Phytoestrogen Intake and Endometrial Cancer Risk

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Background: **The development of endometrial cancer is largely related to prolonged exposure to unopposed estrogens. Phytoestrogens (i.e., weak estrogens found in plant foods) may have antiestrogenic effects. We evaluated the associations between dietary intake of seven specific compounds representing three classes of phytoestrogens (isoflavones, coumestans, and lignans) and the risk of endometrial cancer.** ***Methods:*** **In a case–control study from the greater San Francisco Bay Area, we collected dietary information from 500 African American, Latina, and white women aged 35–79 years who were diagnosed with endometrial cancer between 1996 and 1999 and from 470 age- and ethnicity-matched control women identified through random-digit dialing. Unconditional logistic regression analyses were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).** ***Results:*** **Isoflavone (OR = 0.59, 95% CI = 0.37 to 0.93 for the highest versus lowest quartile of exposure) and lignan (OR = 0.68, 95% CI = 0.44 to 1.1) consumptions were inversely related to the risk of endometrial cancer. These associations were slightly stronger in postmenopausal women (OR = 0.44, 95% CI = 0.26 to 0.77 and OR = 0.57, 95% CI = 0.34 to 0.97 for isoflavones and lignans, respectively). Obese postmenopausal women consuming relatively low amounts of phytoestrogens had the highest risk of endometrial cancer (OR = 6.9, 95% CI = 3.3 to 14.5 compared with non-obese postmenopausal women consuming relatively high amounts of isoflavones); however, the interaction between obesity and phytoestrogen intake was not statistically significant.** ***Conclusion:*** **Some phytoestrogenic compounds, at the levels consumed in the typical American-style diet, are associated with reduced risk of endometrial cancer. [J Natl Cancer Inst 2003;95: 1158–64]**

The development of endometrial cancer is largely related to prolonged exposure to estrogens without cyclic exposure to progesterone *(1,2).* Unopposed estrogens increase mitotic activity in endometrial cells, whereas progesterone reduces this activity *(3).* The identification of factors that lower endogenous estrogen levels is therefore important in efforts to prevent this disease.

Estrogens found in plant foods (i.e., phytoestrogens), such as isoflavones found in soybeans and lignans found in whole grains, seeds, and dried fruit, have been shown to lower endogenous estrogen levels *(4–6).* Phytoestrogens also stimulate the production of sex hormone–binding globulin (SHBG) by the liver. Higher SHBG levels result in more bound and thus less free estradiol, reducing the amount of estrogens available for binding with estrogen receptors *(7,8).* Phytoestrogens also bind competitively to estrogen receptors, thereby blocking binding by estradiol and other estrogens *(9–14).* Because of their weak estrogenic potential (≤0.1% that of estradiol), phytoestrogens do not elicit a strong estrogenic response and thus have an antiestrogenic effect that inhibits the growth and proliferation of estrogen-dependent cancer cells *(13,15).*

Only one study has directly examined the effects of phytoestrogen-rich foods on endometrial cancer risk *(16).* In Hawaii's multiethnic population, greater consumption of tofu alone or in combination with other soy products was associated with a 50% reduction in endometrial cancer risk. The risk reduction was strongest among women who had never given birth and those who had never used estrogen replacement therapy. Risk reduction was slightly stronger for obese women relative to lean women, but this association was not statistically significant. Here, we present results from the first analytic epidemiologic study that has quantified the intake of specific phytoestrogenic compounds as they relate to endometrial cancer risk.

