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ARTICLE

Legume, Soy, Tofu, and Isoflavone Intake and Endometrial Cancer Risk in Postmenopausal Women in the Multiethnic Cohort Study

Nicholas J. Ollberding, Unhee Lim, Lynne R. Wilkens, Veronica Wendy Setiawan, Yurii B. Shvetsov, Brian E. Henderson, Laurence N. Kolonel, Marc T. Goodman

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Correspondence to: Nicholas J. Ollberding, PhD, University of Hawaii Cancer Center, 1236 Lauhala St, Ste 407E, Honolulu, HI 96813 (e-mail: nollberding@cc.hawaii.edu).

Background Phytochemicals found in soy and other legumes have been speculated to reduce the risk of endometrial cancer; however, inconsistent findings have been reported in the few epidemiological studies conducted to date.

Methods We conducted a prospective analysis of 46 027 nonhysterectomized postmenopausal women who were recruited into the Multiethnic Cohort (MEC) Study between August 1993 and August 1996 and provided detailed baseline information on diet and other endometrial cancer risk factors. A total of 489 women diagnosed with incident endometrial cancer were identified through the Surveillance, Epidemiology, and End Results tumor registry linkages during a median follow-up period of 13.6 years. Cox proportional hazards models were used to estimate multivariable-adjusted relative risks (RRs) and 95% confidence intervals (CIs) for endometrial cancer associated with dietary intake of legumes, soy, and tofu, and for total isoflavones and specific isoflavones (daidzein, genistein, or glycitein). Truncated (age 50–89 years) age-adjusted incidence rates were calculated by applying age-specific rates within isoflavone quintiles to the overall MEC population eligible for endometrial cancer. To estimate the percentage of endometrial cancers that may have been prevented by consuming the highest quintile of total isoflavones, the partial population attributable risk percent was calculated.

Results A reduced risk of endometrial cancer was associated with total isoflavone intake (highest vs lowest quintile, ≥7.82 vs <1.59 mg per 1000 kcal/d, RR = 0.66, 95% CI = 0.47 to 0.91), daidzein intake (highest vs lowest quintile, ≥3.54 vs <0.70 mg per 1000 kcal/d, RR = 0.64, 95% CI = 0.46 to 0.90), and genistein intake (highest vs lowest quintile, ≥3.40 vs <0.69 mg per 1000 kcal/d, RR = 0.66, 95% CI = 0.47 to 0.91). No statistically significant association with endometrial cancer risk was observed for increasing intake of legumes, soy, tofu, or glycitein. Truncated age-adjusted incidence rates of endometrial cancer for the highest vs lowest quintile of total isoflavone intake were 55 vs 107 per 100 000 women per year, respectively. The partial population attributable risk percent for total isoflavone intake lower than the highest quintile was 26.7% (95% CI = 5.3% to 45.8%).

Conclusion This study suggests that greater consumption of isoflavone-containing foods is associated with a reduced risk of endometrial cancer in this population of nonhysterectomized postmenopausal women.

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Endometrial cancer is the most common gynecologic malignancy in the United States, with an estimated 43 470 new cancers diagnosed and 7950 deaths occurring annually (1,2). International variation in the rates of endometrial cancer incidence, coupled with the increased rates among Asian women migrating to the United States, suggests that modifiable risk factors may be important in the etiology of this disease (3,4). Established risk factors for endometrial cancer include unopposed estrogen therapy (estrogen therapy alone without progesterone), earlier age at menarche, later age at menopause, nulliparity, obesity, diabetes, and hypertension (5–8). It has been hypothesized that many of these factors increase risk by prolonging uterine exposure to the proliferative effects of unopposed estrogen (9). By contrast, tobacco smoking and oral contraceptive use may reduce circulating estrogen levels and have been associated with reductions in endometrial cancer risk (8).

Isoflavones, a class of nonsteroidal plant-based polyphenols found in legumes and in especially high concentrations in soy, are structurally similar to estrogen and are thought to have both estrogenic and antiestrogenic properties (10). Although the physiological effects of isoflavones in vivo have yet to be fully elucidated, they have been reported to bind to both α and β estrogen receptors (10), stimulate steroid hormone–binding globulin production (11),

CONTEXTS AND CAVEATS

Prior knowledge

Population-based case–control studies in Asian or largely Asian populations have reported that higher intake of legumes and soy are associated with reduced risk of endometrial cancer, but a prospective study conducted in the United States found no association with higher legume intake. Prospective studies of total or specific isoflavones have not been conducted.

Study design

Prospective analysis of nonhysterectomized postmenopausal women from the Multiethnic Cohort Study for associations between endometrial cancer risk and dietary intake of total and specific isoflavones (daidzein, genistein, or glycitein) and intake of legumes, soy, and tofu.

Contribution

Highest quintiles of total isoflavone, daidzein, and genistein intake were associated with a reduced relative risk of endometrial cancer by 34%, 36%, and 34%, respectively, compared with lowest intake quintile. The truncated age-adjusted incidence rates of endometrial cancer for the highest and lowest quintile of total isoflavone intake were 55 and 107 per 100 000 women per year, respectively. No association was found for increasing intake of legumes, soy, tofu, or glycitein.

Implication

Study supports an association between higher intake of isoflavone-containing foods and reduced risk of endometrial cancer in nonhysterectomized postmenopausal women. However, a large proportion of isoflavones in the diet may be derived from nontraditional soy-based food items.

Limitations

Findings are based on baseline data, and dietary changes over time were not known. Residual confounding cannot be ruled out because of the large variation in soy and isoflavone intake across racial or ethnic groups.

From the Editors

and inhibit aromatase (12), all of which may reduce uterine exposure to circulating estrogen.

