, 37)	28 (16, 46)	35 (16, 78)	28 (19, 40)	28 (16, 49)	36 (6, 199)	28 (16, 52)
Enterolactone							
Unadjusted	355 (299, 421)	399 (288, 553)	435 (252, 753)	319 (256, 399)	464 (340, 635)	605 (217, 1690)	455 (323, 639)
Adjusted	352 (297, 418)	359 (259, 499)	413 (250, 684)	334 (267, 419)	463 (330, 649)	600 (232, 1550)	455 (326, 636)
Total							
Unadjusted	464 (395, 544)	536 (400, 719)	517 (301, 889)	421 (342, 519)	573 (423, 777)	734 (278, 1940)	562 (403, 784)
Adjusted	460 (392, 540)	488 (359, 663)	493 (308, 790)	438 (355, 541)	556 (411, 752)	736 (291, 1860)	562 (405, 778)
Total phytoestrogens							
Unadjusted	1380 (1190, 1590)	1540 (1200, 1990)	1340 (873, 2060)	1310 (1080, 1590)	1630 (1250, 2120)	1200 (457, 3130)	1730 (1300, 2300)
Adjusted	1370 (1190, 1590)	1450 (1100, 1910)	1310 (856, 2010)	1350 (1110, 1630)	1590 (1220, 2090)	1220 (534, 2780)	1720 (1290, 2300)

[1] All values are geometric means (95% CIs) unless otherwise indicated. Values can be converted from nmol/L to ng/mL by dividing by the following conversion factors: genistein, 3.70; daidzein, 3.93; O-DMA, 3.87; equol, 4.13; enterodiol, 3.31; and enterolactone, 3.35. *Different from no endometriosis group, $P < 0.05$. ENDO, Endometriosis, Natural History, Diagnosis, and Outcomes; O-DMA, *O*-desmethylangolensin.
[2] Adjusted for age and BMI (in kg/m^2).

from urine are often adjusted to creatinine concentrations to account for dilution, we also adjusted for creatinine along with several other potential confounders, including race, site, supplement use, use of soy products, physical activity, caffeine consumption, and the sum of the remaining individual phytoestrogens and found similar null results. No significant interactions were observed between phytoestrogens and age or BMI and endometriosis. No associations were observed when restricting the analysis to women with moderate-to-severe disease. Furthermore, no associations were observed between self-reported high soy intake and disease.

Discussion

Despite endometriosis being an estrogen-dependent disease, we found no evidence that urinary phytoestrogen concentrations were associated with a higher risk of an endometriosis diagnosis in both a general population and operative sample. These results extend previous findings to include a more complete population from which to evaluate factors associated with incident endometriosis. These results further highlight that urinary phytoestrogens do not seem to affect endometriosis at concentrations characteristic of the US population.

Prior studies on the association between phytoestrogens and endometriosis are limited, and most tended to focus on isoflavones as measured through dietary assessment of soy products or urinary isoflavone concentrations. In a study of 138 infertile nulliparous Japanese women (17), Tsuchiya et al. observed urinary isoflavones to be associated with a reduced risk of endometriosis; they further examined potential interactions with the *ESR2* gene polymorphism and found that the *RsaI* polymorphism seemed to modify the effects of genistein on advanced endometriosis (17). Although we were unable to evaluate interactions with the *ESR2* gene, there are other important differences between the study by Tsuchiya et al. and ours. In particular, their study was restricted to infertile and nulliparous women and thus may have included a particularly unique and perhaps more sensitive population given that factors associated with endometriosis may differ by parity (30, 31). The results from ENDO may therefore be more generalizable because we were able to identify endometriosis from both a clinical and population-wide perspective and made no restrictions by parity or infertility diagnosis. Our study extends these

TABLE 3 Associations between urinary phytoestrogen concentrations and risk of endometriosis in the ENDO study[1]