METHODS

We conducted a population-based case–control study of endometrial cancer risk among non-Asian women in the San Francisco Bay Area. All participants were between the ages of 35 and 79 years; resided in Alameda, Contra Costa, San Francisco, San Mateo, or Santa Clara County, California; self-identified as African American, Latina, or white; spoke sufficient English or Spanish to complete the interview; and had not been diagnosed with endometrial cancer before the initiation of the study. From the Greater Bay Area Cancer Registry, a population-based registry that is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)[1] Program and the statewide California Cancer Registry, we identified 1310 eligible women diagnosed with endometrial cancer between October 1, 1996, and September 30, 1999. Of these 1310 women, 124 (9%) were deceased and physicians indicated contraindications to contacting 21 (2%). To verify race/ethnicity, we first conducted a telephone screening. Of the 1165 individuals approached for screening, 1013 (87%) were screened, 79 (7%) declined to be screened, 20 (2%) were not fluent in English or Spanish, and 53 (5%) were not screened for other reasons. We invited all women who self-identified as African American or Latina and a random sample of 60% of women who self-identified as white, for a total of 647 women, to participate in an extensive in-person interview. Of these women, 500 (77%) were interviewed, including 59 (75%) of 79 Latina women, 50 (75%) of 67 African American women, and 391 (78%) of 501 white women. One hundred fourteen (18%) women declined to participate, and 33 (5%) were not interviewed for other reasons.

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See "Notes" following "References."

DOI: 10.1093/jnci/djg015

We identified control subjects through random-digit dialing (RDD). The RDD method we used was based on identifying primary sampling units (PSUs) from cancer registry data, with the assumption that cancer patients are distributed randomly in the general population. PSUs were generated for each race/ethnic group on the basis of the phone number of all recently diagnosed cancer patients of that race/ethnicity (regardless of sex, age, or cancer site). To avoid bias, the cancer patient phone numbers used to generate the PSUs were not included in the RDD enumeration. We called 74 673 telephone numbers, of which 45 378 were known or presumed to be residential. Despite trying 10 times on different days and times during a 2- to 4-week period, 10 012 of these numbers were never answered. Of the 35 366 households reached, 28 775 (81%) were enumerated (i.e., the age and race/ethnicity of all female household members was reported). We selected 1088 control subjects who were frequency-matched to case subjects on age (5-year groups) and race/ethnicity (three groups) and invited them to participate in the telephone screening interview. Of these invited women, 940 (86%) were screened, 83 (8%) declined to be screened, and 65 (6%) were not screened for other reasons. After excluding 307 women who did not meet the eligibility criteria (i.e., they had a history of endometrial cancer or hysterectomy, or were ineligible because of age or race/ethnicity), 633 control subjects were invited to participate in the in-person interview. Of these 633 women, 470 (74%) were interviewed, including 86 (80%) of 107 Latina women, 52 (72%) of 72 African American women, and 332 (73%) of 454 white women. One hundred twenty-four (20%) declined to participate, and 39 (6%) were not interviewed for other reasons.

After obtaining written informed consent in either English or Spanish, we conducted in-person interviews using a standardized structured questionnaire that covered a wide variety of topics, including dietary intake and vitamin and mineral supplement use, level of physical activity, body characteristics, residential history, occupational history, menstrual and reproductive events, hormone use, medical history, demographics, and language use. Whenever possible, we drew phrasing of questions from established and validated instruments. We assessed dietary intake during the year before diagnosis (for case subjects) or selection (for control subjects) via a food-frequency questionnaire (FFQ). The FFQ was adapted from Block's Health History and Habits Questionnaire *(17–19),* and we included a large number of phytoestrogen-rich foods and foods less rich in phytoestrogens but that contribute substantially to phytoestrogen intake in this population because of the frequency at which they are consumed *(20).* The FFQ included an assessment of 100 food and beverage items as well as questions regarding alcohol use, overall intake of fruits and vegetables, and use of low-fat or nonfat versions of foods. To increase accuracy of portion size reporting, we used visual aids including abstract models (i.e., various portions of small wood cubes), several meat models, standard size dinner plates, and different size bowls, glasses, and measuring spoons. Interviews were conducted in Spanish for 21 case subjects and 58 control subjects. In translating all subject materials, we used standard translation methodology, including forward and backward translation and review for colloquial phrasing *(21,22).* All components of the study were approved by the Institutional Review Boards of the Northern California Cancer Center and the University of California, San Francisco.

