Published in final edited form as:

Cancer Causes Control. 2009 September ; 20(7): 1117–1127. doi:10.1007/s10552-009-9336-9.

PHYTOESTROGEN CONSUMPTION AND ENDOMETRIAL CANCER RISK: A POPULATION-BASED CASE-CONTROL STUDY IN NEW JERSEY

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Abstract

Phytoestrogens have been shown to exert anti-estrogenic and estrogenic effects in some tissues, including the breast. However, only a few studies have evaluated their role in endometrial cancer risk. We evaluated this association in a population-based case-control study in New Jersey. A total of 424 cases and 398 controls completed an interview, including a food frequency questionnaire with supplemental questions for phytoestrogen foods. Risk estimates were derived using unconditional logistic regression, adjusting for major risk factors for endometrial cancer. There was some suggestion of a decreased risk with quercetin intake (OR: 0.65; 95% CI: 0.41–1.01 for the highest compared to the lowest quartile; p for trend: 0.02). We found limited evidence of an association with any of the lignans evaluated, total lignans, coumestrol, individual isoflavones, total isoflavones, or total phytoestrogens. However, there was some suggestion of an inverse association with total isoflavone intake limited to lean women (BMI <25) (OR for the highest tertile: 0.50, 95% CI: 0.25–0.98) and those with a waist-to-hip ratio ≤0.85 (OR: 0.59; 95% CI: 0.33–1.05). There was no evidence of effect modification by HRT use. This study suggests a reduction in endometrial cancer risk with quercetin intake and with isoflavone intake in lean women.

Keywords

Endometrial neoplasms; phytoestrogens; isoflavones; lignans; quercetin; diet

INTRODUCTION

Endometrial cancer is the most common female gynaecological cancer in the United States, ranking fourth among all cancers in women in age-adjusted incidence [1]. There is a growing interest in the role of phytoestrogens in female hormonal cancers [2], particularly on breast

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Published in *Cancer Causes and Control* <http://www.springerlink.com/content/680m9w4126898326/>

cancer risk [3]. However, despite the well-established association of estrogens unopposed by progesterone and endometrial cancer [4], the role of phytoestrogens in endometrial cancer risk has received little attention.

Phytoestrogens are non-steroidal plant-derived compounds, structurally similar to endogenous estrogens, but capable of showing both estrogenic and antiestrogenic effects [5]. The main sources of phytoestrogens are isoflavonoids, coumestans, and lignans. While the main food source of isoflavones is the soybean, coumestrol, the main dietary coumestan, is found in alfalfa sprouts and beans, and lignans precursors are present in fiber-rich foods, such as flaxseed and unrefined grain products [6]. Other phytoestrogens include the flavonoids (quercetin, kaempferol), the stilbenes (resveratrol), and the mycotoxins (zearalenol) [7]. Although their effects are not totally understood, it has been postulated that phytoestrogens may exert antiestrogenic effects in high-estrogen environments and have weak estrogenic effects in low-estrogen environments [8]. Because phytoestrogens share some structural similarity with estradiol, they are capable of binding to estrogen receptors while exerting mild estrogenic activity compared to that of endogenous estrogens. Their potential effect at the estrogen receptor level, as well as their possible influences in estrogen metabolism, have generated substantial interest in the possible health effects of phytoestrogens, in particular as a “natural” alternative to estrogen replacement therapy (ERT) in postmenopausal women. However, their role in cancer remains controversial.

To our knowledge, only three case-control studies [9–11] have reported on the role of phytoestrogens on endometrial cancer risk, with conflicting results. A few additional studies examining the impact of soy foods, the main source of isoflavones, tended to suggest an inverse association [10,12]. Our study evaluated the impact of consumption of the major phytoestrogens and endometrial cancer risk in the EDGE Study, a population-based study conducted in Northern New Jersey.

METHODS

The methods used in the EDGE Study (Estrogen, Diet, Genetics, and Endometrial Cancer) have been described elsewhere [13]. In brief, women older than 21 years and able to understand English or Spanish, and living in one of six NJ counties (Bergen, Essex, Hudson, Middlesex, Morris, and Union) were eligible to participate in the study. Newly diagnosed, histologically confirmed cases of epithelial endometrial cancer were identified between July 1, 2001 and June 30, 2005 using rapid case ascertainment by the New Jersey Department of Health and Senior Services, supplemented with review of state Cancer Registry data to identify cases diagnosed out of the area. Representative glass slides of endometrial carcinomas were re-reviewed by a gynecologic pathologist whenever possible to confirm the diagnosis. A total of 1,559 eligible women were identified, of whom 1,104 could be contacted within one year of diagnosis. Four hundred sixty-nine (42%) completed the interview.

