Dietary Phytoestrogens and Lung Cancer Risk

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Context Despite lung-specific in vitro and in vivo studies that support a chemopreventive role for phytoestrogens, there has been little epidemiologic research focused on dietary intake of phytoestrogens and risk of lung cancer.

Objective To examine the relationship between dietary intake of phytoestrogens and risk of lung cancer.

Design, Setting, and Participants Ongoing US case-control study of 1674 patients with lung cancer (cases) and 1735 matched healthy controls. From July 1995 through October 2003, participants were personally interviewed with epidemiologic and food frequency questionnaires to collect demographic information and to quantify dietary intake of 12 individual phytoestrogens.

Main Outcome Measure Risk of lung cancer, estimated using unconditional multivariable logistic regression analyses stratified by sex and smoking status and adjusted for established and putative lung cancer risk factors.

Results Reductions in risk of lung cancer tended to increase with each increasing quartile of phytoestrogen intake. The highest quartiles of total phytosterols, isoflavones, lignans, and phytoestrogens were each associated with reductions in risk of lung cancer ranging from 21% for phytosterols (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.64-0.97; $P=.03$ for trend) to 46% for total phytoestrogens from food sources only (OR, 0.54; 95% CI, 0.42-0.70; $P<.001$ for trend). Sex-specific effects were also apparent. For men, statistically significant trends for decreasing risk with increasing intake were noted for each phytoestrogen group, with protective effects for the highest quartile of intake ranging from 24% for phytosterols (OR, 0.76; 95% CI, 0.56-1.02; $P=.04$ for trend) to 44% for isoflavones (OR, 0.56; 95% CI, 0.41-0.76; $P<.001$ for trend), while in women, significant trends were only present for intake of total phytoestrogens from food sources only, with a 34% (OR, 0.66; 95% CI, 0.46-0.96; $P=.01$ for trend) protective effect for the highest quartile of intake. The apparent benefits of high phytoestrogen intake were evident in both never and current smokers but less apparent in former smokers. In women, statistically significant joint effects were evident between hormone therapy use and phytoestrogen intake. Specifically, high intake of the lignans enterolactone and enterodiol and use of hormone therapy were associated with a 50% (OR, 0.50; 95% CI, 0.31-0.68; $P=.04$ for interaction) reduction in risk of lung cancer.

Conclusions While there are limitations and concerns regarding case-control studies of diet and cancer, these data provide further support for the limited but growing epidemiologic evidence that phytoestrogens are associated with a decrease in risk of lung cancer. Confirmation of these findings is still required in large-scale, hypothesis-driven, prospective studies.

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DIETARY PHYTOESTROGENS ARE plant-derived nonsteroidal compounds with weak estrogen-like activity. Most phytoestrogens exist in the diet as inactive compounds and, following consumption, undergo enzymatic conversion in the gastrointestinal tract, resulting in the formation of compounds with a steroidal structure similar to that of estrogens.[1] Phytoestrogens are subdivided into 3 main classes: isoflavones, lignans, and cumestrans. The isoflavones and the lignans are the 2 main groups of hormone-like diphenolic dietary phytoestrogens. On ecologic analysis, both have been found in high levels in the plasma of individuals living in areas with relatively low cancer incidence.[2]

Isoflavones are the most common form, and most extensively investigated, of the phytoestrogens. The 2 major forms of isoflavones, genistein and daidzein, are formed from the precursors genistin and daidzin and are found in a variety of sources, including soy products, soybeans, chickpeas, and red clover.[2,3] The lignan metabolites, enterolactone and enterodiol, are formed from the precursors matairesinol and secoisolariciresinol. Lignans are derived from rye grains, linseeds, carrots, tea, spinach, broccoli, and other vegetables.[1,2] Coumesterol is the predominant estrogenic phytoestrogen in the cumestran group and is mainly found in beans, peas, clover, spinach, and sprouts.[4] A fourth group of plant-derived steroidal compounds that is believed to have estrogenic properties are

See also pp 1505 and 1550.

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the phytosterols, which are derived from the intestinal absorption of vegetable oils, margarines, spreads, grains, and certain fruits and vegetables.[5,6] Although structurally similar to cholesterol, phytosterols (which include beta-sitosterol, campesterol, and stigmasterol) could affect levels of endogenous hormones through alterations in bile acid metabolism and estrogen reabsorption or by acting as substrates for synthesis of steroid hormones.[7]

Previously, we have documented that self-reported use of hormone therapy was a significant protective factor for lung cancer in women.[8] We wished to further explore the compelling concept that estrogen or estrogen-like compounds play a role in chemoprevention. Specific chemopreventive effects putatively associated with phytoestrogens include cell cycle regulation, inhibition of invasion and metastasis, antioxidant activity, induction of apoptosis, inhibition of endothelial cell proliferation, and inhibition of angiogenesis.[9-20] In further support for a chemopreventive role of phytoestrogens, epidemiologic studies have revealed a relatively consistent association between higher intake of phytoestrogens and reduced risk for cancers of the breast,[21,22] endometrium,[23,24] and prostate.[25-27] In spite of the lung-specific in vitro and in vivo studies[9-20] that support a chemopreventive role for phytoestrogens, at present there is limited epidemiologic evidence for a role of phytoestrogens in risk of lung cancer, but, overall, results have been suggestive of a protective effect.[28-33]

To shed more light on the role of phytoestrogens in risk of lung cancer, we analyzed dietary intake and risk factor data from a case-control study designed to study genetic susceptibility to lung cancer. To our knowledge, this is the largest case-control study to examine dietary phytoestrogens and risk of lung cancer in a US population.

METHODS

Study Population

From July 1995 through October 2003, 1674 patients with lung cancer (cases) and 1735 matched healthy controls were accrued from an ongoing and previously described case-control study of lung cancer.[34] Case patients with histologically confirmed lung cancer were recruited prior to initiation of radiotherapy or chemotherapy from The University of Texas M. D. Anderson Cancer Center, Houston. There were no age, sex, ethnic, or stage restrictions. Healthy controls, without a previous diagnosis of cancer, were recruited from the Kelsey-Seybold Clinics, Houston's largest private multispecialty physician group, which includes a network of 23 clinics and more than 300 physicians. Controls were frequency matched to the cases on age (±5 years), sex, ethnicity, and smoking status (current, former, never). All cases and controls were US residents. To date, the response rate among both cases and controls has been approximately 75%. This research was approved by the M. D. Anderson Cancer Center and Kelsey-Seybold institutional review boards, and all participants provided written informed consent.

