Published OnlineFirst December 11, 2019; DOI: 10.1158/1055-9965.EPI-19-0456

Phytoestrogens and Thyroid Cancer Risk: A Population-Based Case–Control Study in Connecticut

Qian Wang[1,2], Huang Huang[2], Nan Zhao[3], Xin Ni[4], Robert Udelsman[5], and Yawei Zhang[2,6]

ABSTRACT

Background: Very few previous studies have examined the relationship between thyroid cancer risk and intake of phytoestrogens (PE); furthermore, these studies have reached inconsistent results.

Methods: We analyzed data from a population-based case–control study in Connecticut from 2010 to 2011, including 387 histologically confirmed thyroid cancer cases and 433 population-based controls, with compound data available concerning specific PEs. Multivariate unconditional logistic regression models were used to estimate the associations between specific PEs and the risk of thyroid cancer, adjusting for potential confounders.

Results: An elevated risk of thyroid cancer was associated with moderate to high levels of coumestrol intake [OR = 2.48, 95% confidence interval (CI), 1.39–4.43 for 40–80 μg/day; OR = 2.41, 95% CI, 1.32–4.40 for 80–130 μg/day; and OR = 2.38, 95% CI, 1.26–4.50 for >200 μg/day compared with <40 μg/day], and the main elevation in risk appeared among microcarcinomas (≤1 cm). A decreased risk of papillary macrocarcinomas (>1 cm; OR = 0.26, 95% CI, 0.08–0.85 for 1,860–3,110 μg/day compared with <760 μg/day) was associated with moderate genistein intake among women.

Conclusions: Our study suggests that high coumestrol intake increases the risk of thyroid cancer, especially microcarcinomas, whereas moderate amounts of genistein intake appear to be protective for females with thyroid macrocarcinomas.

Impact: The study highlights the importance of distinguishing between microcarcinomas and macrocarcinomas in future research on the etiology of thyroid cancer.

Introduction

Over the past few decades, the age-adjusted incidence rate of thyroid cancer has been rapidly increasing worldwide (1). Compared with all other cancer types, the age-adjusted incidence rate of thyroid cancer has increased the fastest, from 8.74/100,000 in women and 3.38/100,000 in men in 1994 to 21.43/100,000 in women and 7.371/100,000 in men in 2015 (https://seer.cancer.gov/archive/csr/1975_2015/). It is now the fifth most common cancer among women in the United States (2). Although improvements in diagnostic technology such as fine-needle aspiration with ultrasound guidance may be associated with increased detection of microcarcinomas (diameter ≤ 1 cm), the incidences of both smaller-size tumors and larger-size tumors are increasing (1, 3, 4). Furthermore, studies have shown that approximately 50% of the variability in thyroid cancer incidence rates in the United States could not be explained by the theory of "overdiagnosis" (5, 6). Established risk factors for thyroid cancer include female gender, radiation exposure to the head and neck, high body mass index (BMI), history of benign thyroid diseases, and family history of thyroid cancer (7–10). It has been suggested that nutritional factors are associated with the development of thyroid cancer (11, 12). However, research on the effects of consuming foods rich in phytoestrogens (PE) has been controversial (7, 8, 13–18).

PEs include isoflavonoids (genistein, daidzein, and glycitein), lignans, and coumestans (including coumestrol). Dietary PEs mostly come from beans, soy products, and foods with added soy protein or soy flour (19). Previous studies have indicated that PE-rich diets may be associated with a decreased risk of breast cancer and prostate cancer (12, 20–24). As endocrine-disrupting compounds (EDC), PEs could also potentially affect thyroid cancer risk by affecting synthesis of thyroid hormones (TH), altering thyroid stimulating hormone (TSH) levels (25), and interacting with estrogen receptors (ER; refs. 24, 26–28).

After the FDA declared that PEs have a protective effect against coronary heart disease in 1999, the sale of soy foods (only those marketed as soy products, not including foods with added soy flour and/or protein) expanded from $1 billion in 1996 to $4.5 billion in 2009 (12). Therefore, the possible influence of soy foods and their major component PEs on thyroid cancer risk warrants further investigation.

Materials and Methods

The study population has been described elsewhere (29–34). In brief, cases were histologically confirmed thyroid cancer patients (ICD-O-3: 8021, 8050, 8052, 8130, 8260, 8290, 8330–8332, 8335, 8340–8346, 8450, 8452, 8510) in Connecticut diagnosed between 2010 and 2011. Subjects eligible for the study were aged between 21 and 84 years at diagnosis, alive at the time of interview, and had no prior cancer diagnoses, except for nonmelanoma skin cancer. Cases were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA). A total of 701 eligible thyroid cancer cases were identified during the study period with 462 (65.9%) completing in-person interviews. Population-based