Dietary analyses included the responses of 482 (96%) case subjects and 460 (98%) control subjects. We excluded data from 18 case subjects and 10 control subjects whose daily caloric intake was judged to be under- or overreported, i.e., less than 600 or more than 5000 kcal per day, respectively. We examined seven phytoestrogenic compounds representing three classes of phytoestrogens found in plant foods: isoflavones (genistein, daidzein, formononetin, and biochanin A), coumestans (coumestrol), and lignans (matairesinol and secoisolariciresinol) *(18).* The phytoestrogen values for the foods/food groups included in the FFQ had been previously determined using high-performance liquid chromatography–mass spectrometry analyses *(18).*

For menopausal status–specific analyses, we considered women postmenopausal if their periods had stopped more than 1 year before diagnosis (case subjects) or selection (control subjects) and they had never used hormone replacement therapy (HRT) or had used HRT only after the cessation of menses. We also considered women postmenopausal if they began using HRT before the cessation of menses but were aged 60 years or older at the time of diagnosis or selection (i.e., the age at which virtually 100% of natural menopause had occurred in this population and therefore the presumptive age by which ovarian function would have ceased). We considered menopausal status to be undeterminable for women who had begun using HRT before the cessation of menses but who were younger than age 60 because their ovarian function could not be determined with certainty. Finally, all other women were considered premenopausal. For obesity-specific analyses, body mass index (BMI = $lb/in^2 \times 705$; all data were converted to kg/m^2 for our analyses) was derived on the basis of self-reported weight in the year before diagnosis or selection and usual adult height defined as height at age 25–30 years; BMI categories were based on those defined in Sizer and Whitney *(23).*

We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of interest by using unconditional logistic regression analyses and controlling first for the matching variables, age (continuous) and race/ethnicity (African American, Latina, white). Later models controlled for matching variables and potential confounders, i.e., age at menarche (<14, ⩾14 years), nulliparity (yes, no), use of oral contraceptives (never, ever), use of HRT (never, <5 years, ⩾5 years), BMI (<32.3, ⩾32.3 kg/m^2), and average daily caloric intake (continuous). These cut points for confounders were determined after confirming that finer categories did not provide any additional control for confounding. Trends were evaluated over quartiles of exposure by coding quartiles ordinally from 1 (lowest) to 4 (highest). P_{trend} values are two-sided. To adjust phytoestrogen intake for caloric intake, we conducted unconditional logistic regression analyses in two ways, i.e., using the standard method and the residual method, which have complementary implications for interpretation *(24).* Under the standard method, phytoestrogens were expressed in μg/day of absolute intake, and average daily caloric intake was included as a separate variable in the multivariable model. Under the residual method, phytoestrogen levels were expressed relative to the average expected level based on each individual's caloric intake. This second method was accomplished by using the residual that results for each individual from a regression model in which the log of phytoestrogen intake is the dependent variable and the log of total caloric intake is the independent variable. The model assessing disease risk includes the residual and caloric intake as separate variables and can be interpreted as the impact of phytoestrogen consumption

under an isocaloric situation, i.e., one in which calories are held constant and only phytoestrogen consumption is varied. We assessed the interactions using stratified analyses and by including cross-product terms in logistic models to obtain two-sided *P* values *(25,26).* Analyses were performed using SAS software version 8.0 (SAS Institute, Cary, NC).

RESULTS

We first evaluated the association between individual factors and endometrial cancer risk in the study population, adjusting each for age and race/ethnicity (Table 1). In a final multivariable model adjusting for age, race/ethnicity, and the following factors, risk of endometrial cancer was associated with menarche before age 14 years (OR = 1.4, 95% CI = 1.0 to 2.0 compared with menarche at age ⩾14 years), nulliparity (OR = 1.7, 95% CI = 1.2 to 2.5 compared with parous women), ever use of oral contraceptives (OR = 0.61, 95% CI = 0.44 to 0.86 compared with never used), use of HRT for 5 years or longer (OR = 2.0, 95% CI = 1.4 to 2.9 compared with never used), and obesity (BMI ⩾32.3 kg/m^2; OR = 2.3, 95% CI = 1.6 to 3.4 compared with BMI <32.3 kg/m^2).