Epidemiologic and Phytoestrogen Data

All study participants completed a personal interview to obtain information on demographics, socioeconomics (ie, annual income and education), and smoking history. Women were asked whether they had taken hormone therapy in the previous 6 months, and, if known, the type of hormone therapy was recorded. Ever smokers were defined as individuals who had smoked at least 100 cigarettes in their lifetime; of those, former smokers were defined as ever smokers who had quit smoking at least 1 year before diagnosis (cases) or before interview (controls). Race/ethnicity information (white, Hispanic, African American, or other) was obtained for matching purposes and to control for confounding and was self-reported by participants either as open-ended responses or by choosing race-ethnicity from an investigator-provided list.

Additionally, a food frequency questionnaire (a modified version of the National Cancer Institute's Health Habits and History Questionnaire[35]) was used to collect dietary data. The questionnaire includes a semiquantitative food frequency list made up of food and beverage items, ethnic foods commonly consumed in the Houston area, an open-ended section, and other dietary behavior questions regarding such factors as dining at restaurants and food preparation methods. The questionnaire has been shown to be a valid and reliable food frequency tool across various populations.[36,37] Study participants were asked about their diet during the year prior to diagnosis (cases) and the year prior to enrollment into the study (controls).

Nutrient intake was calculated using the DIETSYS+Plus version 5.9 dietary analysis program (Block Dietary Data Systems, Berkeley, Calif). The DIETSYS+Plus database has been expanded to include phytoestrogen values in edible parts of plant foods consumed in the United States. Detailed methods of the creation of the database, its limitations,[38] and its application to assess risk of prostate[25] and testicular[39] cancer have been published previously. To update the database, a detailed literature search was conducted for food values published after a study by Pillow et al,[38] and updated values were calculated and assigned to each food using published guidelines.[38] New food values were derived from published literature[40-44] and from a database maintained by the US Department of Agriculture, Agricultural Research Service.[45] Additionally, the DIETSYS+Plus database was updated using release 16-1 of the US Department of Agriculture National Nutrient Database for Standard Reference.[46] For multi-ingredient dishes not available in release 16-1 or the updated phytoestrogen database, nutrient values were estimated as needed from appropriate recipes found in the Continuing Survey of Food Intakes by Individuals, 1994-1996, 1998.[47] Recipe adjustments were made, where required, for moisture changes and nutrient loss due to cooking.

Summary measures of total phytoestrogen intakes were generated for

phytosterols (summation of beta-sitosterol, campesterol, and stigmasterol), isoflavones (biochanin A, daidzein, genistein, and formononetin), lignans (enterolactone, enterodiol, matairesinol, and secoisolariciresinol), soy-derived isoflavones (daidzein and genistein), lignan precursors (enterolactone and enterodiol), and lignan metabolites (matairesinol and secoisolariciresinol). Summary measures of total phytoestrogen intake were generated based on the summation of each individual phytoestrogen and of those derived from food sources only, excluding phytoestrogens abundantly derived from coffee and tea, ie, beta-sitosterol, formononetin, matairesinol, and secoisolariciresinol.

Statistical Analysis

All analyses were performed using Intercooled STATA version 8.0 (Stata Corp, College Station, Tex). The Pearson χ^2 test was used to test the differences between the cases and controls in terms of sex, ethnicity, smoking status, education, and income. The *t* test was used to test differences in mean age, cigarettes smoked per day, years of smoking, and total intakes of energy, protein, fat, and carbohydrates. The Wilcoxon rank-sum test was used to test for differences in phytoestrogen intake. The Spearman rank correlation coefficient was used to test the correlation between each individual phytoestrogen. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as an estimate of the relative risk. With 95% power and a 2-sided significance level of 5%, the study had statistical power to detect a significant OR of 0.76 (ie, a 24% reduced risk) for individuals in the highest quartile of intake.

Unconditional multivariable logistic regression analyses were performed to control for confounding by age, sex, ethnicity, smoking status, cigarettes smoked per day, years of smoking, education, income, body mass index (calculated as weight in kilograms divided by the square of height in meters), and total energy, where appropriate. The final logistic regression model includes variables that were considered biologically relevant and statistically significant in the multivariable model. Statistically significant variables were added if they improved the fit and predictive power of the model and if they were statistically significant by the likelihood ratio test. Matching variables were retained in the

Table 1. Characteristics of Cases and Controls

Variable	Cases (n = 1674)	Controls (n = 1735)	*P* Value*
Age, mean (SD), y	62.1 (10.3)	61.5 (9.4)	.11
Sex, No. (%)			
Men	900 (53.8)	887 (51.1)	.12
Women	774 (46.2)	848 (48.9)	
Race/ethnicity, No. (%)			
White	1324 (79.1)	1340 (77.2)	.35
Black	242 (14.5)	265 (15.3)	
Hispanic	108 (6.4)	130 (7.5)	
Smoking			
Status, No. (%)			
Never	266 (15.9)	290 (16.7)	.10
Former	730 (43.6)	804 (46.3)	
Current	678 (40.5)	641 (37.0)	
Years of smoking, mean (SD), No.			
Former	32.6 (12.7)	27.8 (12.1)	<.001
Current	40.1 (11.0)	38.5 (11.2)	.008
Cigarettes per day, mean (SD), No.			
Former	26.7 (15.0)	26.7 (15.4)	.98
Current	27.4 (13.2)	21.5 (12.1)	<.001
Education, No. (%)			
Did not complete high school	309 (18.5)	150 (8.6)	<.001
Completed high school	478 (28.5)	315 (18.2)	
Some college	465 (27.8)	634 (36.5)	
Completed college or beyond	422 (25.2)	636 (36.7)	
Annual income, No. (%), $			
≤29 999	570 (34.0)	356 (20.5)	<.001
30 000 to 74 999	647 (38.6)	767 (44.2)	
≥75 000	359 (21.5)	505 (29.1)	
Refused to answer	98 (5.9)	107 (6.2)	<.001
Body mass index, mean (SD)†			
Overall	26.2 (5.2)	28.2 (5.5)	<.001
Men	26.4 (4.7)	28.3 (4.7)	<.001
Women	26.0 (5.8)	28.1 (6.1)	<.001
Total nutrient intake, mean (SD)			
Energy, kcal/d			
Overall	2026.7 (674.1)	2031.0 (659.4)	.85
Men	2264.6 (681.9)	2254.6 (664.5)	.75
Women	1750.1 (547.8)	1797.1 (566.8)	.09
Protein, g/d			
Overall	72.9 (23.7)	74.5 (25.1)	.02
Men	80.5 (23.8)	83.0 (26.1)	.03
Women	64.0 (20.3)	66.1 (20.8)	.04
Fat, g/d			
Overall	88.1 (33.2)	87.8 (34.4)	.82
Men	97.2 (33.9)	96.8 (35.6)	.84
Women	77.5 (29.0)	78.3 (30.4)	.56
Carbohydrates, g/d			
Overall	229.1 (84.2)	230.6 (80.5)	.60
Men	252.6 (86.9)	252.5 (81.9)	.98
Women	201.8 (71.8)	207.6 (72.2)	.10

