Phytoestrogens and Thyroid Cancer Risk: The San Francisco Bay Area Thyroid Cancer Study[1]

Pamela L. Horn-Ross,[2] K. J. Hoggatt, and Marion M. Lee

Northern California Cancer Center, Union City, California 94587 [P. L. H-R., K. J. H., M. M. L.], and Department of Epidemiology and Biostatistics, University of California School of Medicine, San Francisco, California 94143 [M. M. L.]

Abstract

Epidemiological and pathological data suggest that thyroid cancer may well be an estrogen-dependent disease. The relationship between thyroid cancer risk and dietary phytoestrogens, which can have both estrogenic and antiestrogenic properties, has not been previously studied. We present data from a multiethnic population-based case-control study of thyroid cancer conducted in the San Francisco Bay Area. Of 817 cases diagnosed between 1995 and 1998 (1992 and 1998 for Asian women), 608 (74%) were interviewed. Of 793 controls identified through random-digit dialing, 558 (70%) were interviewed. Phytoestrogen consumption was assessed via a food-frequency questionnaire and a newly developed nutrient database. The consumption of traditional and nontraditional soy-based foods and alfalfa sprouts were associated with reduced risk of thyroid cancer. Consumption of "western" foods with added soy flour or soy protein did not affect risk. Of the seven specific phytoestrogenic compounds examined, the isoflavones, daidzein and genistein [odds ratio (OR), 0.70; 95% confidence interval (CI), 0.44–1.1; and OR, 0.65, 95% CI, 0.41–1.0, for the highest *versus* lowest quintile of daidzein and genistein, respectively] and the lignan, secoisolariciresinol (OR, 0.56; 95% CI, 0.35–0.89, for the highest *versus* lowest quintile) were most strongly associated with risk reduction. Findings were similar for white and Asian women and for pre- and postmenopausal women. Our findings suggest that thyroid cancer prevention via dietary modification of soy and/or phytoestrogen intake in other forms may be possible but warrants further research at this time.

Introduction

Thyroid cancer is three times more common in women than men, with age-adjusted incidence rates of 6.5 and 2.5 per 100,000 per year, respectively, in California (1). It is, however, one of the five most common cancers occurring among young women (ages, 15–44) and among recent Asian immigrants to the United States (1–3). These observations suggest that female hormones and changeable life-style factors (*e.g.*, dietary intake) may be important in thyroid carcinogenesis. To the extent that diet is involved in the etiology of thyroid cancer, its effects may be in part mediated through hormonal mechanisms.

Established risk factors for thyroid cancer include radiation to the head or neck, goiter and thyroid nodules, and a family history of proliferative thyroid disease (4–9). The influence of menstrual and reproductive factors on thyroid cancer risk is uncertain but the usual events measured in epidemiological studies (*e.g.*, age at first birth) appear to play only a weak role (10, 11). Recently it has been shown that among parous women of reproductive age a recent pregnancy is associated with approximately a doubling in thyroid cancer risk (12).[3] Because pregnancy is associated with elevations in both estrogen and thyroid hormone levels (13, 14), this finding provides support for the role of estrogens in thyroid carcinogenesis; as does the observation of estrogen receptors in normal and malignant thyroid tissue (15–17).

Phytoestrogens are estrogenic compounds found in plant foods or derived from plant precursors (18–20). In some tissues, however, phytoestrogens have antiestrogenic effects through competitive binding with estrogen receptors (but which, once bound, have a far weaker estrogenic potency than endogenous estrogens) or through their influence on hormone metabolism (resulting in a less estrogenic milieu; Refs. 18, 20–23). To date, the study of dietary intake and thyroid cancer risk has focused predominantly on the effects of fish and shellfish (often interpreted as proxy measures of iodine exposure) and on vegetables containing goitrogens, *i.e.*, chemical substances that can cause hypertrophy and hyperplasia of the thyroid gland (6–8, 24–27). The relationship between phytoestrogens and thyroid cancer risk has not been examined previously, with the exception of one hospital-based case-control study conducted in Japan, which reported no association between tofu intake (a major source of phytoestrogens) and thyroid cancer risk (OR,[4] 1.4; 95% CI, 0.7–2.8, for the highest *versus* lowest level of consumption; Ref. 28). Dietary data collected as part of a population-based case-control study conducted in the ethnically and culturally diverse San Francisco

Received 5/18/01; revised 10/26/01; accepted 11/15/01.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] Supported by Grant R01 CA63284 from the National Cancer Institute, 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 National Cancer Institute and 050M-8701/8-S1522 from the California Cancer Registry).
[2] To whom requests for reprints should be addressed, at the Northern California Cancer Center, 32960 Alvarado-Niles Road, Suite 600, Union City, CA 94587. Phone: (510) 429-2514; Fax: (510) 991-4475; E-mail: phornros@nccc.org.