Average consumption of phytoestrogens was similar for case subjects and control subjects, with the exception of the primary lignan secoisolariciresinol, for which average consumption was higher among control subjects than among case subjects (Table 2). When women in the highest versus the lowest quartiles of intake were compared, greater consumptions of total isoflavones and of total lignans were associated with a reduced risk of endometrial cancer (OR = 0.59, 95% CI = 0.37 to 0.93 and OR = 0.68, 95% CI = 0.44 to 1.1, respectively) (Table 3). When examining specific compounds and adjusting only for age, race/ethnicity, and total caloric intake, reduced risk of endometrial cancer was associated with consumption of the two major isoflavones, genistein (OR = 0.67, 95% CI = 0.45 to 1.0 for the highest versus lowest quartile of intake; P_{trend} = .08) and daidzein (OR = 0.68, 95% CI = 0.46 to 1.0; P_{trend} = .02), and of the lignan secoisolariciresinol (OR = 0.55, 95% CI = 0.37 to 0.82; P_{trend} = .001). Biochanin A, formononetin, coumestrol, and matairesinol intakes were not associated with statistically significant changes in risk. Adjustment for additional risk factors for endometrial cancer did not change the observed estimates appreciably (except for matairesinol, for which a slightly elevated risk became greater and approached statistical significance). Adjustment for calories using the residual method had the effect of flattening out the dose–response curves over the levels of phytoestrogen exposure observed in this population (data not shown). This effect was more pronounced for the isoflavones than for the lignans and resulted in statistically nonsignificant odd ratios and trends for the isoflavones and for matairesinol (data not shown).

Although the majority of the study population was postmenopausal (74% of case subjects and 73% of control subjects), there was some evidence that menopausal status may modify the association between phytoestrogen consumption and endometrial cancer risk (*P* interaction = .08 for isoflavones and .01 for lignans). There was a statistically significant reduced risk of endometrial cancer associated with increasing phytoestrogen consumption among postmenopausal women (OR = 0.44, 95% CI = 0.26 to 0.77 and OR = 0.57, 95% CI = 0.34 to 0.97 for isoflavones and lignans, respectively, for the highest versus the lowest quartile of intake) (Table 4). Using the residual method for calorie adjustment flattened out the dose–response curves for postmenopausal women, as it did for all women combined. However, both the ORs and trends in risk for this postmenopausal group remained statistically significant (*P*<.05) or close to it (.05<*P*<.08) for both the isoflavones and lignans. Body

Table 1. Selected factors and endometrial cancer risk

Risk factor	Case subjects	Control subjects	OR (95% CI)*
Age at menarche, y			
<12	104	85	1.5 (1.0 to 2.3)
12–13	287	254	1.4 (1.0 to 1.9)
⩾14	105	129	1.0 (referent)
Parity			
0	117	65	1.8 (1.3 to 2.7)
1–2	194	195	1.0 (referent)
3–4	148	142	1.0 (0.76 to 1.4)
⩾5	41	68	0.65 (0.41 to 1.0)
Age at first full-term pregnancy (among parous women), y			
<20	75	96	1.0 (referent)
20–24	173	149	1.4 (0.92 to 2.0)
25–29	90	96	1.0 (0.66 to 1.6)
⩾30	45	59	0.91 (0.54 to 1.5)
Use of oral contraceptives			
None	245	184	1.0 (referent)
<5 y	147	139	0.79 (0.57 to 1.1)
⩾5 y	101	138	0.52 (0.36 to 0.73)
Use of hormone replacement therapy			
None	223	244	1.0 (referent)
<5 y	93	112	0.88 (0.63 to 1.2)
⩾5 y	173	109	1.6 (1.2 to 2.3)
Menopausal status			
Premenopausal	100	104	1.0 (referent)
Postmenopausal	372	345	0.93 (0.60 to 1.4)
Cannot be determined	28	21	1.2 (0.65 to 2.3)
Body mass index			
<19.1 (underweight)	19	14	1.4 (0.67 to 2.9)
19.1–25.7 (normal weight)	184	188	1.0 (referent)
25.8–27.2 (marginally overweight)	44	47	0.93 (0.58 to 1.5)
27.3–32.2 (overweight)	95	96	1.1 (0.74 to 1.5)
32.3–44.7 (severely overweight)	98	51	2.2 (1.4 to 3.2)
⩾44.8 (morbidly obese)	21	5	4.8 (1.7 to 13.0)

*Odds ratios (ORs) and confidence intervals (CIs) adjusted for age and race/ethnicity.