*From the χ^2 test for categorical variables and *t* test for continuous variables. All *P* values are 2-sided.
†Calculated as weight in kilograms divided by square of height in meters.

model to account for the possibility of residual confounding. Phytoestrogen intake was categorized by the quartile intake values in the controls. Trend tests for the quartiles of intake were performed by creating a categorical variable and assigning the score *j* to the *j*th quartile of intake. The categorical variable was treated as an interval predictor in the multivariable logistic models. In the joint-effects analyses, intake was dichotomized at the 75th percentile in the controls; intake above this cutpoint was considered "high." Interaction was tested on the multiplicative scale by entering product terms in the main-effects multivariable models.

RESULTS

Data from 1674 patients with lung cancer and 1735 controls were available for this analysis (TABLE 1). There were no statistically significant differences between the cases and the controls in terms of age, sex, ethnicity, and smoking status. In general, cases reported heavier smoking histories. For current smokers, cases had smoked cigarettes for a mean of 40.1 (SD, 11.0) years compared with 38.5 (SD, 11.2) years for controls ($P=.008$), while among former smokers, mean duration of smoking was 32.6 (SD, 12.7) years for cases compared with 27.8 (SD, 12.1) years for controls ($P<.001$). There was no difference between cases and controls in number of cigarettes smoked per day for former smokers. However, cases were self-reported heavier current smokers (mean, 27.4 [SD, 13.2] cigarettes per day) than were controls (mean, 21.5 [SD, 12.1] cigarettes per day) ($P<.001$). Controls self-reported significantly higher annual incomes and educational attainment compared with the cases. Overall and by sex, controls exhibited significantly higher current body mass index compared with cases (overall mean, 28.2 [SD, 5.5] vs 26.2 [SD, 5.2], respectively; $P<.001$). Although controls reported higher intakes of total protein, there were essentially no case-control differences in total intakes of energy, fat, and carbohydrates.

Overall, consumption of phytoestrogens was statistically significantly higher in controls than in cases (TABLE 2), attributed largely to variation in intake for men. In women, only intake of total phytoestrogens from food sources was statistically significantly higher in controls than in cases. Data on the isoflavone glycitein were excluded, since only 12% of the cases and 15% of the controls reported any intake. For the isoflavones daidzein and genistein, more than 86% of the cases and 96% of the controls reported some intake. All cases and controls reported some quantifiable intake for the other phytoestrogens. The phytoestrogen intakes were not energy adjusted, since there was no difference in total energy intake between cases and controls, total energy was not correlated with any of the phytoestrogens, and there were no appreciable differences in the results when energy-adjusted values were explored.

We also evaluated the top 5 food sources for each phytoestrogen (TABLE 3) and assessed the correlations between each individual phytoestrogen. The correlation coefficients were generally low for most of the phytoestrogens ($\rho=-0.02$ to 0.39), although some were moderately to highly correlated ($\rho=0.49$ to 0.99). The major dietary sources for beta-sitosterol, matairesinol, secoisolariciresinol, and formononetin were coffee and tea, and they were all moderately to highly correlated with each other ($\rho=0.50$ to 0.89). The lignan precursors matairesinol and secoisolariciresinol exhibited moderate correlation ($\rho=0.55$, $P<.001$). Additionally, the lignan metabolites enterolactone and enterodiol were highly correlated ($\rho=0.89$, $P<.001$), and both

Table 2. Phytoestrogen Intake

Variable	Median (IQR) Cases	Median (IQR) Controls	*P* Value*
Total phytosterols, mg/d†			
Overall	256.7 (132.3-619.9)	302.3 (150.6-664.6)	.001
Men	253.6 (137.4-605.4)	307.5 (159.1-663.2)	.004
Women	260.9 (126.9-633.4)	295.3 (144.7-672.2)	.07
Coumesterol, µg/d			
Overall	137.2 (76.6-229.5)	151.6 (86.0-242.9)	<.001
Men	144.2 (82.2-252.9)	174.7 (108.6-280.6)	<.001
Women	130.4 (69.6-207.6)	131.2 (73.9-207.2)	.87
Total isoflavones, µg/d‡			
Overall	527.2 (268.8-940.6)	588.9 (306.6-996.9)	<.001
Men	554.6 (290.1-992.5)	664.5 (404.8-1087.8)	<.001
Women	502.2 (252.7-803.9)	513.5 (263.7-874.6)	.20
Total lignans, mg/d§			
Overall	5.4 (3.3-8.9)	5.8 (3.7-9.6)	<.001
Men	5.7 (3.4-9.5)	6.4 (4.0-10.1)	<.001
Women	5.1 (3.3-8.4)	5.3 (3.3-8.8)	.28
Total phytoestrogens, mg/d			
From all sources‖			
Overall	265.1 (139.4-635.3)	309.3 (158.9-674.8)	<.001
Men	263.8 (145.6-619.4)	314.6 (166.5-672.9)	<.001
Women	267.3 (132.8-646.9)	300.5 (151.1-679.5)	.06
From food sources only¶			
Overall	36.2 (26.3-49.1)	38.9 (27.8-53.5)	<.001
Men	38.7 (27.9-51.5)	41.8 (29.1-56.9)	.002
Women	33.5 (24.8-45.5)	35.9 (26.4-49.4)	.01