Few epidemiological studies have examined associations of dietary soy or isoflavone intake with endometrial cancer risk. Population-based case–control studies have reported increased soy (13,14) and legume (13,15) consumption to be associated with a lower risk of endometrial cancer, although associations with total or specific isoflavones have not been detected (14,16,17). Although data from prospective studies are lacking regarding an influence of dietary soy and isoflavones on endometrial cancer risk, higher legume intake was not found to be associated with a reduced risk of disease in a prospective study of 41 000 US women of predominately white race (18). In this analysis, we examined whether the consumption of legumes, soy, or tofu and the estimated intakes of total isoflavones or the specific isoflavones daidzein, genistein, or glycitein were associated with the risk of endometrial cancer among nonhysterectomized postmenopausal women using data from a large multiethnic cohort with relatively high intakes of these dietary components.

Subjects and Methods

Study Cohort

The Multiethnic Cohort (MEC) Study is a longitudinal study designed to investigate associations between dietary, lifestyle, and genetic factors and the incidence of cancer and has been described previously in detail (19). Briefly, 215 831 men and women residing in Hawaii or California (primarily Los Angeles County), aged 45–75 years at the time of recruitment between August 1993 and August 1996 entered the cohort. Potential participants were identified through drivers' license files, voter registration lists, and Health Care Financing Administration data files to obtain a multiethnic sample of African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites. Participants completed a self-administered 26-page baseline questionnaire that included queries on demographic characteristics, anthropometric measures, medical history, family history of cancer, reproductive and menstrual history, cancer screening practices, occupational history, physical activity, and detailed questions on diet. The study protocol was approved by the Institutional Review Boards of the University of Hawaii and the University of Southern California.

Of the 91 156 postmenopausal women enrolled in the cohort, the current analysis included 46 027 women after excluding the following: those who reported a hysterectomy or bilateral oophorectomy at baseline (n = 36 211), were not in one of the five main racial or ethnic groups recruited into the study (n = 4033), reported implausible values for energy intake or macronutrients (20) (n = 1987), had missing data on any of the following key covariates—body mass index, age at menarche, age at menopause, parity, oral contraceptive use, hormone therapy use, smoking status, hypertension, or diabetes (n = 2225)—or were identified through either the questionnaire or tumor registry linkage to have had a diagnosis of endometrial cancer before entry into the cohort (n = 673). A slightly higher proportion of African American and Latino women and hormone replacement therapy users were excluded. Retained women were otherwise similar to those excluded with respect to other endometrial cancer risk factors.

Follow-up and Identification of Endometrial Cancers

Follow-up began on the date of questionnaire completion or the 45th birth anniversary for the less than 1% of participants who were younger than 45 years of age at enrollment and accrued until either diagnosis of endometrial cancer, death, or the last follow-up date for this analysis (December 31, 2007). Incident endometrial cancers were identified through routine linkages to the Surveillance, Epidemiology, and End Results (SEER) cancer registries for Hawaii (Hawaii Tumor Registry) and California (Cancer Surveillance Program for Los Angeles County and California State Cancer Registry). Deaths were ascertained through routine linkages to death certificate files in Hawaii and California, as well as to the National Death Index to identify deaths among emigrants to other parts of the United States. Incident endometrial cancers were classified according to the *International Classification of Diseases for Oncology*, *Third Edition* code C54.1 (endometrium) and were restricted to invasive carcinomas. Histologically verified uterine sarcomas (n = 44) and other cancers of the corpus uteri (n = 65) were censored at the date of diagnosis for this analysis, resulting in

489 incident endometrial cancers identified during a median follow-up period of 13.6 years. Type 1 and type 2 endometrial cancers (based on histology, grade, and stage) could not be specifically examined because for many of the cancer patients in the SEER database, the information on grade and/or stage was incomplete.

Dietary Assessment

Dietary intake was assessed at baseline using a Quantitative food-frequency questionnaire (QFFQ) that obtained frequency and quantity information on food items consumed during the preceding year (19). Items included on the questionnaire were the minimum set that could capture 85% or higher of the intake of key nutrients for each racial or ethnic group, as well as traditional foods consumed by each racial or ethnic group in the study. As previously reported (21), total soy intake was estimated from QFFQ items on miso, tofu, and vegetarian meat. Legume intake was estimated from items on single legumes and from mixed dishes. Food and nutrient intakes were calculated using food composition tables maintained by the University of Hawaii Cancer Center (19), which include detailed information on isoflavone levels in foods consumed by the racial or ethnic groups represented in the MEC (22,23). Total isoflavone intake was calculated as the sum of the specific isoflavones daidzein, genistein, and glycitein. The energy-adjusted Pearson correlation coefficient measured from the questionnaire and multiple 24-hour recalls was 0.50 for total isoflavones among women in a previous calibration study of greater than 2000 individuals (24).