Table 2. Average daily phytoestrogen intake

Compound (μg/day)	Case subjects Median	Case subjects Interquartile range	Control subjects Median	Control subjects Interquartile range	*P**
Isoflavones					
Genistein	783	467 to 1336	780	500 to 1420	.68
Daidzein	729	495 to 1213	796	521 to 1197	.35
Biochanin A	48	24 to 81	44	21 to 81	.31
Formononetin	20	10 to 36	20	10 to 36	.84
Total isoflavones	1582	1072 to 2633	1662	1150 to 2726	.44
Coumestrol	186	120 to 263	179	125 to 253	.72
Ligans					
Matairesinol	32	20 to 51	30	18 to 49	.12
Secoisolariciresinol	127	85 to 176	138	87 to 197	.05
Total lignans	162	115 to 228	177	121 to 239	.21

*Two-sided; based on the Wilcoxon rank sum test.

Table 3. Associations between phytoestrogen intake and endometrial cancer risk

Phytoestrogen quartiles	Quartile range, μg/day	No. of subjects (case/control)	OR (95% CI)*	OR (95% CI)†
Isoflavones				
Genistein				
Q1	<500	131/115‡	1.0 (referent)	1.0 (referent)
Q2	500–779	110/115	0.78 (0.54 to 1.1)	0.73 (0.49 to 1.1)
Q3	780–1419	128/115	0.80 (0.54 to 1.2)	0.70 (0.46 to 1.1)
Q4	⩾1420	113/115	0.67 (0.45 to 1.0)	0.68 (0.43 to 1.1)
P_{trend}§			.08	.10
Daidzein				
Q1	<521	138/115	1.0 (referent)	1.0 (referent)
Q2	521–795	123/115	0.78 (0.54 to 1.1)	0.80 (0.53 to 1.2)
Q3	796–1196	94/115	0.52 (0.35 to 0.77)	0.50 (0.32 to 0.78)
Q4	⩾1197	127/115	0.68 (0.46 to 1.0)	0.68 (0.43 to 1.1)
P_{trend}§			.02	.03
Biochanin A				
Q1	<21	103/115	1.0 (referent)	1.0 (referent)
Q2	21–43	121/115	1.1 (0.77 to 1.6)	1.1 (0.70 to 1.6)
Q3	44–80	137/115	1.2 (0.84 to 1.8)	1.3 (0.89 to 2.0)
Q4	⩾81	121/115	1.0 (0.70 to 1.5)	1.1 (0.68 to 1.6)
P_{trend}§			.75	.54
Formononetin				
Q1	<10	116/115	1.0 (referent)	1.0 (referent)
Q2	10–19	123/115	0.97 (0.67 to 1.4)	1.0 (0.66 to 1.5)
Q3	20–35	123/115	0.95 (0.65 to 1.4)	0.95 (0.63 to 1.4)
Q4	⩾36	120/115	0.88 (0.59 to 1.3)	0.90 (0.58 to 1.4)
P_{trend}§			.51	.61
Total isoflavones				
Q1	<1150	147/115	1.0 (referent)	1.0 (referent)
Q2	1150–1661	105/115	0.65 (0.45 to 0.94)	0.62 (0.41 to 0.93)
Q3	1622–2725	116/115	0.59 (0.40 to 0.87)	0.56 (0.36 to 0.87)
Q4	⩾2726	114/115	0.57 (0.38 to 0.85)	0.59 (0.37 to 0.93)
P_{trend}§			.006	.02
Coumestrol				
Q1	<125	127/115	1.0 (referent)	1.0 (referent)
Q2	125–178	103/115	0.73 (0.50 to 1.1)	0.84 (0.55 to 1.3)
Q3	179–252	116/115	0.81 (0.56 to 1.2)	0.97 (0.64 to 1.5)
Q4	⩾253	136/115	0.86 (0.57 to 1.3)	1.1 (0.70 to 1.7)
P_{trend}§			.55	.56
Lignans				
Matairesinol				
Q1	<18	100/115	1.0 (referent)	1.0 (referent)
Q2	18–29	125/115	1.2 (0.85 to 1.8)	1.4 (0.94 to 2.2)
Q3	30–48	120/115	1.1 (0.74 to 1.6)	1.4 (0.93 to 2.2)
Q4	⩾49	137/115	1.2 (0.81 to 1.8)	1.6 (0.99 to 2.4)
P_{trend}§			.50	.07
Secoisolariciresinol				
Q1	<87	127/115	1.0 (referent)	1.0 (referent)
Q2	87–137	153/115	1.1 (0.77 to 1.6)	1.3 (0.88 to 2.0)
Q3	138–196	112/115	0.76 (0.52 to 1.1)	0.82 (0.54 to 1.2)
Q4	⩾197	90/115	0.55 (0.37 to 0.82)	0.63 (0.40 to 0.98)
P_{trend}§			.001	.009
Total lignans				
Q1	<121	133/115	1.0 (referent)	1.0 (referent)
Q2	121–176	144/115	0.98 (0.68 to 1.4)	1.1 (0.74 to 1.6)
Q3	177–238	101/115	0.63 (0.43 to 0.93)	0.72 (0.47 to 1.1)
Q4	⩾239	104/115	0.58 (0.39 to 0.86)	0.68 (0.44 to 1.1)
P_{trend}§			.001	.03