Abbreviation: IQR, interquartile range.
*From the Wilcoxon rank-sum (Mann-Whitney) test.
†Summation of beta-sitosterol, campesterol, and stigmasterol.
‡Summation of biochanin A, daidzein, genistein, and formononetin.
§Summation of enterolactone, enterodiol, matairesinol, and secoisolariciresinol.
‖Summation of total phytosterols, coumesterol, total isoflavones, and total lignans.
¶Excluding phytoestrogens from coffee and tea sources, ie, beta-sitosterol, formononetin, matairesinol, secoisolariciresinol.

were derived from a variety of fruit and vegetable sources. Daidzein and genistein were tightly correlated with each other ($\rho = 0.99$, $P < .001$), both being abundantly derived from soy sources.

Overall, there was a 21% reduced risk (OR, 0.79; 95% CI, 0.64-0.97) for individuals in the highest quartile of total phytosterol intake, with a statistically significant trend ($P = .03$) for decreasing risk with increasing intake after adjusting for age, sex, ethnicity, smoking status, cigarettes smoked per day, years of smoking, education, income, body mass index, and total energy (TABLE 4). The highest quartile of phytosterol intake was also associated with borderline significant effects for men (OR, 0.76; 95% CI, 0.56-1.02) and for women (OR, 0.79; 95% CI, 0.58-1.07). In the highest quartile of isoflavone intake, there was a 32% overall reduced risk (OR, 0.68; 95% CI, 0.54-0.85), with reduced risks of 44% (OR, 0.56; 95% CI, 0.41-0.76) and 22% (OR, 0.78; 95% CI, 0.57-1.06) for men and women, respectively. Again, there was a statistically significant trend ($P = .006$) for decreasing risk with increasing intake for total lignan intake, with a 28% reduced risk of lung cancer (OR, 0.72; 95% CI, 0.58-0.89) for the highest quartile of intake, and a similar estimate for lignan intake for men (OR, 0.73, 95% CI, 0.54-0.98). No statistically significant effects or trends were observed for lignan intake in women.

Overall, the reduction in risk of lung cancer was 24% (OR, 0.76; 95% CI, 0.61-0.94) for those with the highest intake of total phytoestrogens from all sources and 46% (OR, 0.54; 95% CI, 0.42-0.70) for highest intake of total phytoestrogens from food sources only. Both total phytoestrogen summary variables yielded statistically significant trends for decreasing risk with increasing intake. The highest quartile of each total phytoestrogen summary measure was also associated with reductions in risk of lung cancer ranging from 27% to 43% for men and 22% to 34% for women (Table 4).

The protective effect for the highest quartile of soy-derived isoflavones was statistically significant both for women (OR, 0.56; 95% CI, 0.42-0.75) and even more so for men (OR, 0.28; 95% CI, 0.21-0.37) (TABLE 5). The OR for the highest quartile of lignan metabolites was borderline significant for men (OR,

Table 3. Top 5 Food Sources for Each Phytoestrogen, as Reported by Cases and Controls

Phytoestrogen	%	Food
Phytosterols		
Beta-sitosterol	77	Tea, black
	7	Tea, green
	3	Oil, vegetable
	1	Salads made with lettuce
	1	Black-eyed peas or kidney beans
Campesterol	15	Oil, vegetable
	12	Breads, dark
	9	Mayonnaise or mayonnaise substitutes
	8	Oranges
	7	Soft margarine
Stigmasterol	19	Salads made with lettuce
	11	Oil, vegetable
	11	Black-eyed peas or kidney beans
	7	Mayonnaise or mayonnaise substitutes
	6	Bananas
Coumesterol	45	Beans, refried or pinto
	19	Chinese dishes
	12	Orange juice
	7	Breads (white, French, Italian)
	5	Doughnuts and other pastries
Isoflavones		
Biochanin A	46	Snow peas
	28	Black-eyed peas or kidney beans
	17	Beans, refried or pinto
	4	Beans (black, navy, white, lima, baked)
	2	Chili
Daidzein	79	Breakfast shakes or diet shakes
	15	Soy sources
	3	Tofu
	2	Chinese dishes
	<1	Breads, dark
Genistein	87	Breakfast shakes or diet shakes
	9	Soy sources
	3	Tofu
	<1	Chinese dishes
	<1	Breads, dark
Formononetin	99	Coffee
	<1	Chinese dishes
	<1	Peanut butter or peanuts
	<1	Beer, light
	<1	Breads, dark
Lignans		
Lignan precursors		
Matairesinol	82	Tea, black
	7	Tea, green
	5	Salads made with lettuce
	<1	Strawberries
	<1	Green beans
Secoisolariciresinol	52	Coffee
	28	Tea, black
	6	Flaxseed or flaxseed bread
	4	Tea, green
	4	Cranberries or cranberry juice
Lignan metabolites		
Enterolactone	11	Carrots
	8	Salads made with lettuce
	7	Bananas
	7	Broccoli
	6	Breads, dark
Enterodiol	14	Salads made with lettuce
	13	Flaxseed or flaxseed products
	11	Onions
	8	White potatoes (boiled, baked, or mashed)
	4	French fries or fried potatoes