Statistical Analysis

Cox proportional hazards models with age as the time metric were used to calculate relative risks (RRs) and 95% confidence intervals (CIs) for endometrial cancer. Foods and constituents (isoflavones) were examined as densities (per 1000 kcal) and constituents as calibration-adjusted densities, because correlations between nutrient estimates from the QFFQ and 24-hour recalls improved after energy-adjustment in our previous calibration study (24). Dietary exposures were divided into quintiles for legumes, tofu, total isoflavones, daidzein, genistein, and glycitein based on the distribution of all women in the cohort. Because a substantial proportion of women in the cohort reported no soy intake (46%), five categories were created to compare women who reported no soy intake (quintile 1) with the quartile distribution of those reporting any soy intake (quintiles 2–5). The lowest intake group served as the referent in all models. Linear trends were tested by entering the appropriate quintile median as a continuous variable in regression models. The heterogeneity of associations between diet and endometrial cancer across the racial or ethnic groups included in the MEC were tested by a Wald test of the cross-product terms. The assumption of proportional hazards was found to be satisfied in all models by examining the relationship of scaled Schoenfeld residuals and time. For each isoflavone quintile, absolute risk estimates were created within 5-year age groups (from age 50–54 to ≥85 years) as the number of cancers diagnosed in the age group divided by the number of person-years attributed to that group. A truncated age-adjusted rate was created by applying the age-specific rates to the overall MEC population eligible for endometrial cancer (all nonhysterectomized women). We also modeled nonlinear relations of dietary exposures to the risk of endometrial cancer nonparametrically with restricted cubic splines (25). Tests for nonlinearity were performed using the likelihood ratio test comparing the model with only the linear term to the model with the linear and the cubic spline terms. In no model was the addition of the cubic spline terms found to improve model fit ($P \geq .05$ for the two-sided likelihood ratio test). Therefore, only the results for linear models entering dietary exposures as natural log-transformed continuous variables are shown.

Basic models adjusted for race or ethnicity as a stratum variable and age at cohort entry as a continuous variable in the log-linear model component. Multivariable models further adjusted for body mass index, age at menarche (≤12, 13–14, ≥15 years), age at menopause (<45, 45–49, 50–54, ≥55 years), duration and type of hormone therapy use (never estrogen use, past estrogen use, current unopposed estrogen use, current estrogen plus progesterone use), oral contraceptive use (<1, 1–5, >5 years), parity (nulliparous, 1, 2–3, ≥4 children), smoking status (never, former, current), hypertension (no, yes), and diabetes (no, yes) in the log-linear model component to examine the potential confounding effects of established risk factors on the associations between diet and endometrial cancer. Physical activity and family history of endometrial cancer were also examined as potential covariates but were not included in the final models as they were not found to change risk estimates for associations between diet and endometrial cancer by greater than 10% (standard cut point when assessing confounding effects in observational studies). Food items including fruits, vegetables, red meat, dietary fiber, total fat, and total sugars were also examined as potential confounders by including them individually as covariates in proportional hazards models and by assessing their associations with the risk of endometrial cancer. Results from these models are not presented here as they were not found to be associated with the risk of endometrial cancer or to change risk estimates for associations between diet and endometrial cancer by greater than 10%. Models were also constructed to assess whether the association of total isoflavone intake with the risk of endometrial cancer could be explained by the consumption of the 10 food items with the greatest contribution to total isoflavone levels among women in the MEC including stir-fried vegetables (14.4%), tofu (11.2%), stir-fried chicken (10.7%), stir-fried beef or pork (9.9%), boiled dried beans (8.5%), sweet rolls (7.2%), miso soup (5.7%), chili (5.3%), fortified diet beverages (4.9%), and vegetarian meat loaf (3.2%).We also performed lag analyses excluding women diagnosed with endometrial cancer within 2 years of completing the baseline questionnaire.

As a result of the large variation in dietary intakes across racial or ethnic groups, we performed analyses examining the association between diet and endometrial cancer stratified by race or ethnicity. For these analyses, we modeled quartiles based on the exposure distribution of all women (common cut points) as well as quartiles based on the exposure distribution within each racial or ethnic group (racial- or ethnic-specific cut points). To increase the precision for these stratified analyses, participants in quartiles 1–3 were collapsed to serve as the referent group and were contrasted against women in the fourth intake quartile (collapsed–categorical analysis). Risk estimates were not calculated separately for Native Hawaiians because of the limited number of women with

endometrial cancer. Analyses stratified by endometrial cancer risk factors were not conducted as the number of endometrial cancers was too low to provide stable risk estimates. The partial population attributable risk percent and 95% confidence intervals, estimating the fraction of endometrial cancers attributable to isoflavone intake below the fifth quintile of exposure, while controlling for the endometrial cancer risk factors included in the multivariable models, were estimated using the publicly available %PAR SAS macro developed by Spiegelman et al. (26). All statistical tests were two-sided, and *P* values less than .05 were considered statistically significant. All data analyses were performed using SAS 9.2 statistical software (SAS Institute Inc, Cary, NC).

Results

Demographic characteristics and the distribution of endometrial cancer risk factors by quintile of total isoflavone intake are given in Table 1. The racial or ethnic composition of women in the highest quintile of total isoflavone intake was Japanese American (60.2%), Latina (20.3%), white (8.6%), Native Hawaiian (5.8%), and African American (5.2%). A lower proportion of women in the highest quintile of isoflavone intake reported being overweight or obese, using oral contraceptives, or currently smoking, partially reflecting the racial or ethnic composition of these women. Few differences in the distribution of other endometrial cancer risk factors were observed across levels of total isoflavone intake. Risk of endometrial cancer was confirmed to be lower among women reporting a greater duration of oral contraceptive use and parity and higher among overweight or obese women and those reporting later age menopause, current unopposed estrogen use, or a history of hypertension. The truncated age-adjusted incidence rates of endometrial cancer for the lowest to highest quintiles of total isoflavone intake were 107 (quintile 1, <1.59 mg per 1000 kcal/d), 85 (quintile 2, 1.59–3.00 mg per 1000 kcal/d), 98 (quintile 3, 3.01–4.77 mg per 1000 kcal/d), 79 (quintile 4, 4.78–7.81 mg per 1000 kcal/d), and 55 (quintile 5, ≥7.82 mg per 1000 kcal/d) per 100 000 women per year.