*Odds ratios (ORs) and confidence intervals (CIs) adjusted for age, race/ethnicity, and daily caloric intake.

†Adjusted for age, race/ethnicity, daily caloric intake, age at menarche, parity, use of oral contraceptives and hormone replacement therapy, and body mass index.

‡Case subject and control subject counts include those with valid dietary data.

§Two-sided test for trend across quartiles.

mass may have also affected the relationship between phytoestrogen consumption and endometrial cancer risk, such that obese postmenopausal women consuming low levels of isoflavones or lignans were at greatest risk of endometrial cancer (OR = 6.9, 95% CI = 3.3 to 14.5 and OR = 4.7, 95% CI = 2.4 to 9.0, for isoflavones and lignans, respectively; Table 5). However, the number of obese women was relatively small, and neither interaction reached statistical significance. No interactions between phytoestrogen consumption and HRT use or nulliparity were detected (data not shown).

Table 4. Phytoestrogen consumption and endometrial cancer risk by menopausal status

Phytoestrogen class	Premenopausal women			Postmenopausal women		
	Case subjects	Control subjects	OR (95% CI)*	Case subjects	Control subjects	OR (95% CI)*
Total isoflavones (μg/day)						
<1150	18†	17	1.0	126	95	1.0
1150–1661	15	29	0.52 (0.16 to 1.7)	87	77	0.67 (0.42 to 1.1)
1662–2725	31	26	1.2 (0.39 to 3.4)	76	83	0.44 (0.26 to 0.73)
⩾2726	30	31	0.68 (0.22 to 2.1)	73	81	0.44 (0.26 to 0.77)
Continuous‡			0.88 (0.57 to 1.4)			0.76 (0.60 to 0.96)
P_{trend} across quartiles§			.87			.001
Total lignans (μg/day)						
<121	25	34	1.0	101	74	1.0
121–176	24	18	2.3 (0.84 to 6.5)	111	92	0.87 (0.55 to 1.4)
177–238	22	27	0.96 (0.33 to 2.8)	76	84	0.63 (0.39 to 1.0)
⩾239	23	24	0.77 (0.26 to 2.3)	74	86	0.57 (0.34 to 0.97)
Continuous‡			1.1 (0.59 to 2.0)			0.73 (0.51 to 1.0)
P_{trend} across quartiles§			.42			.02

*Odds ratios (ORs) and confidence intervals (CIs) adjusted for age, race/ethnicity, daily caloric intake, age at menarche, parity, use of oral contraceptives and hormone replacement therapy, and body mass index.