Table 4. Phytoestrogens (Quartiles) and Risk of Lung Cancer

Variable	No. Cases	No. Controls	Multivariable OR (95% CI)*	*P* for Trend
Total phytosterols, mg/d				
Overall				
≤150.6	505	433	1.00	.03
150.7-302.3	424	435	0.84 (0.69-1.03)	
302.4-664.6	375	434	0.81 (0.66-1.00)	
≥664.7	370	433	0.79 (0.64-0.97)	
Men				
≤159.1	282	221	1.00	.04
159.2-307.5	234	223	0.84 (0.63-1.12)	
307.6-663.2	194	221	0.75 (0.56-1.00)	
≥663.3	190	222	0.76 (0.56-1.02)	
Women				
≤144.7	231	212	1.00	.28
144.8-295.3	182	212	0.84 (0.62-1.13)	
295.4-672.2	184	212	0.90 (0.67-1.22)	
≥672.3	177	212	0.79 (0.58-1.07)	
Total isoflavones, µg/d				
Overall				
≤306.6	470	433	1.00	<.001
306.7-588.9	496	434	0.96 (0.78-1.17)	
589.0-996.9	347	435	0.68 (0.54-0.84)	
≥997.0	361	433	0.68 (0.54-0.85)	
Men				
≤404.8	302	222	1.00	<.001
404.9-664.5	211	222	0.66 (0.50-0.87)	
664.6-1087.8	198	221	0.58 (0.43-0.77)	
≥1087.9	189	222	0.56 (0.41-0.76)	
Women				
≤263.7	205	212	1.00	.31
263.8-513.5	191	212	0.87 (0.65-1.18)	
513.6-874.6	206	212	1.07 (0.79-1.44)	
≥874.7	172	212	0.78 (0.57-1.06)	
Total lignans, mg/d				
Overall				
≤3.7	520	434	1.00	.006
3.8-5.8	378	434	0.79 (0.64-0.97)	
5.9-9.6	392	433	0.76 (0.62-0.93)	
≥9.7	384	434	0.72 (0.58-0.89)	
Men				
≤4.0	297	221	1.00	.03
4.1-6.4	195	222	0.75 (0.56-1.00)	
6.5-10.1	203	222	0.72 (0.54-0.96)	
≥10.2	205	222	0.73 (0.54-0.98)	
Women				
≤3.3	197	212	1.00	.50
3.4-5.3	204	212	1.06 (0.79-1.42)	
5.4-8.8	190	212	0.95 (0.70-1.29)	
≥8.9	183	212	0.88 (0.64-1.21)	

(continued)

0.75; 95% CI, 0.54-1.04) but achieved statistical significance for women (OR, 0.59; 95% CI, 0.43-0.82), while the highest quartile of lignan precursors was associated with a significantly protective estimate for men (OR, 0.73; 95% CI, 0.54-0.98) but not women (OR, 0.89; 95% CI, 0.65-1.22).

Six of the summary measures were further analyzed by smoking status (TABLE 6). For current smokers, the highest quartiles of intake for each of the phytoestrogen groups were associated with significant reductions in risk ranging from 31% to 58%, and statistically significant trends were noted for all phytoestrogen groups except total phytoestrogens from food sources only ($P=.16$). For former smokers, the protective effects were generally attenuated, and statistically significant trends were observed only for total phytoestrogens from food sources and for soy-derived isoflavones. Protective effects were evident for never smokers in all analyses, although the only statistically significant trends were observed for total intake of phytoestrogens from food sources.

As we demonstrated previously,[8] use of hormone therapy was significantly protective in the present analysis (OR, 0.74; 95% CI, 0.59-0.91). The combination of use of hormone therapy and high intake of enterolactone and enterodiol (TABLE 7) was associated with a 50% reduced risk (OR, 0.50; 95% CI, 0.31-0.68; $P=.04$ for interaction), compared with the 26% reduced risk for hormone therapy use alone and the 27% reduced risk for high intake of enterolactone and enterodiol (OR, 0.73; 95% CI, 0.56-0.95). A similar trend but with lesser effects was observed for the joint effects of hormone therapy use and high intake of daidzein and genistein (OR, 0.58; 95% CI, 0.40-0.85; $P=.79$ for interaction) compared with the main effects of high intake (OR, 0.87; 95% CI, 0.67-1.11). There was no evidence for joint effects of hormone therapy use and total intake of phytoestrogens from food sources, and there was no evidence of statistical interaction ($P=.13$ for interaction).

COMMENT

Because we have previously shown that use of hormone therapy was a statistically significant protective factor for lung cancer in women,[8] in this article we used a food frequency questionnaire to assess phytoestrogen intake to determine whether dietary phytoestrogens also modulate risk of lung cancer. Our main

findings were that patients with lung cancer tended to consume lower amounts of phytoestrogens than controls, that there were sex-specific differences both in intake and in protective effects, and that the apparent benefits were evident in both never and current smokers but less so in former smokers.

The present study, with a sample size of 1674 cases and 1735 controls, had reasonable power to detect small to moderate statistically significant ORs. As expected, there was a dose-response relationship evident, with reduction in risk with each increasing quartile of phytoestrogen intake. The highest quartiles of total phytosterols, isoflavones, lignans, and phytoestrogens were each associated with protective effects ranging from 21% to 46%. Sex-specific analyses were performed since there are sex-dependent differences in the presence of estrogen receptors in lungs.[48] For men, statistically significant trends were noted for each phytoestrogen, while in women, significant trends were only present for phytoestrogens from all sources. Although estrogen receptors have been detected to a greater extent in adenocarcinomas than in squamous cell cancers,[49] no appreciable differences in the ORs were observed when the data were explored for histology-specific effects.

In addition to a variety of chemopreventive effects,[9-20] phytoestrogens possess both estrogen agonist and antagonist properties, which in turn may be responsible for some of their putative benefits, such as cardioprotection, reduced osteoporosis, increased cognitive function, and chemoprevention. Many phytoestrogens have a particular affinity for estrogen receptors that are present in normal and malignant lung tissue[50] and could have a role in the regulation[51] or deregulation of cancer growth and hormonal responsiveness.

