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Phytoestrogen Consumption and Breast Cancer Risk in a Multiethnic Population

The Bay Area Breast Cancer Study

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Research on the relation between phytoestrogens and breast cancer risk has been limited in scope. Most epidemiologic studies have involved Asian women and have examined the effects of traditional soy foods (e.g., tofu), soy protein, or urinary excretion of phytoestrogens. The present study extends this research by examining the effects of a spectrum of phytoestrogenic compounds on breast cancer risk in non-Asian US women. African-American, Latina, and White women aged 35–79 years, who were diagnosed with breast cancer between 1995 and 1998, were compared with women selected from the general population via random digit dialing. Interviews were conducted with 1,326 cases and 1,657 controls. Usual intake of specific phytoestrogenic compounds was assessed via a food frequency questionnaire and a newly developed nutrient database. Phytoestrogen intake was not associated with breast cancer risk (odds ratio = 1.0, 95% confidence interval: 0.80, 1.3 for the highest vs. lowest quartile). Results were similar for pre- and postmenopausal women, for women in each ethnic group, and for all seven phytoestrogenic compounds studied. Phytoestrogens appear to have little effect on breast cancer risk at the levels commonly consumed by non-Asian US women: an average intake equivalent to less than one serving of tofu per week. *Am J Epidemiol* 2001;154:434–41.

breast neoplasms; ethnic groups; isoflavones; lignans; soybeans

In the United States, breast cancer incidence varies rather dramatically by ethnicity. In the San Francisco Bay Area of California, the 1997 incidence rates were highest among White women (134 per 100,000 per year), intermediate among African-American women (103 per 100,000), and lowest among Latina women (75 per 100,000) (1). Some of these ethnic differences may be explained by differences in the relative risk or prevalence of risk factors, including dietary factors, in these subpopulations. To the extent that diet is involved in the etiology of breast cancer, its effect may be mediated in part through hormonal mechanisms.

Phytoestrogens are estrogenic compounds found in plant foods or derived from plant precursors (2–5). Because of their chemical structure, phytoestrogens compete with endogenous estrogens for binding with estrogen receptors, but, once bound, they have a far weaker estrogenic potency than endogenous estrogens and thus may act in some tissues, including the breast, as antiestrogens (2, 4–9). In addition to this possible mechanism, it has been suggested that phytoestrogens reduce cancer risk through other pathways, including their effects on hormone metabolism and their antioxidant effects (2, 10, 11).

Recent research has suggested that consumption of phytoestrogen-rich foods may reduce breast cancer risk (2, 12–15). However, the epidemiologic data on this relation remain limited in scope and contain what may prove to be important inconsistencies. Most epidemiologic studies have involved Asian populations and have examined the effects of traditional soy foods (e.g., tofu), protein from soy foods, or urinary excretion of phytoestrogens on breast cancer risk (2, 12, 13, 15–18). Most studies have not examined menopausal status–specific effects, but the findings that have been reported suggest that phytoestrogens may lower risk in premenopausal women but not in postmenopausal women (12, 17). A potentially important finding for US women was the breast cancer risk reduction associated with greater urinary excretion of phytoestrogens in Australian women aged 30–84 years, among whom the level of consumption of traditional soy-based foods is low (14). This recent finding suggests that intake of phytoestrogens by non-Asian women may be sufficient to beneficially impact breast cancer risk. However, note that in this study, urine specimens were collected prior to cancer treatment but after diagnosis and therefore may not reflect the period of cancer development or preclinical progression. Our study extends

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Abbreviation: HRT, hormone replacement therapy.

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this previous research by using a nutrient database we recently developed (19) to examine the effects of a spectrum of phytoestrogenic compounds on breast cancer risk in non-Asian women in the United States.