†Case subject and control subject counts include those with valid dietary data and known menopausal status.

‡Phytoestrogen exposure is expressed on the log scale when examined in its continuous form.

§Two-sided test for trend.

Table 5. Joint associations between phytoestrogen consumption and obesity on endometrial cancer risk in postmenopausal women

	BMI <32.3			BMI ⩾32.3			*P* value interaction
	Case subjects	Control subjects	OR (95% CI)*	Case subjects	Control subjects	OR (95% CI)*	
Isoflavones (μg/day)							
⩾1500	118†	141	1.0	44	24	2.2 (1.2 to 4.1)	.27
<1500	135	116	1.9 (1.2 to 2.8)	43	12	6.9 (3.3 to 14.5)	
Lignans (μg/day)							
⩾177	106	128	1.0	35	18	2.3 (1.2 to 4.5)	.43
<177	147	129	1.4 (0.97 to 2.1)	52	18	4.7 (2.4 to 9.0)	

*Odds ratios (ORs) and confidence interval (CIs) adjusted for age, race/ethnicity, daily caloric intake, age at menarche, parity, and use of oral contraceptives and hormone replacement therapy.

†Case subject and control subject counts include postmenopausal women with valid dietary data and complete body mass index (BMI) data.

DISCUSSION

Average intake of total isoflavones in our study population (i.e., 1.6 mg/day for case subjects and 1.7 mg/day for control subjects) is what would be expected in a Western population, with daily intake estimated to be between 1 and 3 mg. Overall, greater consumption of phytoestrogenic compounds was associated with a reduced risk of endometrial cancer. There was some suggestion that this association is stronger in postmenopausal women than in women overall; however, the small number of premenopausal women did not allow precise estimation of the phytoestrogen associations among this subgroup or of the interaction term for these variables.

The risk reduction associated with higher phytoestrogen intake was apparent for three of the four individual phytoestrogenic compounds that are present in the diet in the highest amounts, i.e., genistein, daidzein, and secoisolariciresinol, and for total isoflavones and total lignans, the two major classes that these three compounds represent. The lack of association between biochanin A and formononetin intakes and cancer risk is most likely due mainly to their overall low concentrations (and thus the lack of exposure heterogeneity) in the typical U.S. diet and to the fact that these compounds also share common metabolic pathways with the more commonly consumed phytoestrogens (i.e., biochanin A is metabolized to genistein, formononetin to daidzein, and both plant lignans to the mammalian lignan enterolactone). However, the influence of different binding affinities, estrogenic and antiestrogenic potentials, and other properties of the individual compounds cannot be ruled out as an explanation for the somewhat differing results for different compounds. Furthermore, the method of caloric adjustment may also have had some effect on our risk estimates. Studies of dietary fat consumption and postmenopausal breast cancer have shown that use of the residual method for calorie adjustment flattens dose–response curves more than the standard method *(27)*. However, for the lignans or when expressing isoflavone intake as a continuous variable, both methods of caloric adjustment suggest strong inverse associations between their consumption and endometrial cancer risk. Overall, our findings support the hypothesis that phytoestrogen intake is associated with reduced risk of endometrial carcinogenesis, particularly in postmenopausal women, presumably through antiestrogenic effects.