[1]Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, New York. [2]Department of Environmental Health Sciences, Yale School of Public Health, Yale University, New Haven, Connecticut. [3]Central Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China. [4]Beijing Children's Hospital, Capital Medical University, Beijing, China. [5]Endocrine Neoplasm Institute, Miami Cancer Institute, Miami, Florida. [6]Department of Surgery, Yale School of Medicine, Yale University, New Haven, Connecticut.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Yawei Zhang, Yale School of Medicine, Yale School of Public Health, Yale Cancer Center, 60 College Street, LEPH 440, New Haven, CT 06510. Phone: 203-785-6210; Fax: 203-737-6023; E-mail: yawei.zhang@yale.edu

Cancer Epidemiol Biomarkers Prev 2020;29:500–8

doi: 10.1158/1055-9965.EPI-19-0456

Published OnlineFirst December 11, 2019; DOI: 10.1158/1055-9965.EPI-19-0456

controls with Connecticut addresses were recruited using a random digit dialing method based on both cell phone and landline numbers. A total of 498 subjects participated in the study, with a participation rate of 61.5%. Cases and controls were frequency matched by age (≤5 years apart). Distributions of age, gender, and race were similar between the participants and nonparticipants for both cases and controls.

All procedures were performed following a protocol approved by the Human Investigations Committee at Yale and the Connecticut Department of Public Health. Eligible participants were reached by letter and then by phone once approved by the hospitals and by each subject's physician (for cancer cases), or following selection through random sampling (for the control population). After obtaining written consent, eligible participants were interviewed by trained interviewers and a food frequency questionnaire (FFQ) was administered to determine their diverse diets. The frequency and amount of consumption of previously validated PE-rich food were captured (35). These include soy-based foods (including tofu, soy burgers or soy meat-substitutes, soymilk, bean soup, and beans), foods with added soy flour (including doughnuts, sweet rolls, Danish, pop-tarts, white bread, pancakes, waffles and French toast), as well as foods with added soy protein (including canned tuna). Additionally, a standardized, structured questionnaire was used to obtain information on major known or suspected risk factors that might confound the association between PE-rich food intake and risk of thyroid cancer. Specific PE amounts were calculated by using Diet*Calc Analysis Software version 1.5.0, which generates nutrient estimates based on the FFQ. The six compounds examined represent two major PE types found in foods: the isoflavones: genistein, daidzein, biochanin A, formononetin, and glycitein; and the coumestan: coumestrol.

Unconditional logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (95% CI). All cutoff points of each PE subtype and of PE-rich food intake were based on the distribution among controls. We also restricted our analyses to papillary and well-differentiated thyroid cancer subtypes (the papillary and follicular subtypes were combined due to the small sample size of follicular carcinoma). In order to exam the effects of PEs on tumor size, analyses were conducted by dividing the cases into two groups according to the tumor size (microcarcinomas ≤ 1 cm, macrocarcinomas > 1 cm) among papillary carcinomas. We also analyzed thyroid cancer among women because the number of men was too small for a meaningful analysis.

After excluding participants who did not respond to the FFQ, 387 cases (83.8%) and 433 controls (86.9%) were included in the final analysis. Age, gender, race, family history of cancer of any kind, education, BMI, previous benign thyroid diseases, history of radiation exposure, previous alcohol consumption, smoking history, daily caloric intake, percentage of calories from fat, total carotenoid intake, vitamin C intake, vitamin E intake, and fiber intake were considered as potential confounding variables. Among female subjects, additional controlled confounders included age at menarche, use of oral contraceptives, age at first full-term pregnancy, menopausal status, and estrogen use. Decisions on which covariates to include in the final model were based on a greater than 10% change in the estimates. Tests for linear trends were calculated by using each individual PE variable as continuous variables in the multivariate unconditional logistic regression models. Statistical analyses for this study were performed using SAS version 9.4 (SAS Institute Inc.). Results were considered statistically significant when two-sided P values were <0.05.

Results

As illustrated in **Table 1**, cases tended to be less educated and had a higher BMI when compared with controls. Cases were more likely to have prior benign thyroid diseases and less likely to consume alcohol.

Table 1. Selected characteristics among thyroid cancer cases and controls.