[3] L. C. Sakoda and P. L. Horn-Ross. Reproductive and menstrual history and papillary thyroid cancer risk: the Bay Area Thyroid Cancer Study, Cancer Epidemiol. Biomark. Prev., *11:* 51–57, 2002.
[4] The abbreviations used are: OR, odds ratio; CI, confidence interval; FFQ, food-frequency questionnaire.

Bay Area was examined to determine whether phytoestrogen exposure was associated with thyroid cancer risk.

Materials and Methods

The design and methods used in this population-based case-control study have been described previously (7). Briefly, all of the participants were women between the ages of 20 and 74; residents of one of the five counties comprising the area; spoke sufficient English, Spanish, Tagalog, Cantonese, Mandarin, or Vietnamese to complete the interview; and had no prior history of thyroid cancer. Cases were identified through the Greater Bay Area Cancer Registry, a population-based cancer registry that is part of the Surveillance, Epidemiology, and End Results (SEER) program and the California Cancer Registry. All of the women diagnosed with thyroid cancer between June 1, 1995 and May 31, 1998 (June 1, 1992 and May 31, 1998 for Asian women) were eligible as cases. Of the 817 cases identified, 608 (74%) were interviewed, 106 (13%) declined to participate, and 103 (13%) were not interviewed for other reasons.

Controls were identified through random-digit dialing and matched to cases on 5-year age group and broad racial/ethnic group (*i.e.*, white, African American, Latina, Asian, or Native American). Of the 793 eligible controls selected, 558 (70%) were interviewed, 154 (19%) declined to participate, and 81 (10%) were not interviewed for other reasons.

In-person interviews were conducted using a standardized structured questionnaire that included questions on a wide variety of topics (7). Dietary intake during the year before diagnosis or interview for cases and controls, respectively, was assessed using a FFQ designed to capture the diverse diet of the Bay Area population. Portion size was determined using visual aids. Our nutrient database is based on the work of Dr. Gladys Block (29) and updated from other sources, including the United State Department of Agriculture (USDA) databases. To quantify the intake of seven specific phytoestrogenic compounds, we used the nutrient database that we had developed for the assessment of phytoestrogen intake via FFQs (30). The seven compounds examined represent three classes of phytoestrogens found in plant foods: the isoflavones: genistein, daidzein, biochanin A, and formononetin; the coumestan: coumestrol; and the lignans: matairesinol and secoisolariciresinol.

ORs and 95% CIs were estimated using unconditional logistic regression analyses, controlling as appropriate for age (at diagnosis for cases and at selection for controls), race/ethnicity, daily caloric intake, history of goiter or thyroid nodules diagnosed more than 2 years before the cancer diagnosis (for cases) or the date of selection (for controls), history of radiation to the head or neck more than 5 years before diagnosis/selection, and family history of proliferative thyroid disease (*i.e.*, thyroid cancer, goiter, or thyroid nodules), age at menarche, ever use of oral contraceptives, age at first full-term pregnancy/nulliparity (allowing for separate effects for women <45 and ≥ 45 years of age), and a composite variable including menopausal status and number of pregnancies in the last 5 years among premenopausal women (31, 32). Dietary analyses excluded 18 (3%) cases and 14 (3%) controls who substantially over- or underreported their intake, *i.e.*, reported a usual diet that consisted of more than 5000 or less than 600 calories per day.

Results

As illustrated in Table 1, interviewed cases and controls were similar with respect to age, menopausal status, and race/ethnicity. Seventy-two percent of participants were under age 50 and 70% were premenopausal. Fifty-one percent of participants were white, 35% Asian, and 14% of other race/ethnic background. Despite a slightly lower average caloric intake, controls consumed on average a diet higher in plant-derived nutrients, particularly antioxidant vitamins, than did cases.

Table 1 Selected characteristics of women participating in the multiethnic Bay Area Thyroid Cancer Study

Characteristic	Cases	Controls
Age (mean ± SD)	42.3 ± 12.7	43.2 ± 13.4
Race/ethnicity (%)		
Asian	36%	35%
White	49%	52%
Other	15%	13%
Medical radiation to the head/neck (%)[a]	3%	1%
History of goiter or thyroid nodules (%)[b]	21%	6%
Family history of proliferative thyroid disease (%)[c]	14%	5%
Recent pregnancy (%)[d]	35%	28%
Menopausal status (%)		
Premenopausal	72%	68%
Postmenopausal	20%	23%
Cannot determine[e]	8%	10%
Daily caloric intake (kcal/day)	2,188 ± 842	2,101 ± 821
% of calories from fat	32%	31%
Consumption of cruciferous vegetables (g/day)	55 ± 63	58 ± 63
Total carotenoid intake (mcg/day)[f]	13,127 ± 9,572	14,545 ± 11,414
Vitamin C intake (mg/day)[f]	347 ± 528	388 ± 556
Vitamin E intake (α-TE/day)[f]	52 ± 119	77 ± 157
Fiber intake (g/day)	22 ± 10	23 ± 11

[a] More than 5 years prior to diagnosis/selection.
[b] Diagnosed more than 2 years prior to diagnosis/selection.
[c] Defined as goiter, thyroid nodules, or thyroid cancer.
[d] Defined as within the 2 years before diagnosis/selection; analysis limited to women under age 45.
[e] Women who began taking hormone replacement therapy before the cessation of menses and who had not yet attained age 55.
[f] Including intake from food sources and supplements.