Women who had a hysterectomy were excluded from the control group. Controls were identified from various sources. Women aged <65 y were initially located through random digit dialing conducted by a commercial research service. One hundred seventy-five of the 355 eligible women (49%) completed the interview. For women aged ≥65 y, we initially identified potential controls by random selection from lists purchased from the Centers for Medicare and Medicaid (CMS). We identified 316 women, of whom 68 (22%) completed the interview, while the remainder declined; for 40% of those who declined, eligibility was unknown. Beginning in August 2003, we undertook area sampling for controls, initially seeking women aged ≥65 y and later including women aged ≥55 y. We contacted by mail and home visits 30 consecutive households in each randomly-chosen neighborhood. We identified 524 eligible women, of whom 224 (43%) completed the interview. In total, 467 controls completed the interview.

Informed consent was obtained from all participants and the study was approved by the Institutional Review Boards at Robert Wood Johnson Medical School, Memorial Sloan-Kettering Cancer Center, and the New Jersey Department of Health and Senior Services.

Data Collection

Interviews, conducted by telephone for most respondents, covered established and possible risk factors for endometrial cancer. In addition to the interview, participants were mailed a package with instructions for providing buccal specimens and waist and hip circumference measurements and the Block 98.2 food frequency questionnaire (FFQ). Participants were instructed to report their usual intake of the food items in the questionnaire during the six months before diagnosis (for cases) or the date of the interview (for controls). Four hundred and twenty four cases (90.4%) and 398 controls (85.2%) returned the FFQ. The participants who returned the FFQ tended to be older, but there were no significant differences in education, BMI, unopposed ERT use, or HRT use (data not shown).

The Block 98.2 FFQ includes 110 food items and was developed using the NHANES (National Health and Nutrition Examination Survey) III dietary recall data. It also includes questions on portion size for each food and pictures are provided to facilitate estimation. The questionnaire includes a variety of foods containing phytoestrogens, such as several kinds of beans, tofu, soymilk, canned tuna fish, meat substitutes (e.g., veggie burgers, veggie chicken), and whole wheat bread. To supplement the list of foods, we added one page with 21 additional food items, based on the LACE questionnaire [14] and including other food items that have been identified as important sources of phytoestrogens [15]. The additional foods in the supplemental page that were not included in the Block 98.2 questionnaire are listed in the Appendix. We also asked about the use of phytoestrogen/soy supplements including frequency and duration of use. Berkeley Nutrition Services provided nutrient calculations using the USDA Nutrient Database for Standard Reference. For phytoestrogen calculations we used a database with detailed analyses of phytoestrogen content of foods, including detailed analyses of lignans [16].

Statistical Analysis

We evaluated the association of endometrial cancer risk with total phytoestrogens, isoflavones (total, daidzein, genistein, formononetin, and glycitein), lignans (total, matairesinol, lariciresinol, pinoresinol, secoisolariciresinol), coumestrol, as well as the flavonoid quercetin. We excluded 7 cases and 3 controls with missing values for major covariates, such as menopausal status or body mass index (BMI), resulting in a final analytical sample of 417 cases and 395 controls. Participants were categorized into quartiles of intake based on the distribution of intake in controls. Odds ratios and 95 confidence intervals were estimated by unconditional multiple logistic regression. Tests for trend were derived by assigning the median value to each quantile. Potential confounding variables considered were age; race; BMI, calculated as weight (in kg) divided by height (in m²); education (high school or less, college, graduate school); parity (0–1, 2, ≥3); age at menarche (>13, 12–13, ≤11 years); menopausal status/age at menopause (premenopausal, age at menopause <40, age at menopause 40–54, age at menopause ≥55 and postmenopausal with age at menopause unknown); oral contraceptive use (ever, never used); use of hormone replacement therapy (HRT) (never used any HRT, used unopposed estrogen only, used combined therapy, i.e., estrogen and progesterone); total energy intake (as a continuous variable), smoking status; alcohol use (g/1000 kcal); and physical activity (METs). We adjusted for total energy intake using the multivariate nutrient density model, by computing nutrient density for each variable expressed in mcg (or mg) per 1000 kcal of intake and including total calories as a continuous variable in the model [17]. We repeated analyses adjusting for smoking in pack-years but results were essentially the same. Total fat and total fiber intakes as continuous variables were also considered as covariates.

We evaluated possible effect modification by evaluating the association between the different phytoestrogens under consideration and endometrial cancer by categories of BMI, waist-to-hip ratio (WHR), and HRT use. We were unable to conduct stratified analyses by menopausal status because the number of premenopausal women in our study was small (60 cases and 48 controls). However, results were similar when analyses were restricted to postmenopausal women (data not shown). We evaluated interactions by including cross-product terms in logistic regression models. SAS version 9.1 (SAS Institute, Cary NC) was used for analysis.