	Operative sample					General sample				
	Quartile (range)	*n*	Unadjusted (*n* = 472)	Adjusted[2] (*n* = 466)	Adjusted[3] (*n* = 387)	Quartile (range)	*n*	Unadjusted (*n* =127)	Adjusted[2] (*n* =127)	Adjusted[3] (*n* = 117)
Isoflavones, nmol/L										
Genistein	Q1[4]	123	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(0.01–22.3)					(0.32–22.7)				
	Q2	124	1.18	1.14	1.12	Q2	33	1.61	1.58	3.49
	(22.4–77.0)		(0.78, 1.80)	(0.75, 1.74)	(0.70, 1.79)	(22.8–88.8)		(0.39, 6.76)	(0.37, 6.73)	(0.57, 21.44)
	Q3	124	1.49	1.39	1.33	Q3	33	0.65	0.63	0.58
	(77.1–284)		(1.00, 2.22)	(0.93, 2.08)	(0.84, 2.10)	(88.9–339)		(0.11, 3.87)	(0.10, 3.83)	(0.05, 7.00)
	Q4	123	1.06	1.02	0.97	Q4	33	1.29	1.31	4.99
	(285–76,500)		(0.69, 1.63)	(0.66, 1.57)	(0.56, 1.68)	(340–21,900)		(0.29, 5.77)	(0.29, 5.88)	(0.67, 37.02)
	Linear[5]		1.01	1.01	1.02			0.94	0.94	1.04
			(0.95, 1.08)	(0.95, 1.07)	(0.93, 1.11)			(0.72, 1.22)	(0.71, 1.23)	(0.70, 1.55)
Daidzein	Q1	124	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(0.01–44.0)					(0.19–50.3)				
	Q2	123	1.14	1.08	1.17	Q2	33	1.17	1.23	3.37
	(45.0–138)		(0.76, 1.71)	(0.72, 1.63)	(0.75, 1.85)	(50.4–178)		(0.32, 4.37)	(0.32, 4.74)	(0.50, 22.62)
	Q3	124	1.08	1.03	1.07	Q3	33	0.52	0.54	0.76
	(139–645)		(0.72, 1.62)	(0.68, 1.56)	(0.65, 1.74)	(179–998)		(0.09, 2.82)	(0.10, 2.98)	(0.07, 8.73)
	Q4	123	1.04	1.00	1.11	Q4	33	0.70	0.75	2.20
	(646–13,600)		(0.69, 1.58)	(0.66, 1.52)	(0.66, 1.85)	(999–39,200)		(0.16, 3.15)	(0.16, 3.45)	(0.29, 16.41)
	Linear		1.00	1.00	1.00			0.94	0.95	1.09
			(0.94, 1.07)	(0.93, 1.06)	(0.91, 1.09)			(0.73, 1.21)	(0.73, 1.22)	(0.79, 1.51)
O-DMA	Q1	123	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(0.003–0.33)					(0.003–0.37)				
	Q2	124	0.78	0.75	0.82	Q2	33	0.68	0.62	0.27
	(0.34–9.25)		(0.52, 1.19)	(0.49, 1.14)	(0.51, 1.29)	(0.38–14.3)		(0.15, 3.05)	(0.13, 2.96)	(0.04, 1.94)
	Q3	124	0.96	0.90	0.90	Q3	33	0.68	0.68	0.39
	(9.26–70.8)		(0.65, 1.42)	(0.61, 1.34)	(0.58, 1.41)	(14.4–113)		(0.15, 3.05)	(0.15, 3.12)	(0.05, 2.89)