Genistein accounted for 51% of total phytoestrogen consumption in this population, daidzein for 42%, other isoflavones for 1%, coumestrol for 4%, and the lignans for 2%. The primary sources of phytoestrogens were tofu (47%), soy milk (22%), and foods that often contain added soy flour or soy protein (*e.g.*, doughnuts, white bread, and canned tuna; 15%). The associations between these and related foods are presented in Table 2. In general, a reduction in thyroid cancer risk of 35 to 55% was associated with increased consumption of nonfermented traditional and nontraditional soy-based foods and sprouts. Consumption of foods with added soy flour or soy protein was not associated with risk.

Table 3 presents the associations between the seven specific phytoestrogenic compounds studied and total isoflavones, total lignans, and total phytoestrogens consumed. Increased consumption of four of the seven specific phytoestrogenic compounds as well as the three summary measures were associated with reduced risk of thyroid cancer in minimally adjusted

Table 2 Consumption of selected phytoestrogen-rich foods and thyroid cancer risk among women participating in the Bay Area Thyroid Cancer Study

Food (g/day)	Cases	Controls	OR[a]	95% CI	OR[b]	95% CI
Traditional soy-based foods						
Nonfermented						
Tofu						
Nonconsumers	263	213	1.0		1.0	
Consumers						
0.1–4.9	167	145	0.88	0.65–1.2	0.88	0.64–1.2
5.0–14.9	71	64	0.80	0.53–1.2	0.84	0.55–1.3
15.0–49.9	53	67	0.56	0.36–0.87	0.58	0.36–0.91
≥50.0	36	55	0.44	0.26–0.72	0.50	0.30–0.84
Soy milk						
Nonconsumers	497	449	1.0		1.0	
Consumers						
0.1–14.9	55	39	1.2	0.77–1.9	1.3	0.79–2.1
15.0–49.9	15	30	0.42	0.22–0.81	0.45	0.23–0.89
≥50.0	23	26	0.77	0.43–1.4	0.81	0.44–1.5
Fermented						
Miso soup						
Nonconsumers	369	332	1.0		1.0	
Consumers						
0.1–4.9	111	97	1.0	0.75–1.4	1.1	0.75–1.5
5.0–9.9	43	49	0.75	0.48–1.2	0.76	0.48–1.2
≥10.0	67	66	0.87	0.59–1.3	0.92	0.62–1.4
Nontraditional soy-based foods						
Soy-burgers & meat substitutes						
Nonconsumers	500	421	1.0		1.0	
Consumers						
0.1–0.9	40	46	0.74	0.47–1.2	0.81	0.50–1.3
1.0–3.9	25	39	0.53	0.31–0.89	0.51	0.29–0.89
≥4.0	25	38	0.54	0.32–0.92	0.63	0.37–1.1
Sprouts						
Soybean sprouts[c]						
Nonconsumers	101	74	1.0		1.0	
Consumers						
0.1–2.9	32	28	0.85	0.47–1.5	0.83	0.45–1.6
3.0–4.9	28	31	0.66	0.36–1.2	0.80	0.43–1.5
5.0–14.9	25	22	0.83	0.43–1.6	0.92	0.47–1.8
≥15.0	24	33	0.51	0.28–0.94	0.59	0.31–1.1
Alfalfa sprouts						
Nonconsumers	293	245	1.0		1.0	
Consumers						
0.01–0.25	107	115	0.80	0.58–1.1	0.76	0.55–1.1
0.26–0.99	133	111	1.0	0.74–1.4	1.1	0.77–1.5
≥1.0	57	73	0.64	0.43–0.94	0.62	0.41–0.93
Foods with added soy flour						
Doughnuts						
Nonconsumers	108	108	1.0		1.0	
Consumers						
0.1–0.9	133	130	1.0	0.72–1.5	0.99	0.68–1.5
1.0–1.9	122	114	1.1	0.72–1.5	1.0	0.71–1.6
2.0–4.9	82	65	1.2	0.80–1.9	1.3	0.81–2.0
5.0–9.9	74	83	0.85	0.56–1.3	0.89	0.57–1.4
≥10.0	71	44	1.5	0.91–2.4	1.5	0.90–2.5
White bread						
Nonconsumers	123	116	1.0		1.0	
Consumers						
2.0–9.9	164	146	1.0	0.75–1.5	1.1	0.74–1.5
10.0–19.9	92	76	1.1	0.74–1.7	1.1	0.71–1.7
20.0–29.9	110	110	0.89	0.61–1.3	0.97	0.65–1.4
≥30.0	101	96	0.93	0.63–1.4	0.92	0.61–1.4
Pancakes, waffles						
Nonconsumers	102	96	1.0		1.0	
Consumers						
0.1–1.9	141	141	0.98	0.68–1.4	0.99	0.67–1.5
2.0–3.9	129	114	1.1	0.73–1.6	1.0	0.70–1.6
4.0–9.9	99	98	0.94	0.63–1.4	0.98	0.64–1.5
≥10.0	119	95	1.1	0.75–1.7	1.0	0.68–1.6
Foods with added soy protein						
Canned tuna						
Nonconsumers	114	130	1.0		1.0	
Consumers						
0.1–3.9	149	132	1.3	0.94–1.9	1.3	0.88–1.8
4.0–9.9	203	165	1.4	1.0–2.0	1.5	1.0–2.1
10.0–29.9	68	59	1.3	0.86–2.1	1.3	0.82–2.1
≥30.0	56	58	1.1	0.69–1.7	1.1	0.70–1.8