RESULTS

The mean age was 61.6 years for cases and 64.3 years for controls (data not shown). Table 1 shows demographic characteristics for the study population and distribution of cases and controls by major risk factors. As shown in the table, the study population was mostly white (85.4% of the cases and 88.8% of the controls). Only 6 cases and 3 controls were Asian (data not shown). Overall, as expected, obesity was associated with an increased endometrial cancer risk, while parity, oral contraceptive use, and smoking were associated with a reduced risk. Unexpectedly, risk was not increased among the small group of women using unopposed estrogens, but the confidence interval included the null. We repeated our phytoestrogen analyses excluding this group of women and results remained essentially the same. Phytoestrogen supplement use was uncommon and infrequent in our population (data not shown), with only 6% of cases and less than 5% of controls reporting ever using phytoestrogen pills ($p=0.43$) and only 6% of cases and less than 4% of controls reporting ever using isoflavone/soy powders ($p=0.12$). Therefore, subsequent analyses were based only on food sources of phytoestrogens.

As Table 2 shows, cases tended to consume lower levels of phytoestrogens than controls. In multivariate analyses, after adjusting for major risk factors, there was little indication of an association with the major phytoestrogen groups (Table 3a). The adjusted odds ratio for women in the highest category of isoflavone intake was below one (OR: 0.8), but the confidence interval included the null value. We also evaluated the role of individual phytoestrogens (Table 3b). There was some suggestion of a reduced risk associated with high consumption of daidzein and genistein, but the ORs did not reach statistical significance. There was little evidence for an association with other isoflavones or any of the lignans under consideration (matairesinol, lariciresinol, pinoresinol, secoisolariciresinol) or coumestrol. We found a suggestion of a reduction in endometrial cancer risk with quercetin intake, with those in the highest quartile of consumption having an adjusted OR of 0.65 (95% CI: 0.41–1.01; p for trend: 0.02). The relationship persisted after adding the variables total fat and fiber consumption as covariates (OR: 0.63; 95% CI: 0.40–0.99 for the highest vs. the lowest quartile of consumption; data not shown).

We evaluated possible effect modification of the phytoestrogens under consideration by BMI, WHR, and HRT use. Results for total phytoestrogens and total isoflavones are shown in Table 4. Overall, stratified analyses did not reveal effect modification for any of the variables considered except for total isoflavone consumption. Total isoflavones appeared to reduce endometrial cancer risk only among lean women, with ORs for the highest tertile of intake compared to the lowest of 0.50 (95% CI: 0.25–0.98) for women with a BMI <25 and 0.59 (95% CI: 0.33–1.05) for women with a WHR of 0.85 or less (Table 4). The pattern of stronger effect among lean women persisted after adding the variables fat and fiber intakes to the model, but the confidence intervals included the null. The OR for the highest tertile of isoflavone intake compared to the lowest for lean women with further adjustment for fat and fiber was 0.53 (95% CI: 0.26–1.06).

In Table 5, risk estimates for the major food sources of isoflavones in this population are shown. Sixty-eight percent of isoflavone consumption was attributable to tofu and soy milk. However, because the use of these foods was so infrequent in this population, we were only able to evaluate risk for tofu consumption as never/ever. Overall, there was some suggestion that tofu consumption, even at this low level (mean consumption was 0.2 cups per month for both cases and controls), was associated with a reduction in endometrial cancer risk (OR: 0.68; 95% CI: 0.45–1.03 for ever vs. never consuming tofu). Adding smoking, physical activity, and alcohol to the model essentially did not change estimates. However, additional inclusion of fat and fiber intakes, resulted in modest attenuation of the effect (adjusted OR of ever/never consuming tofu was 0.76; 95% CI: 0.49–1.17). We also conducted continuous analyses (data not shown) for tofu and estimated an OR per 25 g/day of tofu intake of 0.96 (95% CI: 0.36–2.54), adjusted for age, race, education, parity, age at menarche, menopausal status, OC use, HRT use, BMI, and total calories. With further adjustment for physical activity, alcohol, smoking, fat, and fiber, the OR was 1.11 (95% CI: 0.39–3.16) per 25 g per day of intake. There was little evidence of a relationship with any of the other soy foods at these low levels of consumption.

DISCUSSION

Our population-based study of the relationship of major phytoestrogens, including detailed analyses of lignan consumption, with endometrial cancer risk, suggested an inverse association with quercetin intake and with consumption of isoflavones in lean women. There was little evidence of an association with any of the lignans considered or with total lignan intake. Further exploration of the association with the major food sources of isoflavones in this population suggested an inverse association with tofu intake. However, the relationship disappeared after covariates such as physical activity, smoking, and fat and fiber intakes were taken into account.