	Q4	123	0.96	0.91	0.94	Q4	33	0.97	0.95	1.47
	(70.9–10,700)		(0.65, 1.42)	(0.61, 1.34)	(0.58, 1.52)	(114–14,300)		(0.24, 3.87)	(0.23, 3.86)	(0.22, 10.04)
	Linear		0.99	0.99	0.99			0.96	0.96	0.96
			(0.96, 1.03)	(0.95, 1.03)	(0.95, 1.03)			(0.84, 1.10)	(0.83, 1.10)	(0.79, 1.17)
Equol	Q1	124	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(0.003–1.24)					(0.003–4.13)				
	Q2	123	0.71	0.74	0.69	Q2	33	0.70	0.74	1.05
	(1.25–8.09)		(0.46, 1.10)	(0.48, 1.15)	(0.43, 1.10)	(4.14–8.80)		(0.16, 3.15)	(0.17, 3.34)	(0.17, 6.48)
	Q3	124	1.33	1.32	1.14	Q3	33	0.25	0.24	0.53
	(8.10–19.0)		(0.92, 1.94)	(0.90, 1.92)	(0.75, 1.75)	(8.81–15.0)		(0.03, 2.24)	(0.03, 2.18)	(0.05, 5.70)
	Q4	123	0.93	0.92	0.76	Q4	33	1.45	1.61	4.51
	(19.1–11,800)		(0.62, 1.40)	(0.61, 1.39)	(0.45, 1.27)	(15.1–8240)		(0.41, 5.15)	(0.45, 5.82)	(0.70, 29.13)
	Linear		1.01	1.01	0.97			0.99	1.00	1.08
			(0.96, 1.07)	(0.95, 1.06)	(0.91, 1.04)			(0.80, 1.24)	(0.80, 1.25)	(0.82, 1.42)
Total isoflavones	Q1	123	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(0.05–87.1)					(14.6–95.8)				
	Q2	124	1.11	1.08	1.08	Q2	33	1.17	1.22	3.06
	(87.2–287)		(0.74, 1.67)	(0.72, 1.63)	(0.69, 1.71)	(95.9–307)		(0.32, 4.37)	(0.32, 4.65)	(0.49, 19.29)
	Q3	124	1.10	1.03	0.99	Q3	33	0.52	0.54	0.70
	(288–1290)		(0.74, 1.66)	(0.68, 1.56)	(0.61, 1.61)	(308–1870)		0.09, 2.82)	(0.10, 3.01)	(0.06, 7.70)
	Q4	123	1.08	1.06	1.06	Q4	33	0.70	0.74	2.08
	(1300–18,400)		(0.71, 1.63)	(0.70, 1.60)	(0.64, 1.74)	(1880–61,700)		(0.16, 3.15)	(0.16, 3.36)	(0.32, 13.62)
	Linear		1.00	1.00	0.98			0.89	0.90	1.06
			(0.93, 1.08)	(0.93, 1.07)	(0.89, 1.07)			(0.67, 1.19)	(0.67, 1.20)	(0.75, 1.51)
Lignan metabolites, nmol/L										
Enterodiol	Q1	123	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(0.003–20.6)					(0.004–17.0)				
	Q2	124	1.14	1.05	0.88	Q2	33	1.94	1.90	1.92
	(20.7–60.2)		(0.76, 1.73)	(0.69, 1.60)	(0.56, 1.40)	(17.1–65.5)		(0.49, 7.75)	(0.47, 7.67)	(0.42, 8.75)