The relative risks of endometrial cancer according to quintiles of legume, soy, tofu, total isoflavone, daidzein, genistein, and glycitein intake are presented in Table 2. In both basic and risk factor–adjusted (multivariable) models, the highest quintiles for density-adjusted intake of total isoflavones, daidzein, and genistein were associated with a reduced risk of endometrial cancer compared with the lowest intake quintiles. In multivariable models, total isoflavone intake was associated with a 34% reduced risk (highest vs lowest quintile, ≥7.82 vs <1.59 mg per 1000 kcal/d, RR = 0.66, 95% CI = 0.47 to 0.91), daidzein intake was associated with a 36% reduced risk (highest vs lowest quintile, ≥3.54 vs <70 mg per 1000 kcal/d, RR = 0.64, 95% CI = 0.46 to 0.90), and genistein intake was associated with a 34% reduced risk (highest vs lowest quintile, ≥3.40 vs <0.69 mg per 1000 kcal/d, RR = 0.66, 95% CI = 0.47 to 0.91) of endometrial cancer. In both basic and multivariable models, statistically significant linear trends were observed between the risk of endometrial cancer and intake of total isoflavones (P_{trend} = .02), daidzein (P_{trend} = .01), and genistein (P_{trend} = .02). Similar inverse associations with endometrial cancer risk were also observed for density-adjusted intakes of total isoflavones (the log of the unit change in relative risk per unit change in log isoflavone density [β] = −0.13, *P* = .07), daidzein (β = −0.17, *P* = .06), and genistein (β = −0.18, *P* = .07) when values were entered as log-transformed continuous variables in the multivariable models (data not shown). No statistically significant associations were detected for total soy, legumes, tofu, or glycitein in any model examined or for the 10 food items with the greatest contribution to total isoflavone levels (data not shown). Risk estimates for calibration-adjusted nutrient densities were found to be similar to density-adjusted estimates in all models; however, non-statistically significant associations with risk were obtained for all dietary exposures when entered as absolute intakes (data not shown). Relative risks for endometrial cancer were similar for basic and multivariable models, indicating no substantial confounding effects by established risk factors on the associations between diet and endometrial cancer. Tests for heterogeneity of effect suggested no difference in the associations between diet and endometrial cancer by race or ethnicity ($P_{hereogeneity}$ > .10).

Next, we performed analyses examining the association between diet and endometrial cancer stratified by race or ethnicity using a collapsed–categorical approach, comparing women in the highest intake quartile with women with lower intakes of the foods and nutrients of interest (Table 3). Associations between diet and endometrial cancer were generally found to be consistent across the racial or ethnic groups included in the MEC, although previously statistically significant associations for total isoflavones, daidzein, and genistein, as shown in Table 2, were attenuated in this analysis. Similar results were obtained when we assessed associations using racial- or ethnic-specific cut points (data not shown).

The partial population attributable risk percent was used to estimate the proportion of endometrial cancers that may have been avoided in the cohort during the follow-up period by the elimination of low total isoflavone intake, assuming that associations for other risk factors remained unchanged. If all women in the MEC were to have increased their total isoflavone intake to the level of those in the highest quintile (≥7.82 mg per 1000 kcal/d), an estimated 26.7% (95% CI = 5.3% to 45.8%) of endometrial cancers may have been prevented.

Discussion

In this study, in a large multiethnic cohort of women from the MEC Study who were followed for a median period of 13.6 years, we found a lower risk of endometrial cancer among postmenopausal women with the highest intakes of total isoflavones, daidzein, and genistein. Associations remained after controlling for established endometrial cancer risk factors and for dietary factors related with total soy and isoflavone consumption. Although point estimates for total soy and tofu were in the direction of a decreased risk for the highest consumers of these foods, no statistically significant associations were detected for any particular soy-based food item or for the individual food items that had the greatest contributions to total isoflavone intake. Associations between endometrial cancer risk and soy and isoflavone intake were attenuated when examined as absolute intakes; however, this attenuation was considered a reflection of the confounding effects of energy intake when not accounting for isoflavone exposure relative

Table 1. Baseline characteristics of postmenopausal women in the Multiethnic Cohort Study (1993–2007) according to total isoflavone intake*