To our knowledge, the role of phytoestrogen consumption on endometrial cancer risk has been evaluated in only two additional case-control studies. Horn-Ross et al. [9] evaluated the association between several phytoestrogens and endometrial cancer risk in a population-based case-control study (500 cases and 470 controls) among non-Asian women in the San Francisco Bay Area. As in our study, there was little evidence of an association between phytoestrogen intake and endometrial cancer risk. The other case-control study evaluating the association was a population-based study in China with 832 cases and 842 controls [10]. This study focused more on the evaluation of soy foods, but reported on isoflavone consumption and endometrial cancer risk, with similar results to our study. Adjusted ORs for the highest quartile of intake compared to lowest was 0.77 (95% CI: 0.56–1.05; *p* for trend 0.05) in the study in China and 0.80 (95% CI: 0.50–1.27; *p* for trend: 0.29) in our study.

Other epidemiologic studies have focused on the role of foods high in phytoestrogens. Goodman et al. [12] reported inverse associations for tofu, soy products, whole grains, vegetables, fruits, beer, and seaweed in a population-based case-control study in Hawaii. Conceivably, the benefits of consuming these foods may be unrelated to their phytoestrogen content. Furthermore, although the interest in phytoestrogens as anticarcinogenic agents is based primarily on their potential hormonal effects, there is increasing evidence that other non-hormonal mechanisms may be involved, particularly for soy foods. These isoflavonoid compounds may not only influence estrogen metabolism, but may also have antioxidant and antiangiogenesis effects, and may influence signal transduction and inhibit the action of DNA topoisomerases [8]. The study by Xu et al. [10] mentioned above, suggested an inverse association for soy food fiber and soy protein, but little evidence of an association for major sources of phytoestrogen such as soy milk and tofu. A meta-analysis [18] of four case-control studies reporting on tofu and endometrial cancer [10,12,19,20] estimated a summary risk estimate of 0.73 (95% CI: 0.57–0.94) for the highest vs. the lowest category of intake reported. This meta-analysis also estimated an OR of 0.88 (95% CI: 0.78–1.00) per 25 g/day of tofu

intake based on the results of three case-control studies [10,12,20]. Our continuous analysis offered little support for an association with tofu intake at this low level of intake, with an OR of 0.96 per 25 g/day of tofu (95% CI: 0.36–2.54) using a similar model as the studies included in the meta-analysis.

We found the inverse association with isoflavone intake limited to lean women (p for interaction = 0.047), while other studies found a stronger inverse association for the highest category of BMI with isoflavone consumption [9], soy protein consumption [10], or soy product consumption [12]. The interaction in these other studies was not statistically significant and, therefore, additional evidence is needed before conclusions can be drawn regarding possible effect modification by BMI.

A possible alternative explanation to consider in the interpretation of the findings is confounding by other factors that have been shown to affect endometrial cancer risk. For example, it is possible that consumption of phytoestrogens and soy foods is more common among more health conscious women, who may avoid smoking, high fat foods, and consume high-fiber foods, and exercise more. Smoking [21], fiber intake [18], and physical activity [18,22,23] have been shown to decrease endometrial cancer risk, whereas fat intake may increase risk [24]. An inverse association between alcohol consumption and endometrial cancer has also been reported [25]. To rule out these confounding effects, we further adjusted our risk estimates for phytoestrogens for these variables. Further adjustment for these variables seemed to have an impact in our risk estimate associated with tofu intake, but not for isoflavones or quercetin intakes.

The response rate in our study was low. Response rates in epidemiologic studies have been declining over the past 30 years and low response rates are now common in epidemiologic studies [26,27]. Participation rates around 50% in population-based studies are not unusual in recent studies, particularly among controls [27]. It is also well known that participants tend to be more educated and healthier than non-participants [26]. In our study, for cases, we were able to compare those who participated to all women diagnosed with endometrial cancer in these counties in this time period. The cases included were younger and more likely to have localized disease. The mean age of those included was 61.7 yrs., compared to 63.6 yrs. in all women. About 81% of the women included in our study had SEER summary stage classified as localized, compared to 70% in all eligible cases. For controls, we unfortunately do not have any information on those who could not be reached or who refused to participate. We are reassured by the distribution of characteristics that are established risk factors for the disease (e.g., BMI) among cases and controls, with odds ratios for these factors (shown in Table 1) being similar to those reported in the literature, with the exception of estrogen replacement therapy. However, only 8% of cases and controls used ERT, and when we repeated our analyses with phytoestrogens excluding unopposed estrogen users, our results did not change. Furthermore, non-response bias would only affect study validity if willingness to participate is related to the factors under evaluation [26,27]. This is unlikely because the possible role of dietary factors in the etiology of endometrial cancer is not well known, and even less so that of phytoestrogens and soy foods. Also, the fact that our results are in agreement with the current literature provides further reassurance.