MATERIALS AND METHODS

Study participants

This population-based case-control study was conducted 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 breast cancer prior to initiation of this study. Cases were identified through the Greater Bay Area Cancer Registry, a population-based cancer registry that is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and the statewide California Cancer Registry. All breast cancer cases diagnosed between April 1, 1995, and April 30, 1998, and identified to the cancer registry as White, African American, or Latina were screened by telephone to verify their race/ethnicity. Of 7,591 identified cases, 297 (4 percent) were deceased, and physicians indicated contraindications to contacting 120 (2 percent). Of 7,174 cases approached regarding screening, 6,157 (86 percent) were screened, 487 (7 percent) declined or were too ill to participate, and 530 (7 percent) were not screened for other reasons (including our inability to locate them, their not being fluent in the languages in which we were interviewing, etc.). All women who self-identified as African American or Latina, and a 10 percent random sample of those identifying as White, were invited to participate in an extensive in-person interview. Of these 1,539 women, 1,326 (86 percent) were interviewed, including 469 (88 percent) of 536 Latina women, 409 (85 percent) of 480 African-American women, and 448 (86 percent) of 523 White women. A total of 149 (10 percent) women declined to participate, and 64 (4 percent) were not interviewed for other reasons.

Controls were identified through random digit dialing. The method used was a modification of the Waksburg method, where primary sampling units were identified by using cancer registry data. By assuming that people with cancer are distributed randomly in the general population, we generated primary sampling units for each ethnic group based on the telephone numbers of all cancer patients of that ethnicity diagnosed during several recent years (regardless of sex, age, or cancer site). This method substantially improves the efficiency of locating persons of minority groups. We selected 2,389 controls, frequency matched to cases on age (5-year groups) and ethnicity (three groups), and invited them to participate in the screening interview. Of these women, 2,062 (86 percent) were screened; 168 (7 percent) declined, were too ill, or were deceased; and 159 (7 percent) were not screened for other reasons. After 89 women who did not meet the eligibility criteria were excluded (i.e., they had a history of breast cancer or were of ineligible age or race/ethnicity), 1,973 controls were invited to participate in the in-person interview. Of these 1,973 women, 1,657 (84 percent) were interviewed, including 699 (87 percent) of 808 Latina women, 460 (82 percent) of 562 African-American women, and 498 (83 percent) of 603 White women. A total of 251 (13 percent) declined to participate, and 65 (3 percent) were not interviewed for other reasons.

Data collection

In-person interviews were conducted by using a standardized, structured questionnaire that covered a wide variety of topics: demographics and language use, physical activity, sun exposure, dietary intake and vitamin and mineral supplement use, body characteristics, residential history, occupational history, menstrual and reproductive events, hormone use, and medical history. Whenever possible, phrasing of questions was drawn from established and validated instruments. Interviews were conducted in Spanish for 166 cases and 272 controls. Standard translation methodology, including forward and backward translation and review for colloquial phrasing, was used in translating all subject materials (20, 21). All study components were approved by the Institutional Review Board of the Northern California Cancer Center (Union City, California).

Dietary intake during the year prior to diagnosis (for cases) or selection (for controls) was assessed via a modified version of the Block food frequency questionnaire (22, 23). To quantify the intake of seven specific phytoestrogenic compounds, we used a nutrient database we had developed to assess phytoestrogen intake by using food frequency questionnaires (19). These seven compounds represent three classes of phytoestrogens found in plant foods: isoflavones (genistein, daidzein, formononetin, and biochanin A), coumestans (coumestrol), and lignans (matairesinol and secoisolariciresinol). A validation/calibration study of our phytoestrogen assessment and nutrient database is currently in progress. Other studies have shown that intake of soy foods or isoflavones (measured from a limited number of soy-based foods) is positively related to urinary isoflavone levels (24–27) and that vegetarian and macrobiotic dietary patterns are associated with urinary lignan excretion (28).