Characteristic	Total Isoflavone Intake, mg per 1000 kcal/d				
	Total	Quintile 1 (median = 0.87)	Quintile 3 (median = 3.81)	Quintile 5 (median = 11.)	RR† (95% CI)
Total women, No.	46 027	9072	8996	9789	
Total women with endometrial cancer, No.	489	122	109	71	
Age at cohort entry, y					
Mean (SD)	61.6 (7.7)	61.7 (7.8)	61.2 (7.7)	62.3 (7.5)	
Race or ethnicity, %					
African American	16.0	25.1	17.6	5.2	
Native Hawaiian	6.6	2.9	9.1	5.8	
Japanese American	30.7	2.9	28.4	60.2	
Latina	21.6	21.1	22.0	20.3	
White	25.2	48.0	23.1	8.6	
Body mass index (kg/m^2), %					
Normal/underweight (<25)	49.4	44.2	47.0	58.7	1.00
Overweight (25 to <30)	31.2	32.7	32.3	27.6	1.38 (1.09 to 1.74)
Obese (≥30)	19.4	23.2	20.7	13.7	2.68 (2.10 to 3.42)
P_{trend}‡					<.01
Age at menarche, %					
≤12 y	47.1	49.4	47.8	42.9	1.00
13–14 y	39.9	38.9	39.6	41.2	0.95 (0.79 to 1.15)
≥15 y	13.0	11.8	12.6	16.0	0.77 (0.57 to 1.05)
P_{trend}‡					.13
Age at natural menopause, %					
<45 y	15.9	17.6	15.2	13.8	1.00
45–49 y	31.7	32.5	32.6	29.9	0.91 (0.68 to 1.22)
50–54 y	41.6	39.6	41.9	44.0	1.20 (0.91 to 1.57)
≥55 y	10.9	10.3	10.3	12.3	1.32 (0.94 to1.85)
P_{trend}‡					.02
Parity, %					
Nulliparous	11.9	14.6	10.9	11.7	1.00
1	10.7	11.6	10.7	10.6	0.70 (0.49 to 1.00)
2–3	44.1	42.1	43.2	46.1	0.75 (0.58 to 0.97)
≥4	33.4	31.7	35.3	31.6	0.52 (0.39 to 0.69)
P_{trend}‡					<.01
Duration of oral contraceptive use, %					
Never	63.1	59.1	61.1	71.1	1.00
1–5 y	22.8	23.7	23.8	19.5	0.97 (0.76 to 1.22)
>5 y	14.1	17.3	15.1	9.4	0.64 (0.46 to 0.89)
P_{trend}‡					.02
Hormone therapy use, %					
Never estrogen use	54.2	54.2	53.4	55.8	1.00
Past estrogen use	18.0	18.7	18.1	16.4	1.09 (0.85 to 1.39)
Current estrogen–progesterone use	23.6	22.9	24.2	23.5	1.26 (1.00 to 1.60)
Current unopposed estrogen use	4.1	4.2	4.3	4.4	1.61 (1.09 to 2.39)
P_{trend}‡					.01
Smoking history, %					
Never smoker	56.3	48.4	55.1	66.0	1.00
Former smoker	29.9	34.0	29.9	25.2	0.95 (0.78 to 1.16)
Current smoker	13.8	17.7	15.1	8.9	0.77 (0.56 to 1.05)
P_{trend}‡					.13
Hypertension, %					
No history of hypertension	62.3	62.7	61.5	63.1	1.00
History of hypertension	37.7	37.3	38.5	36.9	1.24 (1.03 to 1.50)
Diabetes, %					
No history of diabetes	89.4	90.2	88.9	88.9	1.00
History of diabetes	10.6	9.8	11.1	11.1	0.94 (0.71 to 1.26)

* Median follow-up time was 13.6 years. CI = confidence interval; RR = relative risk; SD = standard deviation.

† Relative risks obtained from Cox proportional hazards models adjusted for age (underlying time metric), race or ethnicity (strata variable), and age at cohort entry, total calories/d (log transformed), and all other risk factors in the table in the log-linear model component.

‡ *P* values were calculated using a two-sided test for linear trend modeling categories as a continuous variable.

Table 2. RR of endometrial cancer for increasing intake of legumes, total soy, tofu, and isoflavones*

Dietary exposure†	RR (95% CI)						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}‡	$P_{heterogeneity}$§
Total soy, g/1000 kcal/d							
Quintile median (range)	0.00 (0.00)	0.79 (0.01–1.75)	3.17 (1.76–5.02)	7.25 (5.03–10.98)	20.34 (≥ 10.99)		
No. of women with endometrial cancer/No. at risk	247/20987	64/5739	63/5885	69/6572	46/6844		
Basic model‖	1.00 (referent)	1.00 (0.76 to 1.32)	1.06 (0.76 to 1.46)	1.14 (0.80 to 1.64)	0.76 (0.50 to 1.15)	.10	.98
Multivariable model¶	1.00 (referent)	1.02 (0.77 to 1.35)	1.08 (0.78 to 1.49)	1.19 (0.83 to 1.71)	0.81 (0.53 to 1.23)	.18	.97
Legumes, g/1000 kcal/d							
Quintile median (range)	3.54 (0.00–6.18)	8.50 (6.19–10.85)	13.41 (10.86–16.54)	20.87 (16.55–27.90)	42.56 (≥ 27.91)		
No. of women with endometrial cancer /No. at risk	109/8502	98/9035	99/9300	81/9535	102/9655		
Basic model‖	1.00 (referent)	0.92 (0.70 to 1.21)	0.93 (0.71 to 1.23)	0.76 (0.57 to 1.02)	0.97 (0.72 to 1.30)	.90	.61
Multivariable model¶	1.00 (referent)	0.91 (0.69 to 1.20)	0.92 (0.69 to 1.21)	0.77 (0.57 to 1.03)	0.99 (0.74 to 1.32)	.94	.64
Tofu, g/1000 kcal /d							
Quintile median (range)	0.01 (0.00–0.21)	0.48 (0.22–0.85)	1.50 (0.86–2.71)	4.69 (2.72–7.55)	13.71 (≥ 7.56)		
No. of women with endometrial cancer /No. at risk	119/9294	104/8989	91/8484	94/8948	81/10312		
Basic model‖	1.00 (referent)	0.94 (0.72 to 1.22)	0.90 (0.68 to 1.19)	0.97 (0.70 to 1.34)	0.79 (0.54 to 1.16)	.23	.98
Multivariable model¶	1.00 (referent)	0.92 (0.71 to 1.21)	0.90 (0.68 to 1.19)	0.98 (0.70 to 1.36)	0.82 (0.56 to 1.21)	.35	.98
Total isoflavones, mg per 1000 kcal/d							
Quintile median (range)	0.87 (0.00–1.58)	2.27 (1.59–3.00)	3.81 (3.01–4.77)	6.00 (4.78–7.81)	11.23 (≥ 7.82)		
No. of women with endometrial cancer /No. at risk	122/9072	92/8735	109/8996	95/9435	71/9789		
Basic model‖	1.00 (referent)	0.82 (0.62 to 1.07)	0.99 (0.75 to 1.29)	0.87 (0.65 to 1.16)	0.65 (0.47 to 0.90)	.02	.74
Multivariable model¶	1.00 (referent)	0.82 (0.63 to 1.08)	0.99 (0.76 to 1.29)	0.88 (0.66 to 1.18)	0.66 (0.47 to 0.91)	.02	.79
Daidzein, mg per 1000 kcal/d							
Quintile median (range)	0.38 (0.00–0.69)	1.01 (0.70–1.34)	1.70 (1.35–2.15)	2.70 (2.16–3.53)	5.09 (≥ 3.54)		
No. of women with endometrial cancer /No. at risk	121/9109	93/8703	108/9020	98/9382	69/9813		
Basic model‖	1.00 (referent)	0.84 (0.64 to 1.10)	0.98 (0.75 to 1.29)	0.91 (0.68 to 1.22)	0.64 (0.46 to 0.89)	.01	.76
Multivariable model¶	1.00 (referent)	0.84 (0.64 to 1.10)	0.99 (0.76 to 1.30)	0.92 (0.69 to 1.23)	0.64 (0.46 to 0.90)	.01	.79
Genistein, mg per 1000 kcal/d							
Quintile median (range)	0.38 (0.00–0.68)	0.98 (0.69–1.30)	1.65 (1.31–2.07)	2.61 (2.08–3.39)	4.87 (≥ 3.40)		
No. of women with endometrial cancer/No. at risk	123/9111	91/8707	108/9015	96/9383	71/9811		
Basic model‖	1.00 (referent)	0.81 (0.61 to 1.06)	0.97 (0.74 to 1.27)	0.88 (0.66 to 1.18)	0.65 (0.47 to 0.90)	.02	.62
Multivariable model¶	1.00 (referent)	0.81 (0.62 to 1.07)	0.97 (0.74 to 1.27)	0.89 (0.66 to 1.19)	0.66 (0.47 to 0.91)	.02	.67
Glycitein, mg per 1000 kcal/d							
Quintile median (range)	0.10 (0.00–0.18)	0.26 (0.19–0.35)	0.43 (0.36–0.54)	0.67 (0.55–0.88)	1.28 (≥ 0.89)		
No. of women with endometrial cancer /No. at risk	119/8956	91/8808	102/9033	97/9527	80/9703		
Basic model‖	1.00 (referent)	0.82 (0.62 to 1.08)	0.95 (0.72 to 1.25)	0.90 (0.68 to 1.20)	0.74 (0.54 to 1.00)	.09	.76
Multivariable model¶	1.00 (referent)	0.82 (0.62 to 1.08)	0.96 (0.73 to 1.26)	0.91 (0.68 to 1.21)	0.75 (0.55 to 1.01)	.11	.76