[a] Adjusted for age, race/ethnicity, and daily caloric intake.
[b] Adjusted for age, race/ethnicity, daily caloric intake, goiter or thyroid nodules, radiation to the head or neck, and family history of proliferative thyroid disease.
[c] Among Asian women only.

Table 3 Phytoestrogen consumption and thyroid cancer risk among women participating in the Bay Area Thyroid Cancer Study

Phytoestrogen (μg/day)	Cases	Controls	OR[a]	95% CI	OR[b]	95% CI
Isoflavones						
Genistein						
<525	106	108	1.0		1.0	
525–887	145	109	1.3	0.89–1.9	1.3	0.88–2.0
888–1471	135	109	1.1	0.77–1.7	1.3	0.86–2.0
1472–3680	121	109	0.97	0.65–1.4	1.1	0.72–1.7
≥3681	83	109	0.65	0.42–1.0	0.70	0.44–1.1
Trend across quintiles			$P = 0.02$		$P = 0.14$	
Per 500 μg/day			0.98	0.97–0.99	0.98	0.96–0.99
Daidzein						
<469	112	108	1.0		1.0	
470–749	128	109	1.1	0.77–1.6	1.0	0.70–1.6
750–1235	140	109	1.1	0.78–1.7	1.3	0.85–1.9
1236–3596	131	109	0.92	0.62–1.4	1.0	0.67–1.6
≥3597	79	109	0.60	0.39–0.92	0.65	0.40–1.0
Trend across quintiles			$P = 0.02$		$P = 0.15$	
Per 500 μg/day			0.97	0.96–0.99	0.97	0.96–0.99
Biochanin A						
<11	110	108	1.0		1.0	
12–20	115	109	1.0	0.69–1.5	1.0	0.69–1.6
21–33	121	109	1.0	0.69–1.5	0.97	0.64–1.5
34–51	100	109	0.82	0.55–1.2	0.79	0.52–1.2
≥52	144	109	1.2	0.78–1.7	1.1	0.72–1.7
Trend across quintiles			$P = 0.78$		$P = 0.95$	
Per 10 μg/day			1.02	0.98–1.05	1.01	0.98–1.05
Formononetin						
<9	138	108	1.0		1.0	
10–18	124	109	0.85	0.59–1.2	0.95	0.64–1.4
19–28	111	109	0.76	0.53–1.1	0.84	0.57–1.3
29–51	115	109	0.77	0.53–1.1	0.85	0.57–1.3
≥52	102	109	0.65	0.44–0.96	0.78	0.51–1.2
Trend across quintiles			$P = 0.03$		$P = 0.21$	
Per 10 μg/day			0.97	0.94–0.99	0.98	0.95–1.01
Total isoflavones						
<1046	103	108	1.0		1.0	
1047–1678	134	109	1.1	0.79–1.7	1.1	0.72–1.6
1679–2739	143	109	1.2	0.79–1.7	1.3	0.88–2.0
2740–7285	127	109	0.92	0.61–1.4	1.0	0.66–1.6
≥7286	83	109	0.61	0.40–0.94	0.65	0.41–1.0
Trend across quintiles			$P = 0.02$		$P = 0.13$	
Per 1000 μg/day			0.98	0.96–0.99	0.98	0.96–0.99
Coumestans						
Coumestrol						
<81.3	118	108	1.0		1.0	
81.4–123.1	111	109	0.87	0.60–1.3	0.95	0.63–1.4
123.2–167.7	101	109	0.76	0.52–1.1	0.71	0.46–1.1
167.8–270.4	154	109	1.1	0.78–1.7	1.1	0.71–1.6
≥270.5	106	109	0.73	0.48–1.1	0.78	0.49–1.2
Trend across quintiles			$P = 0.56$		$P = 0.55$	
Per 50 μg/day			0.97	0.94–1.01	0.98	0.94–1.2
Lignans						
Matairesinol						
<18	120	108	1.0		1.0	
19–28	110	109	0.87	0.60–1.3	0.79	0.52–1.2
29–38	105	109	0.79	0.54–1.2	0.78	0.51–1.2
39–56	140	109	1.0	0.70–1.5	1.0	0.67–1.5
≥57	115	109	0.79	0.52–1.2	0.72	0.46–1.1
Trend across quintiles			$P = 0.56$		$P = 0.49$	
Per 10 μg/day			1.00	0.96–1.04	1.00	0.96–1.04
Secoisolariciresinol						
<42	143	108	1.0		1.0	
43–58	114	109	0.73	0.50–1.1	0.75	0.50–1.1
59–80	139	109	0.84	0.58–1.2	0.82	0.55–1.2
81–106	101	109	0.57	0.38–0.85	0.58	0.38–0.89
≥107	93	109	0.47	0.31–0.73	0.56	0.35–0.89
Trend across quintiles			$P = 0.0005$		$P = 0.009$	
Per 25 μg/day			0.87	0.80–0.94	0.89	0.82–0.96