Data analysis

Dietary analyses were based on 1,272 (96 percent) cases and 1,610 (97 percent) controls; excluded were 54 cases and 47 controls whose daily caloric intake was judged to be under- or overreported, that is, <600 or >5,000 kcal per day, respectively. For menopausal-specific analyses, women were considered postmenopausal if their menstrual periods had stopped more than 1 year prior to diagnosis/selection and they had never used hormone replacement therapy (HRT) or had used HRT only after cessation of menses. Also included in this group were women who began using HRT prior to cessation of menses but had attained age 55 years or more at the time of diagnosis/selection. Women who had begun using HRT prior to cessation of menses but had not

attained age 55 years were excluded from these analyses because their menopausal/ovarian status could not be determined. The remainder of the women were considered premenopausal.

After initial examination of the data, we estimated odds ratios and 95 percent confidence intervals by using unconditional logistic regression analyses controlling for age, race/ethnicity, and other potentially confounding factors, as noted in the footnotes to the tables presented in this paper. For the variables used in this study, the risk estimates and confidence intervals obtained from basic models (adjusting for age, race/ethnicity, and daily caloric intake only) did not differ much from those adjusted for multiple covariates; thus, only the latter are presented.

RESULTS

Table 1 presents the association between established breast cancer risk factors and risk in this population. Increased risk was associated with early menarche, nulliparity, self-report of previous biopsy-diagnosed benign breast disease, family history of breast cancer in a first-degree female relative(s), and higher education.

The average phytoestrogen consumption was 3,174 μg per day for cases and 3,326 μg per day for controls; this difference was not statistically significant ($p = 0.46$). On average, for cases and controls, 87 and 88 percent, respectively, of total phytoestrogen consumption was from isoflavones, with tofu, doughnuts, soy milk, and white bread among the largest contributors to daily intake (also refer to Horn-Ross et al. (29)). Table 2 shows the associations of traditional soy-based foods, foods with added soy flour, and foods with added soy protein with breast cancer risk. Consumption of soy milk and soyburgers was associated with a statistically significant reduction in breast cancer risk.

Table 3 presents the associations for daily intake of the specific phytoestrogenic compounds and classes of compounds and of total phytoestrogens. Only small variations in breast cancer risk were observed, even at the highest levels

TABLE 1. Association between established breast cancer risk factors and breast cancer risk among women participating in the multiethnic Bay Area Breast Cancer Study, San Francisco, California, 1995–1998

Risk factor	Cases (n = 1,326)*	Controls (n = 1,657)*	OR†,‡	95% CI†
Age (years) at menarche				
<12	329	344	1.0	
12–13	670	825	0.83	0.69, 0.99
≥14	313	476	0.68	0.56, 0.84
Parity				
Nulliparous	217	187	1.0	
1–2	556	607	0.79	0.63, 1.0
3–4	389	546	0.62	0.49, 0.79
≥5	161	317	0.44	0.33, 0.58
Age (years) at first full-term pregnancy (parous women)				
<20	281	401	1.0	
20–24	414	531	1.1	0.92, 1.4
25–29	240	291	1.2	0.94, 1.5
≥30	156	198	1.2	0.88, 1.5
Self-report of biopsy-diagnosed benign breast disease				
Never	1,056	1,400	1.0	
Ever	264	253	1.3	1.1, 1.6
Family history of breast cancer in first-degree female relative(s)				
No	1,112	1,468	1.0	
Yes	211	189	1.4	1.2, 1.8
Education (years)				
<12	285	513	1.0	
12	266	343	1.4	1.1, 1.7
13–15	433	457	1.7	1.4, 2.1
≥16	339	344	1.8	1.4, 2.3

* Columns totaling less than the total number of cases or controls reflect missing values for those variables.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age and race/ethnicity.

at which these compounds were consumed by these populations. Note that because of the different estrogenic (and antiestrogenic) activity of the various compounds, total intake—reported here as the sum of the various com-