* CI = confidence interval; RR = relative risk.

† Because of the high proportion of women reporting 0 g soy intake per day, groups were created to compare women with no intake (quintile 1) to the quartile distribution of those reporting any soy consumption (quintiles 2–5).

‡ *P* values were calculated using a two-sided test for linear trend modeling categories as a continuous variable.

§ *P* values for the test of heterogeneity were calculated using a two-sided Wald test of the cross-product terms for dietary intake quintiles and race or ethnicity.

‖ RRs obtained from Cox proportional hazards models adjusted for age (underlying time metric), race or ethnicity (strata variable), and age at cohort entry in the log-linear model component.

¶ Relative risks obtained from Cox proportional hazards models adjusted for age (underlying time metric), race or ethnicity (strata variable), and age at cohort entry, body mass index (kg/m^2), age at menarche (≤12, 13–14, ≥15 years), age at menopause (<45, 45–49, 50–54, ≥55 years), duration and type of hormone therapy use (never estrogen use, past estrogen use, current unopposed estrogen use, current estrogen plus progesterone use), duration of oral contraceptive use (<1, 1–5, >5 years), parity(nulliparous, 1, 2–3, ≥4 children), smoking status (never, former, current), hypertension (no, yes), diabetes(no, yes), and total calories (log transformed) in the log-linear model component.

Table 3. RR of endometrial cancer for increasing intake levels of legumes, total soy, tofu, and isoflavones by race or ethnicity*