(Continued)

TABLE 3 *Continued*

	Operative sample					General sample				
	Quartile (range)	*n*	Unadjusted (*n* = 472)	Adjusted[2] (*n* = 466)	Adjusted[3] (*n* = 387)	Quartile (range)	*n*	Unadjusted (*n* =127)	Adjusted[2] (*n* =127)	Adjusted[3] (*n* = 117)
	Q3	123	1.11	1.06	0.93	Q3	33	0.3	0.33	0.59
	(60.3–166)		(0.73, 1.68)	(0.70, 1.61)	(0.58, 1.47)	(65.6–206)		(0.03, 3.20)	(0.03, 3.19)	(0.05, 6.77)
	Q4	124	1.25	1.19	1.19	Q4	33	1.25	1.31	1.47
	(167–25,300)		(0.83, 1.88)	(0.79, 1.79)	(0.74, 1.92)	(207–2360)		(0.28, 5.60)	(0.29, 6.01)	(0.20, 10.68)
	Linear		1.01	1.00	1.00			1.02	1.02	1.03
			(0.96, 1.06)	(0.96, 1.05)	(0.95, 1.06)			(0.86, 1.21)	(0.86, 1.22)	(0.84, 1.28)
Enterolactone	Q1	123	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(0.15–108)					(1.62–170)				
	Q2	123	1.03	1.03	1.01	Q2	33	1.52	1.39	1.71
	(109–516)		(0.67, 1.58)	(0.67, 1.59)	(0.61, 1.67)	(171–559)		(0.36, 6.34)	(0.32, 6.00)	(0.27, 10.77)
	Q3	125	1.32	1.22	1.25	Q3	33	0.32	0.29	0.54
	(517–1380)		(0.88, 1.98)	(0.81, 1.85)	(0.80, 1.96)	(560–1490)		(0.03, 3.10)	(0.03, 2.90)	(0.04, 6.65)
	Q4	123	1.30	1.15	1.11	Q4	33	1.52	1.52	4.39
	(1390–116,000)		(0.87, 1.96)	(0.76, 1.74)	(0.98, 1.81)	(1500–23,100)		(0.36, 6.34)	(0.35, 6.57)	(0.60, 32.29)
	Linear		1.04	1.02	1.01			1.08	1.09	1.29
			(0.97, 1.13)	(0.94, 1.10)	(0.92, 1.10)			(0.80, 1.47)	(0.80, 1.49)	(0.87, 1.91)
Total	Q1	123	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(0.16–159)					(1.63–208)				
	Q2	124	0.97	0.95	0.88	Q2	33	0.91	0.86	0.51
	(160–30)		(0.63, 1.49)	(0.62, 1.47)	(0.54, 1.44)	(209–734)		(0.23, 3.63)	(0.21, 3.52)	(0.08, 3.21)
	Q3	124	1.29	1.18	1.16	Q3	33	0.73	0.70	1.05
	(631–1610)		(0.86, 1.92)	(0.79, 1.78)	(0.74, 1.81)	(735–1630)		(0.16, 3.24)	(0.15, 3.18)	(0.19, 5.75)
	Q4	123	1.28	1.13	1.13	Q4	33	0.68	0.68	1.17
	(1620–128,000)		(0.86, 1.92)	(0.75, 1.70)	(0.70, 1.82)	(1640–24,100)		(0.15, 3.05)	(0.15, 3.18)	(0.17, 7.86)
	Linear		1.05	1.02	1.01			1.08	1.09	1.29
			(0.96, 1.13)	(0.94, 1.11)	(0.92, 1.12)			(0.79, 1.49)	(0.79, 1.51)	(0.85, 1.94)
Total phytoestrogens, nmol/L	Q1	123	Ref	Ref	Ref	Q1	32	Ref	Ref	Ref
	(6.58–435)					(51.2–574)				
	Q2	124	1.21	1.17	1.26	Q2	33	0.58	0.56	0.75
	(436–1310)		(0.79, 1.85)	(0.76, 1.79)	(0.78, 2.02)	(575–1280)		(0.14, 2.43)	(0.13, 2.39)	(0.11, 4.84)
	Q3	124	1.38	1.23	1.24	Q3	33	0.40	0.40	0.65
	(1320–3670)		(0.91, 2.07)	(0.81, 1.86)	(0.78, 1.98)	(1290–4490)		(0.08, 2.06)	(0.08, 2.06)	(0.09, 4.44)
	Q4	123	1.22	1.14	1.12	Q4	33	0.75	0.76	2.53
	(3680–184,000)		(0.80, 1.86)	(0.74, 1.74)	(0.67, 1.90)	(4500–62,600)		(0.20, 2.80)	(0.20, 2.86)	(0.39, 16.36)
	Linear		1.03	1.01	1.00			0.87	0.87	1.06
			(0.94, 1.12)	(0.92, 1.10)	(0.89, 1.12)			(0.62, 1.23)	(0.62, 1.24)	(0.68, 1.66)