Table 3 Continued

Phytoestrogen (μg/day)	Cases	Controls	OR[a]	95% CI	OR[b]	95% CI
Total Lignans						
<64.6	124	108	1.0		1.0	
64.7–90.7	126	109	0.95	0.66–1.4	0.98	0.66–1.5
90.8–120.9	122	109	0.85	0.58–1.2	0.73	0.49–1.1
121.0–160.9	113	109	0.77	0.52–1.1	0.80	0.52–1.2
≥161.0	105	109	0.63	0.41–0.97	0.68	0.43–1.1
Trend across quintiles			$P = 0.02$		$P = 0.07$	
Per 25 μg/day			0.94	0.89–0.99	0.95	0.90–1.00
Total Phytoestrogens						
<1252	114	108	1.0		1.0	
1252–1878	121	109	0.97	0.67–1.4	0.89	0.59–1.3
1879–3028	152	109	1.2	0.81–1.7	1.2	0.84–1.9
3028–7537	119	109	0.87	0.58–1.3	0.94	0.61–1.4
≥7538	84	109	0.60	0.39–0.93	0.62	0.39–0.99
Trend across quintiles			$P = 0.03$		$P = 0.14$	
Per 1000 μg/day			0.98	0.96–0.99	0.98	0.96–0.99

[a] Adjusted for age, race/ethnicity, and daily caloric intake.
[b] Adjusted for age, race/ethnicity, daily caloric intake, goiter or thyroid nodules, radiation to the head or neck, family history of proliferative thyroid disease, age at menarche, use of oral contraceptives, age at first full-term pregnancy/nulliparity (allowing for separate effects for women <45 and ≥45 years of age), and a composite variable including menopausal status and number of pregnancies in the last 5 years among premenopausal women.

Table 4 Phytoestrogen consumption and thyroid cancer risk among white and Asian women participating in the Bay Area Thyroid Cancer Study

Phytoestrogen (μg/day)	White women				Asian women			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Total Isoflavones								
<1046	66	72	1.0		20	15	1.0	
1047–1678	81	69	1.2	0.77–2.0	31	22	1.1	0.45–2.5
1679–2739	85	60	1.4	0.89–2.4	38	34	0.81	0.36–1.8
2740–7285	47	53	0.89	0.51–1.5	57	48	0.86	0.40–1.9
≥7286	17	35	0.49	0.25–0.99	64	69	0.67	0.40–1.9
Trend across quintiles			$P = 0.09$				$P = 0.17$	
Total Lignans								
<64.6	77	62	1.0		32	29	1.0	
64.7–90.7	68	62	0.85	0.52–1.4	44	35	1.1	0.53–2.1
90.8–120.9	56	57	0.74	0.44–1.2	50	37	1.1	0.54–2.1
121.0–160.9	52	55	0.70	0.41–1.2	40	43	0.70	0.34–1.4
≥161.0	43	53	0.55	0.31–0.98	44	44	0.65	0.29–1.4
Trend across quintiles			$P = 0.03$				$P = 0.13$	

[a] Adjusted for age and daily caloric intake.

models [*i.e.*, those adjusted for matching variables (age and race/ethnicity) and daily caloric intake]. Adjusting simultaneously for a variety of established thyroid cancer risk factors and menstrual and reproductive events important in this population did not affect the observed patterns to any major extent, with the slight attenuation in the estimates and increased width of the CIs most likely reflecting diminished statistical power rather than strong confounding effects. Similar findings were observed for both white and Asian women (Table 4) and for both pre- and postmenopausal women; the associations for the highest *versus* lowest quintile of total isoflavone consumption were 0.71 (95% CI, 0.42–1.2) and 0.63 (95% CI, 0.25–1.6) for pre- and postmenopausal women, respectively; and for total lignan consumption were 0.61 (95% CI, 0.36–1.0) and 0.78 (95% CI, 0.29–2.1), respectively.