Given the popular use of alternative therapies to relieve menopausal symptoms, and the potential effects of phytoestrogens on the endometrium, we asked women questions about the use of phytoestrogen or soy supplements (pills and powders). However, the use of these supplements was rare in this population, and the few women who used them, did so very infrequently. Therefore, we were unable to assess whether the use of phytoestrogen supplements has any impact on endometrial cancer risk. Randomized controlled clinical trials have offered inconsistent results on the effect of isoflavones on menopausal symptoms, and

little evidence of an impact on endometrial thickness (reviewed by Murray et al.[28]). However, these studies were generally based on small numbers and short-term interventions. Therefore, the impact, either detrimental or beneficial, of isoflavone supplementation on the endometrium and endometrial cancer risk remains uncertain.

Studies of phytoestrogens confront not only the usual difficulties in accurately measuring dietary intake, but also the high inter- and intra-individual differences in phytoestrogen metabolism due to a variety of factors ranging from the use of antibiotics, intestinal transit time, gut microflora, and genetic polymorphisms [3]. Furthermore, food sources of phytoestrogens may vary in different populations, making international comparisons difficult. As expected, isoflavone intake levels were very low in our population. On the other hand, lignan consumption levels were higher than in the only other study evaluating lignans and endometrial cancer risk [9]. Although our study provided little evidence of a major role of phytoestrogens on endometrial cancer risk, further studies are needed, particularly prospective studies, in populations with a wider range of isoflavone intake, as may be typical in Asian populations.

Another issue to consider in evaluating results is the fact that, while phytoestrogens are capable of binding to two types of estrogen receptors (ER), ER alpha and ER beta, they have been shown to preferentially bind to ER beta, whereas the endometrium contains mostly ER alpha [29]. This may explain the limited evidence found showing an effect for phytoestrogen supplementation on endometrial thickness [28], endometrial hyperplasia [28,30], or endometrial cancer [9].

To our knowledge our study is the first epidemiologic study to evaluate the role of quercetin on endometrial cancer risk. The flavonoid quercetin is found in many foods, including vegetables, fruits, tea, wine, but is particularly high in onions, apples, and green tea [31]. Although included in the phytoestrogen group [7], quercetin is well-known for its strong antioxidant and anti-inflammatory activities [31]. There is some epidemiologic evidence showing beneficial effects of quercetin intake on cancers of the lung [32,33], colon and rectum [34], stomach [35], and prostate [36]. However, other studies failed to find an association with breast [37], ovarian [38], and colorectal cancers [39]. Although our findings will have to be confirmed by other studies, our results contribute to the epidemiologic literature of quercetin intake and cancer risk, by supporting beneficial effects for endometrial cancer.

In summary, our study provided little evidence that phytoestrogen consumption, at the levels consumed in non-Asian populations, had an impact on endometrial cancer risk. However, it does not rule out a possible effect at higher levels of consumption. The possible effect modification by body size and adiposity needs further evaluation. Our results suggest that diets high in quercetin may favor a reduction in endometrial cancer risk. Overall, the currently available evidence is too limited to draw any conclusions on the role of phytoestrogens and soy foods on endometrial cancer risk.

Abbreviations

OR, Odds Ratio; CI, Confidence Interval; FFQ, food frequency questionnaire; BMI, body mass index; WHR, waist-to-hip ratio; HRT, hormone replacement therapy; ERT, estrogen replacement therapy; OC, oral contraceptives.

Acknowledgments

We thank the interviewers and students who were involved in this study (Silvia Brendel, Dina Gifkins, Nora Geraghty, June Kittredge, Elinor Miller, Louise Salant, Mathilde Saxon, Elizabeth Ward, Doreen Wass, Kay Yoon), the New

Jersey Department of Health and Senior Services personnel (Tara Blando, Joan Kay, Betsy Kohler, Kevin Masterson, and Helen Weiss), as well as all the participants who generously donated their time to the study.

Funding: This work was funded by NIH-K07 CA095666 and R01CA83918.

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Table 1
Selected characteristics of women participating in The EDGE Study, New Jersey.

	Cases (n=417) n (%)	Controls (n=395) n (%)	OR (95% CI)*
Education			
High school or less	154	134	1.00 (Ref)
College	183	158	0.92 (0.66–1.27)
Graduate school	80	103	0.60 (0.41–0.88)
Race/ethnicity			
White	355	349	1.00 (Ref)
Black	36	17	1.96 (1.08–3.57)
Other	10	16	0.54 (0.24–1.21)
Hispanic (any race)	15	11	1.14 (0.51–2.54)
BMI			
Normal (<25)	105	189	1.00 (Ref)
Overweight (25–29.9)	121	119	1.94 (1.36–2.75)
Obese (30–34.9)	68	62	2.02 (1.32–3.08)
Very obese (≥35)	123	25	8.47 (5.16–13.89)
Parity			
0–1	147	92	1.00 (Ref)
2	142	140	0.64 (0.45–0.90)
≥3	128	163	0.53 (0.37–0.76)
Smoking status			
Never	231	207	1.00 (Ref)
Past	159	148	0.97 (0.72–1.30)
Current	27	38	0.58 (0.34–0.98)
Oral contraceptive use			
Never	224	199	1.00 (Ref)
Ever	193	196	0.69 (0.51–0.93)
Use of HRT			
Never	335	291	1.00 (Ref)
Unopposed E only	34	31	0.97 (0.58–1.63)
Any combined HRT	48	73	0.54 (0.36–0.81)