TABLE 2. Association between consumption of selected soy-based foods and foods with added soy flour or protein and breast cancer risk among women participating in the multiethnic Bay Area Breast Cancer Study, San Francisco, California, 1995–1998

Food and level of consumption	Cases (n = 1,272)*	Controls (n = 1,610)*	OR†,‡	95% CI†
Traditional soy-based foods				
Nonfermented				
Tofu				
Nonconsumers	931	1,163	1.0	
<1/month	168	237	0.79	0.63, 0.99
≥1/month	173	207	0.89	0.70, 1.1
Soy milk				
Nonconsumers	1,232	1,532	1.0	
Consumers	39	78	0.57	0.38, 0.85
Fermented				
Miso soup				
Nonconsumers	1,094	1,373	1.0	
<1/month	123	137	1.1	0.81, 1.4
≥1/month	97	93	1.1	0.81, 1.5
Nontraditional soy-based foods				
Soyburgers				
Nonconsumers	1,047	1,301	1.0	
<1/month	132	174	0.79	0.62, 1.0
≥1/month	91	134	0.74	0.55, 0.99
Foods with added soy flour§				
Doughnuts				
Nonconsumers	285	340	1.0	
<1/month	203	289	0.77	0.60, 0.99
1–3/month	341	404	0.98	0.79, 1.2
≥4/month	441	577	0.99	0.80, 1.2
White bread				
Nonconsumers	211	301	1.0	
<1/week	287	397	0.98	0.76, 1.2
1–3/week	467	586	1.1	0.88, 1.4
≥4/week	305	325	1.3	1.0, 1.7
Pancakes, waffles				
Nonconsumers	230	327	1.0	
<1/month	294	399	0.90	0.71, 1.1
1–3/month	475	525	1.2	0.93, 1.4
≥4/month	273	358	1.0	0.80, 1.3
Foods with added soy protein§				
Canned tuna				
Nonconsumers	161	226	1.0	
<1/month	165	282	0.69	0.51, 0.92
1–3/month	459	568	0.95	0.74, 1.2
≥4/month	486	534	1.1	0.83, 1.4
Canned chili				
Nonconsumers	614	854	1.0	
<1/month	289	366	1.0	0.82, 1.2
≥1/month	367	389	1.2	0.99, 1.4

* Columns totaling less than the total number of cases or controls reflect missing values for those variables.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age; race/ethnicity; age at menarche; parity; lactation; history of benign breast disease; family history of breast cancer; education; a composite variable including menopausal status, body mass index, and hormone replacement therapy use; and daily caloric intake.
§ Soy additives found in some but not all brands.

TABLE 3. Association between phytoestrogen consumption and breast cancer risk among women participating in the multiethnic Bay Area Breast Cancer Study, San Francisco, California, 1995–1998

Phytoestrogen (μg/day)	Cases (*n* = 1,272)	Controls (*n* = 1,610)	OR*,†	95% CI*
Isoflavones				
Genistein				
<480	304	402	1.0	
480–783	321	403	1.0	0.81, 1.3
784–1,439	359	402	1.2	0.92, 1.4
≥1,440	288	403	0.92	0.72, 1.2
per 100 μg/day			1.00	0.996, 1.001
Daidzein				
<473	288	402	1.0	
473–746	344	403	1.2	0.93, 1.5
747–1,222	323	402	1.1	0.87, 1.4
≥1,223	317	403	1.1	0.85, 1.4
per 100 μg/day			1.00	0.995, 1.001
Biochanin A				
<22	297	402	1.0	
22–41	323	403	1.1	0.91, 1.4
42–82	318	402	1.1	0.89, 1.4
≥83	334	403	1.2	0.85, 1.5
per 10 μg/day			1.00	0.99, 1.01
Formononetin				
<9	265	402	1.0	
9–19	318	403	1.2	0.97, 1.5
20–39	353	402	1.1	0.89, 1.4
≥40	336	403	1.2	0.96, 1.5
per 10 μg/day			1.01	0.99, 1.02
Total isoflavones				
<1,048	292	402	1.0	
1,048–1,647	332	403	1.1	0.87, 1.4
1,648–2,774	349	402	1.2	0.93, 1.5
≥2,775	299	403	1.0	0.79, 1.3
per 1,000 μg/day			0.99	0.98, 1.01