Discussion

In this population-based multiethnic study, we observed that thyroid cancer risk was reduced among women who consumed larger amounts of traditional and nontraditional soy-based foods (*e.g.*, tofu and soy burgers) and soybean and alfalfa sprouts. Soy-based foods and soybeans are rich sources of the isoflavones genistein and daidzein, and alfalfa sprouts contain large amounts of the isoflavone formononetin. Indeed, these isoflavones as well as the lignan secoisolariciresinol were associated with reduced risk. Furthermore, these associations were observed among both white and Asian women and among pre- and postmenopausal women, although, as evidenced by the wide CIs, the number of women in some of these subgroups was small. Western foods containing added soy flour or soy protein (*e.g.*, white bread and canned tuna) were not associated with risk. However, accurate measurement of the isoflavone content of these foods via a FFQ is less accurate (compared with soybean-based foods) because not all brands of these western foods contain soy.

To our knowledge, this is the first study to examine the effects of both soy-foods and specific phytoestrogenic compounds on the development of thyroid cancer in humans. The only previous study touching on this issue (28) found a small (40%), nonsignificant elevation in risk associated with tofu

consumption. In addition, soybeans have been associated with an increased risk of goiter. However, in our study, phytoestrogens (and tofu), like cruciferous vegetables, which are also goitrogenic, seem to decrease the risk of thyroid cancer. Cruciferous vegetables, isoflavones, and lignans have all been associated with increased levels of 2-hydroxyestrogens (or the ratio of 2:16α hydroxyestrones), which is associated with an estrogenic milieu less favorable to the development of estrogen-dependent cancers (33–39). In many (but not all) animal studies, soy protein or isoflavones have been associated with an increase in the thyroid hormone thyroxine (T4; Refs. 40–42). In a small study, thyroxine used to experimentally induce hyperthyroidism in young men, was associated with a statistically significant increase in 2-hydroxyestrone (43).

Two considerations should be noted in interpreting the findings from this study. First, phytoestrogen consumption was not a primary hypothesis of this study at the time at which the FFQ was designed. Thus, whereas many of the major sources of phytoestrogens were captured, a few were not, potentially resulting in the misclassification of exposure levels for some women. For example, garbanzo beans (the major source of biochanin A) and soybeans were not assessed separately from other beans, corn flakes (which contain added soy) were not assessed separately from other cereal, and dried apricots were not assessed separately from canned peaches; and regular (mung) bean sprouts, breakfast and power bars (containing added soy), raisins, prunes, and coffee were not assessed nor was Chinese black bean sauce (which is made from black soybeans) and may be an important source of isoflavones among Chinese women (44). Second, because of different estrogenic (and antiestrogenic) activity of the various compounds, total phytoestrogen intake as reported here as the sum of the various compounds may not be the most informative measure of biological exposure. A more complex measurement (*e.g.*, one weighted by antiestrogenic activity) may have provided additional information. However, because such measures have not been developed or evaluated and given the consistency of findings for the major isoflavones and lignans, it is unlikely that the interpretation of our findings would materially change based on a weighted measure.

In conclusion, our findings suggest the possibility that thyroid cancer risk may be modified by soy and phytoestrogen intake. However, given the lack of other data on this issue, additional research is needed in this area. In addition, because soybeans have been associated with the development of goiter and goiter is a major risk factor for thyroid cancer, some attention to the effects of the soy content of childhood and adolescent diet on thyroid cancer risk is warranted.

Acknowledgments

We thank Florence Lee, Amy Shiau, and Orawan Takaki for technical or administrative contributions to this project.

References

1. Morris, C. R., Cohen, R., Perkins, C. I., Allen, M., Kwong, S. L., Schlag, R., and Wright, W. E. Cancer in California 1988–1996. Sacramento, CA: California Department of Health Services, Cancer Surveillance Section, 1999.

2. Parkin, D. M., Whelan, S. L., Ferlay, J. L., Raymond, L., and Young, J. E. (eds.), Cancer Incidence in Five Continents, Vol. VII, IARC Sci. Publ. No. 143, pp. 240–243. Lyon, France: International Agency for Research on Cancer and International Association of Cancer Registries, 1997.

3. Rossing, M., Schwartz, S., and Weiss, N. Thyroid cancer incidence in Asian migrants to the United States and their descendants. Cancer Causes Control, *6:* 439–444, 1995.

4. McTiernan, A., Weiss, N., and Daling, J. Incidence of thyroid cancer in women in relation to previous exposure to radiation therapy and history of thyroid disease. J. Natl. Cancer Institute (Bethesda), *73:* 575–581, 1984.

5. Franceschi, S., Preston-Martin, S., Dal Maso, L., Negri, E., La Vecchia, C., Mack, W. J., McTiernan, A., Kolonel, L., Mark, S. D., Mabuchi, K., Jin, F., Wingren, G., Galanti, R., Hallquist, A., Glattre, E., Lund, E., Levi, F., Linos, D., and Ron, E. A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. Cancer Causes Control, *10:* 583–595, 1999.

6. Franceschi, S., Boyle, P., Maisonneuve, P., La Vecchia, C., Burt, A., Kerr, D., and MacFarlane, G. The epidemiology of thyroid carcinoma. Crit. Rev. Oncog., *4:* 25–52, 1993.