	Cases (n=417) n (%)	Controls (n=395) n (%)	OR (95% CI) *
Age at menarche			
>13	74	102	0.66 (0.46–0.95)
12–13	233	198	1.00 (Ref)
≤11	109	94	0.93 (0.66–1.31)
Menopause status			
Premenopausal	59	48	0.71 (0.42–1.24)
Postmenopausal			
Age at menopause			
<40	13	12	0.97 (0.43–2.21)
41–54	254	243	1.00 (Ref)
≥55	41	39	1.11 (0.68–1.80)
Unknown	50	53	0.91 (0.59–1.40)

* Adjusted for age

Table 2

Mean phytoestrogen intake from food sources in cases and controls.

Compound (mcg/1000kcal)*	Cases Mean (SD)	Controls Mean (SD)	p value (t-test)
Total isoflavones	786.3 (2370.9)	1105.6 (2643.60)	0.070
Daidzein	298.0 (892.43)	428.1 (1018.00)	0.053
Genistein	455.2 (1410.90)	632.3 (1556.10)	0.089
Formononetin	6.0 (6.34)	6.8 (5.02)	0.044
Glycitein	27.1 (95.32)	38.2 (103.67)	0.112
Total lignans	624.8 (566.82)	637.4 (603.88)	0.759
Matairesinol	5.7 (3.08)	5.5 (3.43)	0.448
Lariciresinol	36.7 (19.29)	39.3 (20.65)	0.062
Pinoresinol	28.6 (21.61)	30.4 (20.00)	0.225
Secoisolariciresinol	553.8 (561.19)	562.2 (602.00)	0.837
Coumestrol	0.8 (0.56)	0.9 (0.56)	0.139
Quercetin *	1300.1 (444.23)	1369.7 (570.96)	0.052
Total phytoestrogens	1411.7 (2420.10)	1743.6 (2700.40)	0.065
Total calories (kcal)	1663.5 (796.13)	1590.0 (644.14)	0.150

* Quercetin in mg/1,000 kcal

Table 3

Table 3a. Phytoestrogen intake from food sources and endometrial cancer risk in The EDGE Study: Main phytoestrogens

	Cases (n)	Controls (n)	OR1	95% confidence interval	OR2	95% confidence interval
Total Isoflavones (mcg/1000 kcal)						
1 (< 55.3)	106	98	1.00		1.00	
2 (55.3–131.3)	114	99	0.99	(0.64–1.52)	0.99	(0.64–1.53)
3 (131.4–666.0)	119	99	0.95	(0.62–1.46)	0.95	(0.61–1.46)
4 (> 666.0)	78	99	0.77	(0.49–1.22)	0.80	(0.50–1.27)
<i>p</i> for trend				0.21		0.29
Total lignans (mcg/1000 kcal)						
1 (<215.5)	112	98	1.00		1.00	
2 (215.5–448.9)	92	99	0.83	(0.53–1.28)	0.85	(0.55–1.33)
3 (449.0–839.3)	109	99	0.97	(0.63–1.49)	0.99	(0.64–1.53)
4 (> 839.3)	104	99	0.95	(0.62–1.46)	0.99	(0.64–1.53)
<i>p</i> for trend				0.90		0.80
Coumestrol (mcg/1000 kcal)						
1 (<0.5)	108	99	1.00		1.00	
2 (0.5–0.79)	150	112	1.56	(1.03–2.37)	1.55	(1.01–2.36)
3 (0.8–1.2)	83	99	1.18	(0.75–1.85)	1.14	(0.72–1.80)
4 (>1.2)	76	85	1.16	(0.73–1.86)	1.15	(0.71–1.87)
<i>p</i> for trend				0.88		0.85
Total phytoestrogens (mcg/1000 kcal)						
1 (<401.4)	109	99	1.00		1.00	
2 (401.4–857.2)	111	99	0.98	(0.64–1.51)	0.98	(0.63–1.51)
3 (857.3–1657.7)	103	99	0.95	(0.62–1.46)	0.94	(0.61–1.45)
4 (>1657.7)	94	98	0.93	(0.60–1.45)	0.98	(0.63–1.53)
<i>p</i> for trend				0.76		0.95

Table 3b. Phytoestrogen intake from food sources and endometrial cancer risk in The EDGE Study: Specific phytoestrogens