Table continues

pounds—may not be the most informative measure of biologic exposure. However, given the lack of association observed in this study, a more complex measure (e.g., one weighted by estrogenic activity) would not have produced different results. As illustrated in table 4, risk did not vary substantially by race/ethnicity or menopausal status.

DISCUSSION

Several epidemiologic studies have shown consumption of tofu, miso soup, or soy protein, or the urinary excretion of phytoestrogens (which reflect exposure in the last 24–48 hours), to be associated with a 20–75 percent reduction in breast cancer risk in Asian (2, 12, 15, 17), Asian-American (13), non-Asian North-American (30, 31), and Australian (14) populations. However, phytoestrogen exposure was not the primary focus of most of these studies, and results were often based on assessment of one or two soy-based food items. In addition, studies of non-Asian populations showed that soy foods often were consumed by only a small portion of the population, for example, by less than 3 percent of the women participating in the Iowa Women's Health Study (31). In examining similar associations, we observed a significant decrease in breast cancer risk associated with consumption of soy milk, but, as in other western populations, this beverage was consumed by only 3 percent of cases and 5 percent of controls.

Contrary to these observations, other Asian studies (16, 18) have found no association between breast cancer risk and consumption of soy protein and/or soy-based foods. Only three studies have examined the effects of soy by menopausal status, all in Asian or Asian-American women (12, 13, 17). Two of the three observed a risk reduction in premenopausal women but no effects in postmenopausal women (12, 17); the third found risk to be reduced in both groups, but the postmenopausal group in that study was restricted to women who were less than age 56 years. That

TABLE 3. Continued

Phytoestrogen (μg/day)	Cases (*n* = 1,272)	Controls (*n* = 1,610)	OR*,†	95% CI*
Coumestans				
Coumestrol				
<119	285	402	1.0	
119–182	322	403	1.1	0.90, 1.4
183–276	336	402	1.2	0.97, 1.5
≥277	329	403	1.4	1.1, 1.7
per 100 μg/day			1.03	0.98, 1.08
Lignans				
Matairesinol				
<18	277	402	1.0	
18–29	334	403	1.3	1.0, 1.6
30–49	363	402	1.3	1.1, 1.7
≥50	298	403	1.1	0.89, 1.5
per 10 μg/day			0.99	0.97, 1.02
Secoisolariciresinol				
<75	295	402	1.0	
75–121	338	403	1.2	0.96, 1.5
122–175	273	402	0.96	0.76, 1.2
≥176	366	403	1.3	1.0, 1.6
per 100 μg/day			1.08	0.99, 1.18
Total lignans				
<104	281	402	1.0	
104–158	349	403	1.3	1.0, 1.6
159–223	300	402	1.1	0.88, 1.4
≥224	342	403	1.3	1.0, 1.6
per 100 μg/day			1.06	0.98, 1.14
Total phytoestrogens				
<1,337	300	402	1.0	
1,337–2,029	316	403	1.0	0.81, 1.3
2,030–3,264	350	402	1.2	0.92, 1.5
≥3,265	306	403	1.0	0.80, 1.3
per 100 μg/day			0.99	0.98, 1.01

* OR, odds ratio; CI, confidence interval.

† Adjusted for age; race/ethnicity; age at menarche; parity; lactation; history of benign breast disease; family history of breast cancer; education; a composite variable including menopausal status, body mass index, and hormone replacement therapy use; and daily caloric intake.

is, the majority were recently postmenopausal. In the present study, we found the effects of phytoestrogens to be absent in both pre- and postmenopausal women at the levels of consumption we were examining.