[1] Values are RRs (95% CIs) unless otherwise indicated. ENDO, Endometriosis, Natural History, Diagnosis, and Outcomes; O-DMA, *O*-desmethylangolensin; Q, quartile; Ref, reference.
[2] Adjusted for age and BMI (in kg/m^2).
[3] Adjusted for age, BMI, race, site, supplement use, use of soy products, physical activity, creatinine, caffeine consumption, and the sum of the remaining individual phytoestrogens.
[4] Poisson regression with robust error variance was used to estimate the RRs of being diagnosed with endometriosis comparing quartiles of urinary phytoestrogen concentrations (the first quartile is the reference group).
[5] Poisson regression with robust error variance was used to estimate the RRs of being diagnosed with endometriosis by individual urinary phytoestrogen concentrations (per log-unit increase in phytoestrogens).

previous findings in a population with a gold-standard assessment of endometriosis in both an operative and general population sample. Another related case report (18) noted that high soy intake was associated with abnormal uterine bleeding with endometrial pathology in 3 women and that symptoms improved after removing soy from the diet, although information was limited regarding the amount of soy consumed and for what period of time. Additional studies have shown possible conflicting associations with the effects on endometrial hyperplasia, but these studies did not evaluate endometriosis diagnosis directly (19, 32, 33). In particular, a study among 376 healthy postmenopausal women found that supplementation with 150 mg isoflavones/d for 5 y was associated with an increased occurrence of endometrial hyperplasia (19). However, in that study, only 6 cases of endometrial hyperplasia were observed overall and among women consuming a high dose of isoflavones; in other studies of shorter duration, no effects were observed (32, 33). These previous findings may also be affected by the relatively short half-life of these compounds, the mean of which varies between 3 and 10 h (34). Our findings extend previous work, particularly with regard to the evaluation of lignan metabolites, to evaluate phytoestrogens from different food sources that may have different physiologic effects. Interestingly, we also did not observe lignan metabolites to be associated with endometriosis. Future studies are needed to further tease apart the potential effects of phytoestrogens as a whole and

specific types of phytoestrogens on the human endometrium and endometriosis.

It is hypothesized that phytoestrogens would be associated with endometriosis given that certain phytoestrogens have been shown to affect endocrine organs in humans and in animal models by influencing estrogen-dependent processes (9, 10). In particular, phytoestrogens can act by altering the interactions between a steroid, its nuclear steroid hormone receptor, and the transcription complex, including associated transcription factors and coactivators and repressors and the downstream gene response elements. Alternatively, the disruptor could alter the interaction between a steroid and a nonnuclear or membrane steroid receptor or by affecting nonsteroid receptors such as the dopamine receptor (35). Additional possible mechanisms include inhibiting hormone synthesis, transport, or metabolism; activating or inactivating orphan receptors; or affecting any of the downstream pathways modulated by normal steroid hormones. These effects can be estrogenic or antiestrogenic depending on the concentration of phytoestrogens, the specific phytoestrogen observed, circulating concentrations of endogenous estrogens, as well as other individual characteristics such as reproductive history and menopausal status.

Phytoestrogens are generally considered to be selective ER modulators, have a high affinity for the nuclear hormone receptor ER-β, and have been reported to inhibit aromatase activity (the rate-limiting enzyme in the conversion of androgens to estrogens) in human endometrial stromal cells (36). Thus, it is not unexpected that dietary phytoestrogens could play a role in the pathophysiology of an estrogen-dependent (37) condition such as endometriosis. At the level of the endometrium, phytoestrogens have been shown to potentially act as agonists in animal models (38–41). However, human studies have suggested that the dosage and length of supplementation may be important to consider because isoflavone treatment for a period of 5 y was associated with endometrial hyperplasia (19), whereas short-term treatments were not (19, 32, 33). In this study, we evaluated phytoestrogens at concentrations representative of the US population. That we see no correlation between phytoestrogens and endometriosis may reflect the fact that these substances are part of a normal diet and that slight differences in intake are not sufficient to imbalance the physiologic regulation of hormone-dependent pathways. Different phytoestrogens have also been shown to vary with regard to potency and mechanism of action, and as such effects may differ at the endometrial level in response to varying distributions of estrogen receptor subtypes on endometrial tissue (19, 42).