In addition to lowering endogenous estrogen levels and binding competitively to estrogen receptors, phytoestrogens may also affect endometrial cancer risk through the inhibition of aromatase, the enzyme responsible for the conversion of androstenedione to estrone *(9,10,28)*. The association between obesity and postmenopausal endometrial cancer risk is thought to be

related to the higher conversion of androstenedione to estrone in adipose tissue *(29,30).* The level of dietary phytoestrogens may be high enough in certain diets to reach sufficient concentrations in adipocytes to reduce the rate of this conversion *(9).* Thus, we originally hypothesized that phytoestrogen consumption might counteract the relationship between obesity and endometrial cancer risk, i.e., the increased risk of endometrial cancer associated with obesity may not be as great among women consuming higher levels of phytoestrogens as it is among women consuming low levels. At the levels of dietary phytoestrogens consumed by our population, however, this hypothesis was only partly supported. Obesity was associated with an increased endometrial cancer risk of approximately twofold among women with high phytoestrogen consumption but 3.5-fold among women with low phytoestrogen consumption, and a statistically significant increased risk was observed in the highest risk subgroup (i.e., obese women consuming low levels of phytoestrogens); however, interaction terms were not statistically significant. These findings are consistent with those of Goodman et al. *(16).*

Although our study addresses a unique question and provides the first quantitative assessment of the association between different phytoestrogenic compounds and endometrial cancer risk, a few limitations should be noted. First, in all case–control studies of diet and disease, recall bias and measurement error in dietary exposure are of potential concern. We tried to minimize recall bias and improve accuracy of reporting through interviewer-administered (as opposed to self-administered) dietary histories, assessing complete diet (as opposed to only selected foods), and including an assessment of portion size using visual models *(31–33).* Second, misclassification of phytoestrogen exposure was minimized by using a single comprehensive database developed for use with our food-frequency questionnaire *(18).* Third, although case subjects were population-based, the overall response rate was low (60% = 89% alive and approached for screening × 87% screening response rate × 77% of randomly selected case subjects interviewed), although interviewed case subjects did not differ substantially from all identified case subjects in terms of age or race/ethnicity. The overall response rate for our population control subjects was similarly low (52% = 81% RDD enumeration × 86% screening response rate × 74% of eligible control subjects interviewed). These response rates, although not that different from those in a number of recent studies that used comparable definitions of response rate *(16,34–36),* do increase concern about bias and impact the generalizability of the results. The use of bicultural bilingual interviewers, the conduct of interviews in English and Spanish, and the RDD methods we used to increase response and minimize selection biases, particularly among hard-to-reach households, were designed to improve generalizability and decrease bias to the extent possible.

It is of note that phytoestrogens were found to reduce the risk of endometrial cancer at levels commonly consumed as part of a typical Western diet. In a companion study of breast cancer *(37)* that used the same methodology and included many of the same control women as used in the present study, we observed no association between phytoestrogen intake and breast cancer risk at this level of consumption. Thus, phytoestrogens at the lower levels consumed in a typical American diet appear to have a stronger effect on cancers that are dependent on estrogen than those that are dependent on both estrogen and progesterone, suggesting that it is, at least in part, the antiestrogenic effects of phytoestrogens that may play a role in the prevention of hormonally dependent cancers. Indeed, phytoestrogen consumption at higher levels, equivalent to the levels consumed by many Asian Americans (i.e., >7 mg/day), appears to decrease risk of breast cancer, although the timing of exposure remains an unresolved issue for this cancer *(38–40).* Thus, it is possible that dietary intake of phytoestrogens contributes to the lower incidence rates of endometrial cancer relative to the incidence rates of breast cancer in most populations.

In summary, by directly studying the associations between phytoestrogenic compounds and endometrial cancer risk, we have shown that the previously reported risk reduction associated with soy foods *(16)* is likely to be due, at least in part, to the phytoestrogenic compounds in these foods; that the stronger associations with endometrial cancer relative to breast cancer probably reflect, at least in part, the antiestrogenic nature of these compounds; and that the reduced risk of endometrial cancer associated with higher consumption of phytoestrogens is observed at levels commonly consumed in the typical American diet.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

Supported by Public Health Service grant R01 CA74877 from the National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services and, in part, by contracts supporting the Greater Bay Area Cancer Registry (N01-CN-65107 from the Surveillance, Epidemiology, and End Results program of the NCI and 050M-8701/8-S1522 from the California Cancer Registry).

Manuscript received December 16, 2002; revised May 13, 2003; accepted May 27, 2003.