Thus, there is some evidence that soy consumption may reduce the risk of breast cancer in non-Asian women; its effects may be stronger in premenopausal women, but the evidence is far from conclusive. The purpose of this study was to expand on these findings by examining 1) the effects on breast cancer risk of seven specific phytoestrogenic compounds by using our newly developed nutrient database for assessing phytoestrogen intake from a wide variety of foods (19) and 2) these associations in three non-Asian ethnic subgroups of pre- and postmenopausal women. For non-Asian women, who usually consume relatively few traditional soy-based foods, foods with added soy protein or flour (which are becoming increasingly common in the United States) and foods rich in lignans (another class of phytoestrogenic compounds that may act similarly to the isoflavones found in soy (5, 11)) may be equally important as traditional soy-based foods are in other populations.

However, our analyses showed no association between phytoestrogen exposure and breast cancer risk in this population. These findings were similar for breast cancer in both pre- and postmenopausal women and for specific phytoestrogenic compounds, classes of compounds, and total exposure. Note that the highest quartile of consumption in this population was about only 3 mg/day, a level equivalent to less than one serving of tofu per week. In contrast, the

TABLE 4. Association between total isoflavone consumption and breast cancer risk among subgroups of women participating in the multiethnic Bay Area Breast Cancer Study, San Francisco, California, 1995–1998

Subgroup and total isoflavones (μg/day)	Cases	Controls	OR*,†	95% CI*
Latina				
<1,048	91	162	1.0	
1,048–1,647	113	157	1.1	0.75, 1.6
1,648–2,774	124	167	1.2	0.80, 1.8
≥2,775	125	189	1.2	0.78, 1.8
per 1,000 μg/day			0.99	0.97, 1.02
African American				
<1,048	117	154	1.0	
1,048–1,647	86	95	1.2	0.80, 1.8
1,648–2,774	99	101	1.2	0.83, 1.9
≥2,775	77	94	1.0	0.65, 1.7
per 1,000 μg/day			0.99	0.97, 1.02
White				
<1,048	84	86	1.0	
1,048–1,647	133	151	0.89	0.60, 1.3
1,648–2,774	126	134	1.0	0.67, 1.6
≥2,775	97	120	0.82	0.52, 1.3
per 1,000 μg/day			0.99	0.96, 1.01
Premenopausal				
<1,048	59	79	1.0	
1,048–1,647	110	120	1.3	0.80, 2.0
1,648–2,774	105	143	0.95	0.59, 1.5
≥2,775	124	129	1.2	0.75, 2.0
per 1,000 μg/day			1.00	0.98, 1.02
Postmenopausal				
<1,048	219	312	1.0	
1,048–1,647	210	270	1.1	0.80, 1.4
1,648–2,774	234	241	1.4	1.0, 1.8
≥2,775	163	254	0.96	0.71, 1.3
per 1,000 μg/day			0.99	0.97, 1.01

* OR, odds ratio; CI, confidence interval.

† Adjusted for age; race/ethnicity; age at menarche; parity; lactation; history of benign breast disease; family history of breast cancer; education; a composite variable including menopausal status, body mass index, and hormone replacement therapy use; and daily caloric intake.

average intake of phytoestrogens in Asian countries has been estimated to range from about 15 to 30 mg/day. Thus, our findings do not preclude the possibility of a threshold effect with a reduction in risk limited to higher levels of exposure (such as those for Asian and Asian-American women). However, also of importance for public health and clinical recommendations is the study by Petrakis et al. (32), which observed that particularly high levels of daily phytoestrogen exposure may increase the risk of premenopausal breast cancer.

Finally, our study found no differences in the relative risk or prevalence of phytoestrogen consumption between women representing the three ethnic groups included in this study. Thus, dietary intake of phytoestrogens does not account for the lower risk of breast cancer observed among Latina women, disproving our previous hypothesis (33).

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