This study is limited in that we did not have dietary assessments to explore other aspects of dietary intake. However, we did adjust for several potential confounding factors and factors related to dietary intake and found similar results, although the potential for residual confounding cannot be ruled out. Importantly, the urinary measures of the isoflavones genistein and daidzein used in this analysis reflect only short-term intake, and as such we assumed that the baseline measurement reflected the usual dietary intake of soy products among the women in this study, which may not adequately capture lifetime dietary habits, especially for such short-lived compounds. However, the use of urinary biomarkers is also a strength of this study in that urinary measurements of isoflavones take into account differences in metabolism and absorption (43–45) and have been found to be useful biomarkers of dietary intake especially as soy in found in many products and assessment is limited using traditional dietary assessment tools (44, 45). Unlike the isoflavones, lignan concentrations tend to be more weakly correlated with dietary intake (fiber intake, in particular), likely because of differences in the composition of gut microflora between individuals (46). Furthermore, the use of a population sample enabled us to extend this work to capture endometriosis cases that otherwise would have been undetected, although we were limited in our analysis because there was a small number of cases observed. Last, although the concentrations in this population are low, they are comparable to those observed in the US population.

Overall, we found no differences in urine phytoestrogen concentrations in women that did or did not have endometriosis, regardless of differences in reported intake of soy supplements. Despite endometriosis being an estrogen-dependent disease, we found no evidence that urinary phytoestrogens were associated with a higher risk of an endometriosis diagnosis in either a sample of premenopausal women or in an operative sample.

Acknowledgments

SLM conceived the study, developed the overall research plan, performed the statistical analyses, wrote the paper, and had primary responsibility for the final content; KK analyzed the urine samples for phytoestrogens; GMBL conceived and designed the study; and SLM, JW, KK, and GMBL interpreted the data and critically revised the manuscript. All authors read and approved the final manuscript.

References

1. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005;20:2698–704.
2. Vignali M, Infantino M, Matrone R, Chiodo I, Somigliana E, Busacca M, Vigano P. Endometriosis: novel etiopathogenetic concepts and clinical perspectives. Fertil Steril 2002;78:665–78.
3. Fjerbaek A, Knudsen UB. Endometriosis, dysmenorrhea and diet—what is the evidence? Eur J Obstet Gynecol Reprod Biol 2007;132:140–7.
4. Hansen SO, Knudsen UB. Endometriosis, dysmenorrhoea and diet. Eur J Obstet Gynecol Reprod Biol 2013;169:162–71.
5. Parazzini F, Vigano P, Candiani M, Fedele L. Diet and endometriosis risk: a literature review. Reprod Biomed Online 2013;26:323–36.
6. Britton JA, Westhoff C, Howe G, Gammon MD. Diet and benign ovarian tumors (United States). Cancer Causes Control 2000;11:389–401.
7. Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, Barbieri RL, Willett WC, Hankinson SE. A prospective study of dietary fat consumption and endometriosis risk. Hum Reprod 2010;25:1528–35.
8. Trabert B, Peters U, De Roos AJ, Scholes D, Holt VL. Diet and risk of endometriosis in a population-based case-control study. Br J Nutr 2011;105:459–67.
9. Hwang CS, Kwak HS, Lim HJ, Lee SH, Kang YS, Choe TB, Hur HG, Han KO. Isoflavone metabolites and their in vitro dual functions: they can act as an estrogenic agonist or antagonist depending on the estrogen concentration. J Steroid Biochem Mol Biol 2006;101:246–53.
10. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson JA. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 1998;139:4252–63.
11. Hooper L, Ryder JJ, Kurzer MS, Lampe JW, Messina MJ, Phipps WR, Cassidy A. Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis. Hum Reprod Update 2009;15:423–40.
12. Bandera EV, Williams MG, Sima C, Bayuga S, Pulick K, Wilcox H, Soslow R, Zauber AG, Olson SH. Phytoestrogen consumption and endometrial cancer risk: a population-based case-control study in New Jersey. Cancer Causes Control 2009;20:1117–27.
13. Horn-Ross PL, John EM, Canchola AJ, Stewart SL, Lee MM. Phytoestrogen intake and endometrial cancer risk. J Natl Cancer Inst 2003;95:1158–64.