	All women (n = 46 027)		African Americans (n = 7378)		Japanese Americans (n = 14 109)		Latinas (n = 9945)		Whites (n = 11 582)	
Dietary exposure	No. of women with endometrial cancer/No. at risk	RR (95% CI)†	No. of women with endometrial cancer/No. at risk	RR (95% CI)†	No. of women with endometrial cancer/No. at risk	RR (95% CI)†	No. of women with endometrial cancer/No. at risk	RR (95% CI)†	No. of women with endometrial cancer/No. at risk	RR (95% CI)†
Total soy, g/1000 kcal/d										
<8.09	421/36 774	1.00 (referent)	95/7278	1.00 (referent)	60/6431	1.00 (referent)	98/9801	1.00 (referent)	138/10 895	1.00 (referent)
≥8.09	68/9253	0.79 (0.58 to 1.08)	1/100	0.83 (0.12 to 6.00)	53/7678	0.78 (0.54 to 1.14)	2/144	1.55 (0.38 to 6.31)	6/687	0.82 (0.36 to 1.86)
Legumes, g/1000 kcal /d										
<23.90	365/33 989	1.00 (referent)	83/6333	1.00 (referent)	86/10 116	1.00 (referent)	46/4933	1.00 (referent)	120/10 006	1.00 (referent)
≥23.90	124/12 038	1.07 (0.86 to 1.34)	13/1045	0.97 (0.54 to 1.75)	27/3993	0.88 (0.57 to 1.36)	54/5012	1.12 (0.75 to 1.67)	24/1576	1.39 (0.89 to 2.16)
Tofu, g/1000 kcal/d										
<6.00	384/33 329	1.00 (referent)	95/7225	1.00 (referent)	38/4074	1.00 (referent)	98/9652	1.00 (referent)	131/10 485	1.00 (referent)
≥6.00	105/12 698	0.90 (0.67 to 1.20)	1/153	0.53 (0.07 to 3.85)	75/10 035	0.84 (0.56 to 1.24)	2/293	0.72 (0.18 to 2.92)	13/1097	1.14 (0.64 to 2.02)
Total isoflavones, mg per 1000 kcal/d										
<6.80	390/33 807	1.00 (referent)	90/6677	1.00 (referent)	66/6963	1.00 (referent)	81/7414	1.00 (referent)	129/10 475	1.00 (referent)
≥6.80	99/12 220	0.81 (0.64 to 1.03)	6/701	0.59 (0.26 to 1.35)	47/7146	0.72 (0.49 to 1.04)	19/2531	0.67 (0.41 to 1.12)	15/1107	1.19 (0.69 to 2.03)
Daidzein, mg per 1000 kcal/d										
<3.08	394/33 801	1.00 (referent)	90/6717	1.00 (referent)	64/6769	1.00 (referent)	84/7589	1.00 (referent)	132/10 481	1.00 (referent)
≥3.08	95/12 226	0.76 (0.60 to 0.97)	6/661	0.62 (0.27 to 1.43)	49/7340	0.73 (0.50 to 1.06)	16/2356	0.60 (0.35 to 1.03)	12/1101	0.95 (0.52 to 1.72)
Genistein, mg per 1000 kcal/d										
<2.96	389/33 827	1.00 (referent)	90/6714	1.00 (referent)	64/6780	1.00 (referent)	82/7582	1.00 (referent)	129/10 495	1.00 (referent)
≥2.96	100/12 200	0.83 (0.65 to 1.06)	6/664	0.63 (0.28 to 1.45)	49/7329	0.73 (0.51 to 1.07)	18/2363	0.70 (0.42 to 1.16)	15/1087	1.23 (0.72 to 2.10)
Glycitein, mg per 1000 kcal/d										
<0.77	386/33 854	1.00 (referent)	85/6258	1.00 (referent)	74/8268	1.00 (referent)	72/6571	1.00 (referent)	127/10 327	1.00 (referent)
≥0.77	103/12 173	0.83 (0.66 to 1.04)	11/1120	0.72 (0.38 to 1.35)	39/5841	0.78 (0.53 to 1.16)	28/3374	0.73 (0.47 to 1.14)	17/1255	1.20 (0.72 to 2.00)

* Native Hawaiians are not included in the table as the number of women with endometrial cancer was too small for stable risk estimates. RRs reflect a comparison of quartile 4 vs quartiles 1–3. CI = confidence interval; RR = relative risk.

† RRs obtained from Cox proportional hazards models adjusted for age (underlying time metric) and age at cohort entry, body mass index (kg/m^2), age at menarche (≤12, 13–14, ≥15 years), age at menopause (<45, 45–49, 50–54, ≥55 years), duration and type of hormone therapy use (never estrogen use, past estrogen use, current unopposed estrogen use, current estrogen plus progesterone use), duration of oral contraceptive use (<1, 1–5, >5 years), parity (nulliparous, 1, 2–3, ≥4 children), smoking status (never, former, current), hypertension (no, yes), diabetes (no, yes), and total calories (log transformed) in the log-linear model component.

to total calories. The non-statistically significant association of isoflavones with endometrial cancer risk in racial or ethnic stratified models likely resulted from the loss of statistical power, as no racial or ethnic heterogeneity was detected for the associations between diet and endometrial cancer in the total study sample. To the best of our knowledge, these findings represent the first published prospective analysis to examine the role of soy and isoflavone consumption on the risk of endometrial cancer.

Several case–control studies have examined the association of legumes and soy products with the risk of endometrial cancer. In an earlier population-based case–control study conducted in Hawaii (13), we found a decreased risk of endometrial cancer among participants in the top quartile of soy products (odds ratio [OR] = 0.46, 95% CI = 0.26 to 0.83), tofu (OR = 0.53, 95% CI = 0.30 to 0.94), and legume intake (OR = 0.51, 95% CI = 0.31to 0.86) compared with participants in the bottom quartile. Similarly, a population-based case–control study conducted among women residing in Shanghai (14) showed a reduction in risk in the top quartile of total soy protein intake compared with the bottom quartile (OR = 0.67, 95% CI = 0.48 to 0.92); however, no association was observed for tofu, soy milk, or processed soy products alone. Legumes were later reported to be associated with a decreased risk of this cancer in this same Shanghai population (15). Despite the previous supportive evidence from case–control studies in Asian or largely Asian populations, the only previous prospective dietary study on this topic was conducted in a population of mostly white women followed for approximately 10 years (18), which failed to detect an association between legume intake and endometrial cancer risk.

For isoflavones thought to mediate the potential protection from soy foods, our findings suggesting an inverse association with the risk of endometrial cancer are in contrast to three previous null reports. In population-based case–control studies conducted in the San Francisco Bay area (16), New Jersey (17), and Shanghai (14), no associations were detected for total isoflavones or the specific isoflavones, daidzein, and genistein. Reasons for the inconsistencies between our findings and previous reports could be because of several factors. First, the consumption of soy foods and isoflavones in previous US-based samples may have been insufficient to observe an effect. We found an association for total isoflavones from foods only at intakes 7.82 mg per 1000 kcal/d or higher, approximately 11 times higher than the estimated US average of 0.7 mg per 1000 kcal/d (27). Second, isoflavone measurements from food sources show considerable variation (28), potentially leading to differences in food composition databases and varying degrees of measurement and misclassification error across studies. Third, total soy in our study was measured using only items on miso, tofu, and vegetarian meats allowing for some misclassification and the potential to attenuate associations for these exposures. Fourth, potential recall biases in case–control studies may have influenced previous estimates.