Most of the epidemiologic evidence supporting a role for phytoestrogens in risk of lung cancer has come from studies in Asian populations,[28-32] who typically consume large quantities of phytoestrogens. Wakai et al[28] observed that nonfermented soy foods protected against lung cancer in Japanese men, and a reduced risk of squamous cell carcinoma was observed for consumption of tofu, a rich source of phytoestrogens, in both men and women. Reduced risk for lung cancer with soy consumption has also been reported in several studies in China.[29-32] In a prospective study in Finland, dietary flavonoids, a broad group of compounds that include isoflavones, were also inversely associated with risk of lung cancer.[33]

Although several of the phytoestrogens in this study were derived from coffee and tea, at present there is inconsistent epidemiologic evidence to support a relationship between coffee or tea consumption and risk of lung cancer. In fact, both have been reported to be protective,[52] to have no effect,[53,54] and to be a putative risk factor for lung cancer.[53,55,56] Thus, to explore the effects of phytoestrogens from food sources only, we excluded the specific phytoestrogens abundantly derived from coffee and tea. The highest quartile of phytoestrogens from food sources was associated with an overall 46% reduction in risk, with substantial protective effects for both men and women, and with statistically significant trends for decreasing risk with in-

Table 4. Phytoestrogens (Quartiles) and Risk of Lung Cancer (cont)

Variable	No. Cases	No. Controls	Multivariable OR (95% CI)*	*P* for Trend
Total phytoestrogens from all sources, mg/d				
Overall				
≤158.9	520	433	1.00	.02
159.0-309.3	408	434	0.77 (0.62-0.94)	
309.4-974.8	375	434	0.77 (0.63-0.95)	
≥974.9	371	434	0.76 (0.61-0.94)	
Men				
≤166.5	287	222	1.00	.03
166.6-314.5	228	221	0.77 (0.57-1.03)	
314.6-672.9	193	223	0.70 (0.53-0.94)	
≥673.0	192	221	0.73 (0.54-0.99)	
Women				
≤151.1	233	212	1.00	.25
151.2-300.5	180	212	0.81 (0.60-1.09)	
300.6-679.5	183	212	0.88 (0.65-1.19)	
≥679.6	178	212	0.78 (0.58-1.06)	
Total phytoestrogens from food sources only, mg/d†				
Overall				
≤27.8	476	434	1.00	<.001
27.9-38.9	468	434	0.93 (0.76-1.14)	
39.0-56.9	424	434	0.85 (0.68-1.06)	
≥57.0	306	433	0.54 (0.42-0.70)	
Men				
≤29.1	260	221	1.00	.003
29.2-41.8	238	223	0.85 (0.64-1.13)	
41.9-56.9	228	221	0.88 (0.66-1.20)	
≥57.0	174	222	0.57 (0.39-0.79)	
Women				
≤26.4	225	212	1.00	.01
26.5-35.9	209	212	0.91 (0.68-1.21)	
36.0-49.4	192	212	0.84 (0.61-1.16)	
≥49.5	148	212	0.66 (0.46-0.96)	

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for age, sex, ethnicity, smoking status, cigarettes smoked per day, years of smoking, education, income, body mass index, and total energy, where appropriate.
†Excluding phytoestrogens from coffee and tea sources, ie, beta-sitosterol, formononetin, matairesinol, secoisolariciresinol.

creasing intake. On the other hand, when the lignan precursors were combined, there was a 27% reduction in risk of lung cancer for the highest quartile of consumption, with a statistically significant trend overall and for men.

Table 5. Phytoestrogen Food Groups (Quartiles) and Risk of Lung Cancer

Variable	No. Cases	No. Controls	Multivariable OR (95% CI)*	*P* for Trend
Soy-derived isoflavones (daidzein and genistein), µg/d				
Overall				
≤8.2	759	431	1.00	<.001
8.3-38.2	381	439	0.47 (0.40-0.58)	
38.3-83.1	248	431	0.33 (0.27-0.40)	
≥83.2	286	434	0.39 (0.32-0.48)	
Men				
≤9.1	471	221	1.00	<.001
9.2-38.2	181	222	0.37 (0.28-0.48)	
38.3-83.1	116	220	0.24 (0.18-0.33)	
≥83.2	132	224	0.28 (0.21-0.37)	
Women				
≤6.1	285	213	1.00	<.001
6.2-38.2	203	211	0.70 (0.53-0.91)	
38.3-83.1	130	212	0.47 (0.35-0.63)	
≥83.2	156	212	0.56 (0.42-0.75)	
Lignan metabolites (enterolactone and enterodiol), µg/d				
Overall				
≤251.6	555	434	1.00	<.001
251.7-354.3	489	434	0.97 (0.80-1.18)	
354.4-478.1	332	433	0.69 (0.56-0.85)	
≥478.2	298	434	0.67 (0.53-0.84)	
Men				
≤261.1	272	221	1.00	.02
261.2-370.5	281	222	1.16 (0.88-1.53)	
370.6-498.5	182	222	0.82 (0.61-1.11)	
≥498.6	165		0.75 (0.54-1.04)	
Women				
≤241.9	275	212	1.00	<.001
242.0-335.9	219	212	0.90 (0.68-1.19)	
336.0-459.2	147	212	0.61 (0.45-0.84)	
≥459.3	133	212	0.59 (0.43-0.82)	
Lignan precursors (matairesinol and secoisolariciresinol), µg/d				
Overall				
≤3412.9	514	434	1.00	.004
3413.0-5357.6	368	434	0.76 (0.62-0.93)	
5357.7-9115.9	407	433	0.80 (0.65-0.98)	
≥9116.0	385	434	0.73 (0.59-0.90)	
Men				
≤3672.5	298	222	1.00	.02
3672.6-5957.9	195	222	0.76 (0.57-1.00)	
5958.0-9697.4	201	221	0.73 (0.55-0.97)	
≥9697.5	206	222	0.73 (0.54-0.98)	
Women				
≤2940.7	195	212	1.00	.51
2940.8-4963.7	198	212	1.04 (0.78-1.40)	
4963.8-8401.8	198	212	0.99 (0.73-1.35)	
≥8401.9	183	212	0.89 (0.65-1.22)	

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for age, sex, ethnicity, smoking status, cigarettes smoked per day, years of smoking, education, income, body mass index, and total energy, where appropriate.

For total isoflavones, there were substantial protective effects with increasing quartiles overall and for men, but statistically significant protective effects were not found for women. The median intake of total isoflavones for women controls was 588.9 µg/d (approximately 0.6 mg/d). By comparison, Seow et al[32] reported an intertertile range of 9.9 to 24.5 mg/d of total isoflavones for healthy Singapore Chinese women, and Horn-Ross et al[23] reported a median intake of 1.7 mg/d among healthy women in the San Francisco Bay Area. Duncan et al[21] estimated isoflavone intakes to be about 25 to 40 mg/d for Asian women and less than 1 mg/d for postmenopausal women living in the United States. Although isoflavone estimates in the present study may be lower compared with those in other studies, they are not necessarily underestimated. Since soy foods are major contributors to isoflavone intake, diets of Asian origin or in areas with a considerable Asian population, such as San Francisco, typically would have much higher soy isoflavone content. Therefore, regional differences could contribute to the differences in the reported values. We could not compare values for men, since at present there are no published data available.