14. Mense SM, Hei TK, Ganju RK, Bhat HK. Phytoestrogens and breast cancer prevention: possible mechanisms of action. Environ Health Perspect 2008;116:426–33.
15. Chen Y, Chen C, Shi S, Han J, Wang J, Hu J, Liu Y, Cai Z, Yu C. Endometriotic implants regress in rat models treated with puerarin by decreasing estradiol level. Reprod Sci 2011;18:886–91.
16. Yavuz E, Oktem M, Esinler I, Toru SA, Zeyneloglu HB. Genistein causes regression of endometriotic implants in the rat model. Fertil Steril 2007;88(4 Suppl):1129–34.
17. Tsuchiya M, Miura T, Hanaoka T, Iwasaki M, Sasaki H, Tanaka T, Nakao H, Katoh T, Ikenoue T, Kabuto M, et al. Effect of soy isoflavones on endometriosis: interaction with estrogen receptor 2 gene polymorphism. Epidemiology 2007;18:402–8.
18. Chandrareddy A, Muneyyirci-Delale O, McFarlane SI, Murad OM. Adverse effects of phytoestrogens on reproductive health: a report of three cases. Complement Ther Clin Pract 2008;14:132–5.
19. Unfer V, Casini ML, Costabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. Fertil Steril 2004;82:145–8.
20. Amaya SC, Savaris RF, Filipovic CJ, Wise JD, Hestermann E, Young SL, Lessey BA. Resveratrol and endometrium: a closer look at an active ingredient of red wine using in vivo and in vitro models. Reprod Sci 2014;21:1362–9.
21. Ji M, Liu YH, Yang SS, Zhai DX, Zhang DY, Bai LL, Wang Z, Yu J, Yu C, Cai Z. Puerarin suppresses proliferation of endometriotic stromal cells in part via differential recruitment of nuclear receptor coregulators to estrogen receptor-alpha. J Steroid Biochem Mol Biol 2013;138:421–6.
22. Buck Louis GM, Hediger ML, Peterson CM, Croughan M, Sundaram R, Stanford J, Chen Z, Fujimoto VY, Varner MW, Trumble A, et al. Incidence of endometriosis by study population and diagnostic method: the ENDO study. Fertil Steril 2011;96:360–5.
23. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997;67:817–21.
24. Kunisue T, Tanabe S, Isobe T, Aldous KM, Kannan K. Profiles of phytoestrogens in human urine from several Asian countries. J Agric Food Chem 2010;58:9838–46.
25. Guo Y, Harel O, Little RJ. How well quantified is the limit of quantification? Epidemiology 2010;21(Suppl 4):S10–6.
26. Schisterman EF, Vexler A, Whitcomb BW, Liu A. The limitations due to exposure detection limits for regression models. Am J Epidemiol 2006;163:374–83.
27. Richardson DB, Ciampi A. Effects of exposure measurement error when an exposure variable is constrained by a lower limit. Am J Epidemiol 2003;157:355–63.
28. Schisterman EF, Whitcomb BW, Louis GM, Louis TA. Lipid adjustment in the analysis of environmental contaminants and human health risks. Environ Health Perspect 2005;113:853–7.
29. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–95.
30. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Malspeis S, Willett WC, Hunter DJ. Reproductive history and endometriosis among premenopausal women. Obstet Gynecol 2004;104:965–74.
31. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol 2004;160:784–96.