One potential mechanism by which isoflavones may lower the risk of endometrial cancer is through their binding affinity for the α and β estrogen receptors (10), thereby limiting the proliferative effects of circulating estrogens. In vivo, daidzein and genistein have been shown to possess a high binding affinity for estrogen receptors α and β (29), which may explain the associations observed for these isoflavones but not glycitein, in this study. As isoflavones in general are weak phytoestrogens, it is of substantial scientific interest whether their association with endometrial cancer risk in the MEC varied according to differences in an individual's lifetime estrogen exposure. Future analyses allowing for a longer follow-up period and accrual of additional endometrial cancers will provide the opportunity to more explicitly examine these relations. In addition, the inverse association of isoflavone consumption with endometrial cancer risk may be limited to critical exposure periods, as isoflavones have been found to act as estrogen antagonists in vitro at normal premenopausal estradiol concentrations, but possess additive agonistic effects at levels commonly observed in postmenopausal women (10,30). Studies assessing soy and isoflavone intake in the entire lifespan are required to specifically address this issue.

We estimated that approximately 27% of the incident endometrial cancers in this multiethnic cohort of nonhysterectomized postmenopausal women may have been prevented if all women had consumed 7.82 mg per 1000 kcal/d or higher levels of total isoflavones. Although this counterfactual exposure scenario represents a rather large relative increase in intake from the current US average (27), a single cup (243 g) of soy milk provides approximately 23 mg of total isoflavones. As such, a single daily serving of soy milk would be more than sufficient to achieve this level of intake for a reference 2000 kcal diet. Should further research support the advisability of increasing isoflavone intake to this level among all US women, based on these estimates, the implementation of such a recommendation could have an appreciable impact on the 43 470 cancers of the uterine corpus diagnosed annually (2).

We found a lower risk of endometrial cancer among postmenopausal women with greater exposure of total isoflavones, daidzein, and genistein but not for greater exposure of soy foods or increased consumption of individual food items contributing to total isoflavone levels. One possible explanation for this finding is that a large proportion of isoflavones in the diets of older non-Asian women in the United States has been shown to come from food sources, such as soy proteins added to commercial baked goods, and through the consumption of foods with low to moderate isoflavone concentrations, such as coffee and orange juice, which are frequently consumed, rather than from traditional soy-based foods (31). Similar findings were obtained for women in this study, with the majority of total isoflavones consumed through nontraditional soy-based foods among African American, Latina, and white women; however, greater than 82% of total isoflavones among Japanese American women were reported to have been consumed in the form of tofu or miso soup. Thus, even for Japanese Americans, the isoflavone contribution from any single food item, as measured by the QFFQ, appeared insufficient to demonstrate an independent association with endometrial cancer risk at levels detectable in our sample.

Our study has several strengths. These include the prospective design and prediagnostic assessment of diet, wide range of soy and isoflavone intake, detailed nutritional database used to obtain dietary estimates, and ability to statistically control for potential confounding by endometrial cancer risk factors or by correlated dietary and lifestyle behaviors.

There are also potential limitations in this study. First, total isoflavone intake was calculated using only daidzein, genistein, and glycitein and did not include values for isoflavones with smaller contributions to total isoflavone intake including biochanin A and formononetin. Second, only baseline data on hysterectomy status was available. Hysterectomies among controls during the follow-up period would reduce the number of person-years at risk, but this possibility is remote. Third, the large variation in soy and isoflavone intake across racial or ethnic groups may have led to insufficient overlap across levels of exposure and potential residual confounding in some models. In addition, a slightly higher proportion of Latinas and African American women were excluded from this analysis largely because of the higher prevalence of hysterectomies in this population. As the distributions of endometrial cancer risk factors were similar among women retained and excluded from the analysis, and no statistically significant racial or ethnic heterogeneity in the associations of dietary exposures with the risk of endometrial cancer were observed, these exclusions were unlikely to have had an appreciable impact on the study results. Fourth, these findings are based solely on baseline data and therefore cannot provide information regarding changes in dietary intake over time. Fifth, in spite of the inherent measurement error in the QFFQ, we had reasonable statistical power to detect the inverse associations found between isoflavone intake and endometrial cancer risk in the MEC. However, we were less optimally powered to detect endometrial cancer risks associated with episodically eaten soy-based foods. The minimum detectable relative risk in our study for the fifth quintile was 0.62 for soy products compared with the observed relative risk of 0.76, and the relative risk was 0.70 for tofu compared with the observed relative risk of 0.79 (Table 2); the corresponding minimum detectable relative risks accounting for potential measurement error in the QFFQ were 0.51 and 0.60 for soy and tofu, respectively.

In conclusion, results of this study suggest that higher intakes of total isoflavones, daidzein, and genistein may be associated with a reduced risk of endometrial cancer in postmenopausal women; however, risk estimates were not examined for dietary intakes obtained from isolated soy or isoflavone products, and the potential for detrimental effects arising from excessive intakes obtained through nonfood sources cannot be ruled out on the basis of this study. Additional prospective investigations in cohorts of women consuming a diverse range of these dietary exposures are needed to confirm the findings obtained in the MEC. As our estimates of dietary intake may partially reflect habitual exposure to isoflavones and soy-based foods consumed at moderate levels throughout life, additional studies examining changes in dietary patterns in adulthood are needed to determine whether dietary interventions among life-long low soy consumers may have an influence on subsequent disease risk. Collectively, these results provide support for a role of dietary isoflavones in the etiology of endometrial cancer and underscore the importance of exposure diversity in future confirmatory analyses.

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Affiliations of authors: University of Hawaii Cancer Center, Epidemiology Program, Honolulu, HI (NJO, UL, LRW, YBS, LNK, MTG); Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA (VWS, BEH).