We analyzed the isoflavones genistein and daidzein together, since they were highly correlated; are abundantly derived from soy food sources; and because soy has been identified as having an important role in reducing the risk of various epithelial cancers, including lung cancer.[9-20,28-33] Statistically significant trend tests were found for the protective effects of increasing soy intake, and there was an overall 61% protective effect (72% reduction for men and 44% for women) in the highest quartile of soy isoflavone intake.

The highest quartile of total lignans was also associated with an overall significant protective effect for men but not for women. Because lignan metabolites are not found in plant foods and are actually derived from lignan precursors, we opted to sum the lignans and to separate the precursors from the

metabolites. There are limited published data on the food values of lignan metabolites because these values are obtained through a metabolic in vitro laboratory assay. Hence, the food values for the lignan precursors include a wider variety of food sources, which explains why the metabolites and precursors appear to be unique from each other in this analysis. When the values for tea and coffee were "zeroed" for the precursors, their major food sources were quite similar to those of the metabolites. Lignans are generally plant-derived micronutrients, so the observed protective effects could also be attributed to 1 or more actions of other micronutrients found in fruits and vegetables, including isothiocyanates,[57] folate,[58] and carotenoids.[59]

Phytosterols are not classified as a phytoestrogen, but they are a weak agonist for estrogen receptors,[60] a potential environmental endocrine disruptor,[61] and have chemopreventive properties including anti-inflammatory, antipyretic,[62] antineoplastic, and immune modulation.[63] In this study, phytosterols were generally correlated with the lignans, derived from

Table 6. Phytoestrogens and Risk of Lung Cancer, by Smoking Status

	Never Smokers			Former Smokers			Current Smokers		
	No.			No.			No.		
Quartiles of Phytoestrogens*	Cases	Controls	Multivariable OR (95% CI)†	Cases	Controls	Multivariable OR (95% CI)‡	Cases	Controls	Multivariable OR (95% CI)‡
Total phytosterols									
1	87	72	1.00	207	201	1.00	208	160	1.00
2	55	73	0.63 (0.36-1.09)	191	201	1.08 (0.79-1.47)	178	161	0.75 (0.53-1.06)
3	63	73	0.57 (0.34-0.97)	170	201	0.91 (0.66-1.24)	149	160	0.75 (0.53-1.08)
4	61	72	0.63 (0.37-1.07)	162	201	0.92 (0.67-1.27)	143	160	0.68 (0.48-0.97)
P for trend			.06			.68			.05
Total isoflavones									
1	75	72	1.00	200	201	1.00	217	160	1.00
2	61	73	0.72 (0.42-1.23)	216	201	1.00 (0.75-1.34)	194	161	0.93 (0.66-1.31)
3	68	73	0.81 (0.47-1.41)	135	201	0.71 (0.52-0.98)	129	160	0.52 (0.36-0.74)
4	62	72	0.53 (0.30-0.93)	179	201	0.87 (0.63-1.20)	138	160	0.57 (0.39-0.82)
P for trend			.25			.23			.009
Total lignans									
1	71	72	1.00	204	201	1.00	227	160	1.00
2	69	73	0.89 (0.52-1.53)	177	201	0.96 (0.70-1.31)	144	161	0.71 (0.50-1.00)
3	65	73	0.73 (0.43-1.25)	181	201	0.98 (0.72-1.33)	149	160	0.64 (0.45-0.90)
4	61	72	0.66 (0.38-1.14)	168	201	1.04 (0.74-1.44)	158	160	0.69 (0.48-0.99)
P for trend			.06			.93			.02
Total phytoestrogens from all sources									
1	84	72	1.00	218	201	1.00	215	160	1.00
2	55	73	0.66 (0.38-1.15)	177	201	0.93 (0.68-1.26)	174	160	0.67 (0.47-0.95)
3	65	73	0.60 (0.35-1.01)	173	201	0.87 (0.64-1.19)	147	161	0.70 (0.49-0.99)
4	62	72	0.66 (0.37-1.12)	162	201	0.88 (0.64-1.21)	142	160	0.65 (0.46-0.92)
P for trend			.15			.59			.02
Total phytoestrogens from food sources only									
1	92	72	1.00	222	201	1.00	171	160	1.00
2	72	73	0.83 (0.49-1.40)	194	201	0.89 (0.66-1.21)	172	160	0.81 (0.57-1.15)
3	56	73	0.46 (0.25-0.83)	186	201	0.85 (0.61-1.17)	195	161	1.07 (0.74-1.54)
4	46	72	0.44 (0.22-0.89)	128	201	0.48 (0.32-0.72)	140	160	0.73 (0.47-1.12)
P for trend			.01			.001			.16
Soy-derived isoflavones (daidzein and genistein)									
1	70	72	1.00	363	201	1.00	335	160	1.00
2	90	73	1.11 (0.66-1.85)	142	205	0.45 (0.34-0.61)	145	163	0.51 (0.37-0.70)
3	53	73	0.71 (0.40-1.25)	108	197	0.39 (0.28-0.53)	89	158	0.33 (0.23-0.47)
4	53	72	0.72 (0.40-1.29)	117	201	0.42 (0.30-0.58)	109	160	0.42 (0.29-0.60)
P for trend			.07			<.001			<.001

Abbreviations: CI, confidence interval; OR, odds ratio.
*Quartiles based on the values in the controls, by smoking status.
†Adjusted for age, sex, ethnicity, education, income, body mass index, and total energy.
‡Adjusted for age, sex, ethnicity, cigarettes smoked per day, years of smoking, education, income, body mass index, and total energy.

food sources similar to those of the other phytoestrogens, and were associated with statistically significant trend tests overall and for men. High dietary intake of phytosterols has been associated with decreased risks for cancers of the lung,[64] prostate,[25] ovary,[65] stomach,[66] and endometrium.[67]