32. Hale GE, Hughes CL, Robboy SJ, Agarwal SK, Bievre M. A double-blind randomized study on the effects of red clover isoflavones on the endometrium. Menopause 2001;8:338–46.
33. Murray MJ, Meyer WR, Lessey BA, Oi RH, DeWire RE, Fritz MA. Soy protein isolate with isoflavones does not prevent estradiol-induced endometrial hyperplasia in postmenopausal women: a pilot trial. Menopause 2003;10:456–64.
34. Setchell KD, Brown NM, Desai P, Zimmer-Nechemias L, Wolfe BE, Brashear WT. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. J Nutr 2001;131 (Suppl 4):1362S–75S.
35. León-Olea M, Martyniuk CJ, Orlando EF, Ottinger MA, Rosenfeld CS, Wolstenholme JT, Trudeau VL. Current concepts in neuroendocrine disruption. Gen Comp Endocrinol 2014;203:158–73.
36. Edmunds KM, Holloway AC, Crankshaw DJ, Agarwal SK, Foster WG. The effects of dietary phytoestrogens on aromatase activity in human endometrial stromal cells. Reprod Nutr Dev 2005;45:709–20.
37. Viganò P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: epidemiology and aetiological factors. Best Pract Res Clin Obstet Gynaecol 2004;18:177–200.
38. García-Pérez MA, Noguera R, del Val R, Noguera I, Hermenegildo C, Cano A. Comparative effects of estradiol, raloxifene, and genistein on the uterus of ovariectomized mice. Fertil Steril 2006;86:1003–5.
39. Heikaus S, Winterhager E, Traub O, Grummer R. Responsiveness of endometrial genes Connexin26, Connexin43, C3 and clusterin to primary estrogen, selective estrogen receptor modulators, phyto- and xenoestrogens. J Mol Endocrinol 2002;29:239–49.
40. Newbold RR, Banks EP, Bullock B, Jefferson WN. Uterine adenocarcinoma in mice treated neonatally with genistein. Cancer Res 2001;61:4325–8.
41. Wober J, Weisswange I, Vollmer G. Stimulation of alkaline phosphatase activity in Ishikawa cells induced by various phytoestrogens and synthetic estrogens. J Steroid Biochem Mol Biol 2002;83:227–33.
42. Lecce G, Meduri G, Ancelin M, Bergeron C, Perrot-Applanat M. Presence of estrogen receptor beta in the human endometrium through the cycle: expression in glandular, stromal, and vascular cells. J Clin Endocrinol Metab 2001;86:1379–86.
43. Arai Y, Uehara M, Sato Y, Kimira M, Eboshida A, Adlercreutz H, Watanabe S. Comparison of isoflavones among dietary intake, plasma concentration and urinary excretion for accurate estimation of phytoestrogen intake. J Epidemiol 2000;10:127–35.
44. Lampe JW. Isoflavonoid and lignan phytoestrogens as dietary biomarkers. J Nutr 2003;133(Suppl 3):956S–64S.
45. Lampe JW, Gustafson DR, Hutchins AM, Martini MC, Li S, Wahala K, Grandits GA, Potter JD, Slavin JL. Urinary isoflavonoid and lignan excretion on a Western diet: relation to soy, vegetable, and fruit intake. Cancer Epidemiol Biomarkers Prev 1999;8:699–707.
46. Peterson J, Dwyer J, Aldercreutz H, Scalbert A, Jacques P, McCullough ML. Dietary lignans: physiology and potential for cardiovascular disease risk reduction. Nutr Rev 2010;68:571–603.