7. Horn-Ross, P. L., Morris, J. S., Lee, M., West, D. W., Whittemore, A. S., McDougall, I. R., Nowels, K., Stewart, S. L., Spate, V. L., Shiau, A. C., and Krone, M. R. Iodine and thyroid cancer risk among women in a multiethnic population: The Bay Area Thyroid Cancer Study. Cancer Epidemiol. Biomark. Prev., *10:* 979–986, 2001.

8. Wingren, G., Hatschek, T., and Axelson, O. Determinants of papillary cancer of the thyroid. Am. J. Epidemiol., *138:* 482–491, 1993.

9. D'Avanzo, B., La Vecchia, C., Franceschi, S., Negri, E., and Talamini, R. History of thyroid diseases and subsequent thyroid cancer risk. Cancer Epidemiol. Biomark. Prev., *4:* 193–199, 1995.

10. Negri, E., Dal Maso, L., Ron, E., La Vecchia, C., Mark, S. D., Preston-Martin, S., McTiernan, A., Kolonel, L., Yoshimoto, Y., Jin, F., Wingren, G., Rosaria Galanti, M., Hardell, L., Glattre, E., Lund, E., Levi, F., Linos, D., Braga, C., and Franceschi, S. A pooled analysis of case-control studies of thyroid cancer II: menstrual and reproductive factors. Cancer Causes Control, *10:* 143–155, 1999.

11. La Vecchia, C., Ron, E., Franceschi, S., Dal Maso, L., Mark, S. D., Chatenoud, L., Braga, C., Preston-Martin, S., McTiernan, A., Kolonel, L., Mabuchi, K., Jin, F., Wingren, G., Galanti, M. R., Hallquist, A., Lund, E., Levi, F., Linos, D., and Negri, E. A pooled analysis of case-control studies of thyroid cancer. III. Oral contraceptives, menopausal replacement therapy and other female hormones. Cancer Causes Control, *10:* 157–166, 1999.

12. Rossing, M. A., Voigt, L. F., Wicklund, K. G., and Daling, J. R. Reproductive factors and risk of papillary thyroid cancer in women. Am. J. Epidemiol., *151:* 765–772, 2000.

13. Glinoer, D. What happens to the normal thyroid during pregnancy? Thyroid, *9:* 631–635, 1999.

14. Pacchiarotti, A., Martino, E., Bartalena, L., Buratti, L., Mammoli, C., Strigini, F., Fruzzetti, F., Melis, G. B., and Pinchera, A. Serum thyrotropin by ultrasensitive immunoradiometric assay and serum free thyroid hormones in pregnancy. J. Endocrinol. Invest, *9:* 185–189, 1986.

15. Hiasa, Y., Nishioka, H., Kitahori, Y., Yane, K., Nakaoka, S., Ohshima, M., Konishi, N., Nishii, K., Kitamura, M., and Matsunaga, T. Immunohistochemical analysis of estrogen receptors in 313 paraffin section cases of human thyroid tissue. Oncology, *50:* 132–136, 1993.

16. Clark, O. H., Gerend, P. L., Davis, M., Goretzki, P. E., and Hoffman, P. G. Estrogen and thyroid-stimulating hormone (TSH) receptors in neoplastic and nonneoplastic human thyroid tissue. J. Surg. Res., *38:* 89–96, 1985.

17. Lee, C., Kao, H., Lin, H., P'Eng, F., and Chi, C. Estrogen receptors and glucocorticoid receptors in human well-differentiated thyroid cancer. Int. J. Mol. Med., *2:* 229–233, 1998.

18. Messina, M. J., Persky, V., Setchell, K. D. R., and Barnes, S. Soy intake and cancer risk: a review of the *in vitro* and *in vivo* data. Nutr. Cancer, *21:* 113–131, 1994.

19. Steinmetz, K. A., and D, P. J. Vegetables, fruit, and cancer: II. Mechanisms. Cancer Causes Control, *2:* 427–442, 1991.

20. Adlercreutz, H., Mousavi, Y., and Clark, J. Dietary phytoestrogens and cancer: *in vitro* and *in vivo* studies. J. Steroid Biochem. Mol. Biol., *41:* 331–337, 1992.

21. Miksicek, R. J. Estrogenic flavonoids: structural requirements for biological activity. Proc. Soc. Exp. Biol. Med., *208:* 44–50, 1995.

22. Adlercreutz, H., Honjo, H., and Higashi, A. Urinary excretion of lignans and isoflavonoid phytoestrogens in Japanese men and women consuming a traditional Japanese diet. Am. J. Clin. Nutr., *54:* 1093–1100, 1991.

23. Kurzer, M. S., and Xu, X. Dietary phytoestrogens. Annu. Rev. Nutr., *17:* 353–381, 1997.

24. Kolonel, L., Hankin, J., Wilkens, L., Fukunaga, F., and Hinds, M. An epidemiologic study of thyroid cancer in Hawaii. Cancer Causes Control, *1:* 223–234, 1990.

25. Preston-Martin, S., Jin, F., Duda, M. J., and Mack, W. J. A case-control study of thyroid cancer in women under age 55 in Shanghai (People's Republic of China). Cancer Causes Control, *4:* 431–440, 1993.