In this study, generally, the highest quartiles of intake were associated with significantly protective effects in current smokers and even greater protective effects in never smokers, although many of the estimates did not achieve statistical significance because of the small number of never smokers in this study. Furthermore, the protective effects were generally attenuated in former smokers. Overall, these data suggest that phytoestrogens are significantly protective for lung cancer in current smokers. However, the effects observed for never smokers are important because never smokers have a relatively low risk of lung cancer, and benefits from chemopreventive agents would be expected to be modest. We have previously shown that use of hormone therapy was associated with a statistically significantly reduced risk of lung cancer in current smokers but not in never or former smokers.[8]

We explored the joint effects of phytoestrogen intake and use of hormone therapy because we, and others,[8,68-70] have previously provided epidemiologic evidence that use of hormone therapy is associated with a decrease in lung cancer risk, and since there has been no study exploring such effects. For these analyses, we specifically explored the lignan metabolites, soy isoflavones, and total phytoestrogens from food sources because they yielded significant main effects and trends for women. The protective effects for high phytoestrogen intake and use of hormone therapy together were greater than the protective effects of high intake alone and use of hormone therapy alone. Additionally, the interaction term between use of hormone therapy and the lignan metabolites was statistically significant. These findings certainly cannot be considered causal, but they do suggest that the protective effects of hormone therapy use and phytoestrogen intake may be independent factors that act together to further reduce risk of lung cancer in women. Although the biological mechanism(s) of hormone therapy on lung cancer is not yet known, estrogen and other steroid receptors are present in both malignant and nonmalignant lung tissue.[48,50,51] Therefore, it is likely that endogenous estrogen and estrogen-like compounds have lung-specific effects.

Although this article provides the first quantitative assessment of the association between phytoestrogens and risk of lung cancer in a US population, there are inherent limitations in such nutritional epidemiology analyses. Selection bias, recall bias, and confounding are major concerns in case-control studies of diet and cancer.[71] Although food frequency questionnaires are subject to inherent limitations such as random and systematic error,[72,73] we attempted to minimize recall bias and improve accuracy of reporting through use of personal interviews, as opposed to self-administered forms, and included an assessment of portion size using visual aids.

Additionally, our updated database developed for use with our food fre-

Table 7. Joint Effects of Hormone Therapy Use and Phytoestrogen Intake in Women

Phytoestrogen Intake*	Hormone Therapy Use†	No. Cases	No. Controls	Multivariable OR (95% CI)‡	*P* for Interaction
Main effects					
	No	465	438		
	Yes	302	405	0.74 (0.59-0.91)	
Enterolactone and Enterodiol					
Main effects					
Low intake		641	636		
High intake		133	212	0.73 (0.56-0.95)	
Joint effects					
Low intake	No	384	345	1.00	.04
High intake	No	81	93	0.95 (0.66-1.36)	
Low intake	Yes	252	288	0.84 (0.66-1.06)	
High intake	Yes	50	117	0.50 (0.31-0.68)	
Daidzein and Genistein					
Main effects					
Low intake		618	636		
High intake		156	212	0.87 (0.67-1.11)	
Joint effects					
Low intake	No	367	326	1.00	.79
High intake	No	98	112	0.90 (0.64-1.26)	
Low intake	Yes	244	305	0.73 (0.58-0.94)	
High intake	Yes	58	100	0.58 (0.40-0.85)	
Total Phytoestrogens From Food Sources Only§					
Main effects					
Low intake		626	636		
High intake		148	212	0.71 (0.54-0.93)	
Joint effects					
Low intake	No	388	327	1.00	.13
High intake	No	77	111	0.58 (0.40-0.85)	
Low intake	Yes	233	306	0.69 (0.55-0.88)	
High intake	Yes	69	99	0.61 (0.42-0.88)	

Abbreviations: CI, confidence interval; OR, odds ratio.
*Phytoestrogen intake dichotomized at the 75th percentile in the controls. Intake ≥75th percentile is categorized as "high" and <75th percentile as "low."
†Data on use of hormone therapy were missing for 7 cases and 5 controls.
‡Adjusted for age, ethnicity, smoking status, cigarettes smoked per day, years of smoking, education, income, body mass index, and total energy.
§Excluding phytoestrogens from coffee and tea sources, ie, beta-sitosterol, formononetin, matairesinol, secoisolariciresinol.

quency questionnaire should minimize misclassification of phytoestrogen intake. In this study, the cases and controls are not population-based, so there are additional concerns about the generalizability of these results. However, our cases and controls were matched on potential confounding factors, which were also adjusted for in the analyses in addition to socioeconomic factors. We found no substantial difference for phytoestrogen intake for either the cases and controls when we explored intake by residency. Differential misclassification of dietary intake between cases and controls may introduce bias that would overestimate the association between diet and cancer.[71] However, in this study, participants were asked about their diet during the year prior to diagnosis (cases) and the year prior to enrollment into the study (controls); thus, we attempted to reduce potential measurement errors attributable to recall bias as well as recent dietary changes after diagnosis of cancer.

Nonetheless, food frequency questionnaires cannot estimate intake from the remote past and have been shown to introduce biased associations.[74] The bioactive compounds in foods are derived from similar dietary food sources, are often highly correlated, and their influence is not completely independent of other nutrients.[72,73] We explored other micronutrients, including folate, carotenoids, and isothiocyanates, as well as daily intake of fruits and vegetables, for confounding and correlation and found their impact on the results was minimal. So, although the results in the present study suggest that intake of dietary phytoestrogens confers a protective effect, we caution against any overinterpretation of these findings pending confirmation of our results in large-scale, hypothesis-driven, prospective studies.

In summary, these data provide further support for the limited but growing epidemiologic evidence that estrogens[8,68-70] and phytoestrogens[28-33] are associated with a decrease in risk of lung cancer, especially in never and current smokers. However, confirmation of these findings is still required in large-scale longitudinal studies.

Author Contributions: Dr Schabath had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design; study supervision: Spitz.
Acquisition of data: Hernandez, Pillow, Spitz.
Analysis and interpretation of data; drafting of the manuscript: Schabath, Hernandez, Wu, Pillow, Spitz.
Critical revision of the manuscript for important intellectual content: Schabath, Hernandez, Pillow, Spitz.
Statistical analysis: Schabath.
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