		Cases (n)	Controls (n)	OR1	95% confidence interval	OR2	95% confidence interval
ISOFLAVONES							
Daidzein (mcg/1000 kcal)							
1 (<15.7)	106	94	1.00		1.00		
2 (15.7–42.1)	111	101	0.90	(0.58–1.39)	0.93	(0.60–1.44)	
3 (42.2–269.9)	126	100	0.94	(0.61–1.44)	0.95	(0.62–1.47)	
4 (> 269.9)	74	98	0.70	(0.44–1.12)	0.73	(0.46–1.18)	
<i>p</i> for trend				0.14		0.20	
Genistein (mcg/1000 kcal)							
1 (< 30.5)	106	99	1.00		1.00		
2 (30.5–76.3)	112	98	0.96	(0.63–1.48)	0.97	(0.63–1.50)	
3 (76.4–369.6)	117	99	0.96	(0.62–1.46)	0.95	(0.62–1.47)	
4 (> 369.6)	82	99	0.78	(0.49–1.23)	0.80	(0.50–1.28)	
<i>p</i> for trend				0.24		0.32	
Formononetin (mcg/1000 kcal)							
1 (<3.4)	112	98	1.00		1.00		
2 (3.4–4.99)	142	96	1.48	(0.97–2.25)	1.48	(0.96–2.27)	
3 (5.0–8.49)	97	102	1.09	(0.70–1.70)	1.08	(0.69–1.71)	
4 (≥ 8.5)	66	99	1.06	(0.65–1.74)	1.11	(0.64–1.93)	
<i>p</i> for trend				0.59		0.83	
Glycitein (mcg/1000 kcal)							
1 (<1.9)	113	103	1.00		1.00		
2 (1.90–3.19)	107	90	1.14	(0.74–1.76)	1.20	(0.77–1.86)	
3 (3.2–19.29)	122	104	1.08	(0.72–1.64)	1.09	(0.71–1.66)	
4 (> 19.3)	75	98	0.82	(0.52–1.30)	0.87	(0.54–1.39)	
<i>p</i> for trend				0.18		0.25	

Table 3b. Phytoestrogen intake from food sources and endometrial cancer risk in The EDGE Study: Specific phytoestrogens

	Cases (n)	Controls (n)	OR1	95% confidence interval	OR2	95% confidence interval
LIGNANS						
Matairesinol (mcg/1000 kcal)						
1 (< 3.6)	97	100	1.00		1.00	
2 (3.6–4.89)	105	100	1.08	(0.70–1.67)	1.08	(0.70–1.68)
3 (4.9–6.29)	86	94	1.04	(0.66–1.61)	1.02	(0.65–1.61)
4 (> 6.3)	129	101	1.25	(0.82–1.91)	1.29	(0.84–2.00)
<i>p</i> for trend				0.31		0.25
Lariciresinol (mcg/1000 kcal)						
1 (< 25.2)	131	99	1.00		1.00	
2 (25.2–33.9)	93	99	0.82	(0.53–1.26)	0.87	(0.56–1.34)
3 (34.0–47.2)	99	99	0.89	(0.58–1.37)	0.91	(0.59–1.41)
4 (> 47.2)	94	98	0.89	(0.58–1.39)	0.97	(0.62–1.52)
<i>p</i> for trend				0.78		0.97
Pinoresinol (mcg/1000 kcal)						
1 (< 16.6)	127	98	1.00		1.00	
2 (16.6–25.6)	104	102	1.00	(0.65–1.53)	1.00	(0.64–1.54)
3 (25.7–37.5)	88	96	1.00	(0.64–1.56)	1.00	(0.64–1.56)
4 (> 37.5)	98	99	1.07	(0.69–1.66)	1.07	(0.68–1.67)
<i>p</i> for trend				0.74		0.74
Secoisolariciresinol (mcg/1000 kcal)						
1 (< 141.3)	110	98	1.00		1.00	
2 (141.3–364.2)	91	99	0.77	(0.49–1.20)	0.81	(0.52–1.27)
3 (364.3–749.3)	106	99	0.95	(0.62–1.47)	0.99	(0.64–1.53)
4 (> 749.3)	110	99	0.99	(0.64–1.51)	1.04	(0.67–1.60)
<i>p</i> for trend				0.66		0.56

Table 3b. Phytoestrogen intake from food sources and endometrial cancer risk in The EDGE Study: Specific phytoestrogens