26. Glattre, E., Haldorsen, T., Berg, J., Stensvold, I., and Solvoll, K. Norwegian case-control study testing the hypothesis that seafood increases the risk of thyroid cancer. Cancer Causes Control, *4:* 11–16, 1993.

27. Galanti, M., Hansson, L., Bergstrom, R., Wolk, A., Hjartaker, A., Lund, E., Grimelius, L., and Ekbom, A. Diet and the risk of papillary and follicular thyroid carcinoma: a population-based case-control study in Sweden and Norway. Cancer Causes Control, *8:* 205–214, 1997.

28. Takezaki, T., Hirose, K., Inoue, M., Hamajima, N., Kuroishi, T., Nakamura, S., Koshikawa, T., Matsuura, H., and Tajima, K. Risk factors of thyroid cancer among women in Tokai, Japan. J. Epidemiol., *6:* 140–147, 1996.

29. Block, G., and Subar, A. F. Estimates of nutrient intake from a food frequency questionnaire: the 1987 National Health Interview Survey. J. Am. Diet. Assoc., *92:* 969–977, 1992.

30. Horn-Ross, P. L., Barnes, S., Lee, M., Coward, L., Mandel, J. E., Koo, J., John, E. M., and Smith, M. Assessing phytoestrogen exposure in epidemiologic studies: development of a database (United States). Cancer Causes Control, *11:* 289–298, 2000.

31. Kleinbaum, D. G., Kupper, L. L., and Morgenstern, H. Epidemilogic Research: Principles and Quantitative Methods. Belmont, CA: Lifetime Learning Publications, 1982.

32. Breslow, N. E., and Day, N. E. Statistical Methods in Cancer Research, Vol. I, The Analysis of Case-Control Studies, IARC Sci. Publ. No. 32. Lyon, France: International Agency for Research on Cancer, 1980.

33. Xu, X., Duncan, A. M., Merz, B. E., and Kurzer, M. S. Effects of soy isoflavones on estrogen and phytoestrogen metabolism in premenopausal women. Cancer Epidemiol. Biomark. Prev., *7:* 1101–1108, 1998.

34. Xu, X., Duncan, A. M., Wangen, K. E., and Kurzer, M. S. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. Cancer Epidemiol. Biomark. Prev., *9:* 781–786, 2000.

35. Michnovicz, J. J., and Bradlow, H. L. Dietary and pharmacological control of estradiol metabolism in humans. Ann. N. Y. Acad. Sci., *595:* 291–299, 1990.

36. Michnovicz, J. J., and Bradlow, H. L. Altered estrogen metabolism and excretion in humans following consumption of indole-3-carbinol. Nutr. Cancer, *16:* 59–66, 1991.

37. Fowke, J. H., Longcope, C., and Hebert, J. R. Brassica vegetable consumption shifts estrogen metabolism in healthy postmenopausal women. Cancer Epidemiol. Biomark. Prev., *9:* 773–779, 2000.

38. Lu, L. J., Cree, M., Josyula, S., Nagamani, M., Grady, J. J., and Anderson, K. E. Increased urinary excretion of 2-hydroxyestrone but not 16α-hydroxyestrone in premenopausal women during a soya diet containing isoflavones. Cancer Res., *60:* 1299–1305, 2000.

39. Haggans, C. J., Travelli, E. J., Thomas, W., Martini, M. C., and Slavin, J. L. The effect of flaxseed and wheat bran consumption on urinary estrogen metabolites in premenopausal women. Cancer Epidemiol. Biomark. Prev., *9:* 719–725, 2000.

40. Potter, S. M., Pertile, J., and Berber-Jimenez, M. D. Soy protein concentrate and isolated soy protein similarly lower blood serum cholesterol but differently affect thyroid hormones in hamsters. J. Nutr., *126:* 2007–2011, 1996.

41. Forsythe, W. A. Soy protein, thyroid regulation and cholesterol metabolism. J. Nutr., *125* (Suppl.)*:* 619S–623S, 1995.

42. Balmir, F., Staack, R., Jeffrey, E., Jimenez, M. D., Wang, L., and Potter, S. M. An extract of soy flour influences serum cholesterol and thyroid hormones in rats and hamsters. J. Nutr., *126:* 3046–3053, 1996.

43. Michnovicz, J. J., and Galbraith, R. A. Effects of exogenous thyroxine on C-2 and C-16α hydroxylations of estradiol in humans. Steroids, *55:* 22–26, 1990.

44. Horn-Ross, P. L. Assessing phytoestrogen exposure via a food-frequency questionnaire (Letter). Cancer Causes Control, *12:* 477–478, 2001.

Phytoestrogens and Thyroid Cancer Risk: The San Francisco Bay Area Thyroid Cancer Study

Pamela L. Horn-Ross, K. J. Hoggatt and Marion M. Lee

Cancer Epidemiol Biomarkers Prev 2002;11:43-49.