	Cases (n)	Controls (n)	OR1	95% confidence interval	OR2	95% confidence interval
COUMESTAN						
Coumestrol (mcg/1000 kcal)						
1 (<0.5)	108	99	1.00		1.00	
2 (0.5–0.79)	150	112	1.56	(1.03–2.37)	1.55	(1.01–2.36)
3 (0.8–1.2)	83	99	1.18	(0.75–1.85)	1.14	(0.72–1.80)
4 (>1.2)	76	85	1.16	(0.73–1.86)	1.15	(0.71–1.87)
p for trend				0.88		0.85
FLAVONONIDS						
Quercetin (mg/1000 kcal)						
1 (<1083.6)	121	98	1.00		1.00	
2 (1083.6–1289.7)	118	100	1.03	(0.68–1.57)	1.00	(0.65–1.53)
3 (1289.8–1507.8)	88	99	0.67	(0.44–1.04)	0.63	(0.40–0.99)
4 (> 1507.8)	90	98	0.68	(0.44–1.05)	0.65	(0.41–1.01)
p for trend				0.03		0.02

OR1: adjusted for age (continuous), education, race, age at menarche (continuous), menopausal status and age at menopause for postmenopausal women, parity, OC use, HRT use, BMI (continuous), and total calories (see methods for details).

OR2: further adjusted for physical activity (METs), smoking status, and alcohol (g/1000 kcal)

Table 4
Total phytoestrogen and isoflavone intakes and endometrial cancer risk by body mass index, waist-to-hip ratio, and HRT use.

Stratifying variable	Cases/controls	Total phytoestrogens (tertiles in mcg/1000 kcal)			Total isoflavones (tertiles in mcg/1000 kcal)		
		T1 (<545.9)	T2 (545.9–1275.7)	T3 (>1275.7)	T1 (<71.7)	T2 (71.7 – 405.3)	T3 (>405.3)
Body mass index							
<25	105/189	1.00	1.01 (0.53–1.92)	0.72 (0.37–1.39)	1.00	0.69 (0.35–1.32)	0.50 (0.25–0.98)
Overweight (25–29.9)	121/119	1.00	1.40 (0.69–2.86)	1.34 (0.67–2.68)	1.00	0.79 (0.39–1.60)	1.10 (0.54–2.24)
Obese (>30)	191/87	1.00	0.62 (0.30–1.26)	0.78 (0.36–1.71)	1.00	1.84 (0.92–3.68)	0.91 (0.42–1.98)
p for interaction				0.28			<0.05
Waist-to-hip ratio*							
≤0.85	177/217	1.00	0.86 (0.50–1.49)	0.84 (0.48–1.47)	1.00	0.94 (0.54–1.63)	0.59 (0.33–1.05)
>0.85	229/172	1.00	1.08 (0.63–1.85)	1.05 (0.60–1.84)	1.00	1.09 (0.64–1.86)	1.05 (0.59–1.86)
p for interaction				0.77			0.23
HRT use							
Never users	335/291	1.00	0.92 (0.59–1.41)	0.90 (0.58–1.41)	1.00	1.09 (0.71–1.69)	0.79 (0.50–1.27)
ERT and HRT users	82/104	1.00	1.18 (0.54–2.59)	1.13 (0.50–2.57)	1.00	1.03 (0.46–2.31)	1.00 (0.45–2.22)
p for interaction				0.70			0.86

Adjusted for age (continuous), education, race, age at menarche (continuous), menopausal status and age at menopause for postmenopausal women, parity, OC use, HRT use (for stratified analyses by BMI and WHR), BMI (continuous), and total calories.

^{*} 11 cases and 6 controls had missing values for waist-to-hip ratio.

Table 5

Endometrial cancer risk associated with major isoflavones food sources in this population.

Ever vs. Never	Cases n (%) ever use	Controls n (%) ever use	OR [*]	95% Confidence Interval
Tofu	65 (15.9%)	86 (22.1%)	0.68	(0.45–1.03)
Soy beans	45 (11.0%)	67 (17.2%)	0.82	(0.52–1.29)
Soy milk	52 (12.8%)	60 (15.5%)	0.85	(0.55–1.33)
Miso	62 (15.7%)	64 (16.9%)	1.31	(0.83–2.07)
Meat substitutes	115 (28.0%)	122 (31.4%)	0.93	(0.66–1.30)

* Adjusted for age, race, education, age at menarche, menopausal status and age at menopause for postmenopausal women, parity, OC use, HRT use, BMI, and total calories (see methods for details).

Appendix- Additional food items in the supplemental page, not included in the Block Food Frequency Questionnaire (version 98.2)

Soy yogurt
Frozen soy yogurt
Soy ice cream
Soy cheese
Soy hot dogs/cold cuts
Other soy meat substitutes
Cooked soybeans or edamame
Roasted soy nuts
Tempeh
Miso soup
Alfalfa sprouts
Soybean sprouts
Protein powders made from soy protein isolate
Soy milk *
Green tea
Garbanzo beans, chick peas, ceci beans or hummus
Dried fruit (e.g., apricots, raisins, prunes)
Seaweed
Sunflower seeds
Black licorice

* Soy milk is included in the Block FFQ but it was included again in the supplemental foods page.