	Cases (n = 387)[a] n (%)	Controls (n = 433)[a] n (%)	P
Age (years)			<0.01
Mean (SD)	51.7 (12.3)	54.8 (12.5)	
<40	68 (17.6)	48 (11.1)	
40–49	93 (24.0)	108 (24.9)	
50–59	125 (32.3)	121 (27.9)	
60–69	74 (19.1)	93 (21.5)	
≥70	27 (7.0)	63 (14.6)	
Gender			<0.01
Female	317 (81.9)	306 (70.7)	
Male	70 (18.1)	127 (29.3)	
Race			0.51
White	348 (89.9)	394 (91.2)	
Black	16 (4.1)	20 (4.6)	
Other	23 (5.9)	18 (4.2)	
BMI (kg/m^2)			<0.01
<25	126 (32.6)	176 (40.7)	
25–29.99	116 (30.0)	146 (33.7)	
≥30	143 (37.0)	106 (24.5)	
Education			<0.01
High school or less	107 (27.7)	73 (16.9)	
Some college	24 (6.2)	23 (5.3)	
College graduate or more	243 (62.8)	323 (74.6)	
Others	12 (3.1)	11 (2.5)	
Family history of any cancer			0.33
None	112 (28.9)	139 (32.1)	
Any cancer	275 (71.1)	294 (67.9)	
Prior benign thyroid disease[b]			<0.01
Yes	227 (58.7)	14 (3.2)	
No	160 (41.3)	419 (96.8)	
Previous radiation exposure[c]			0.63
Yes	385 (99.7)	427 (99.5)	
No	1 (0.3)	2 (0.5)	
Alcohol consumption[d]			<0.01
Never	223 (57.6)	193 (44.3)	
Ever	163 (42.1)	238 (55.2)	
Smoking[e]			0.54
Never	270 (70.0)	293 (68.0)	
Ever	116 (30.0)	138 (32.0)	
Daily caloric intake (kcal/day)	2,399 ± 1,823	2,475 ± 966	0.45
% of calories from fat	36% ± 6%	35% ± 5%	0.12
Total carotenoid intake (μg/day)[f]	7,338 ± 9,229	9,098 ± 12,750	0.03
Vitamin C intake (mg/day)[f]	305 ± 313	321 ±273	0.45
Vitamin E intake (mg/day)[f]	45 ± 99	42 ± 87	0.67
Fiber intake (g/day)	24 ± 20	26 ± 13	0.24

[a]Numbers may not sum to total due to missing data.
[b]Benign thyroid diseases included hyperthyroidism, hypothyroidism, goiter, thyroid nodules, and thyroid adenoma.
[c]Previous radiation exposure included previous diagnostic and therapeutic radiation exposure.
[d]Ever alcohol consumption was defined as ever had more than 12 drinks of alcoholic beverages, such as beer, wine, or liquor. 1 drink beer = 1 can or bottle; 1 drink wine = 14 oz. glass; 1 drunk liquor = 1 shot.
[e]Ever smoking was defined as ever smoked a total of 100 cigarettes or more.
[f]Both food sources and supplements.

Published OnlineFirst December 11, 2019; DOI: 10.1158/1055-9965.EPI-19-0456

Cases were also more likely to be female compared with controls. Distributions of race, family history of cancer of any kind, smoking, previous radiation exposure, daily caloric intake, percentage of calories from fat, vitamin C intake, vitamin E intake, and fiber intake were similar between cases and controls. The baseline characteristics of those who had available PE data were similar to the overall study population.

Compared with those whose consumption of coumestrol was less than 40 μg/day (**Table 2**), individuals who consumed 40 to 80 μg/day (OR = 2.48, 95% CI, 1.39–4.43), 80 to 130 μg/day (OR = 2.41, 95% CI, 1.32–4.40), or >200 μg/day (OR = 2.38, 95% CI, 1.26–4.50) experienced an increased risk of thyroid cancer, although the linear trend was not statistically significant (*P* for linear trend = 0.25). Other specific PEs, total isoflavones, and total PEs were not statistically significantly associated with thyroid cancer risk. Similar patterns were noticed for papillary and well-differentiated carcinomas. No significant associations between intake of soy-based foods, foods with added soy flour, and foods with added soy protein and thyroid cancer risk were observed (Supplementary Tables S1–S5).

After stratification by tumor size (**Table 3**), statistically significant associations with coumestrol intake were observed mainly for microcarcinomas (OR = 4.33, 95% CI, 1.86–10.07 for 40–80 μg/day; OR = 4.38, 95% CI, 1.79–10.71 for 80–130 μg/day; and OR = 3.11, 95% CI, 1.22–7.91 for >200 μg/day compared with <40 μg/day; *P* for linear trend = 0.34). Individuals who consumed 40 to 80 μg/day also showed an increased risk of macrocarcinomas (OR = 2.31; 95% CI, 1.09–4.86).

When the analyses were restricted to females (**Table 4**), a statistically significant increase in risk was only seen among those who had a coumestrol intake of 40 to 80 μg/day (OR = 2.08, 95% CI, 1.01–4.29) compared with those who had an intake of less than 40 μg/day. Similar patterns were observed for well-differentiated and papillary thyroid cancers (Supplementary Table S6). After stratification by tumor size (**Table 5**), an increased risk of papillary microcarcinomas was observed among those with a coumestrol intake of 40 to 80 μg/day (OR = 2.94, 95% CI, 1.12–7.73) and a decreased risk of papillary thyroid cancers with tumor size > 1 cm (OR = 0.26, 95% CI, 0.08–0.85) among those with a genistein intake of 1,860 to 3,110 μg/day.

Discussion

This population-based case–control study suggests that an increased risk of thyroid cancer is associated with coumestrol consumption, which is the most estrogenic PE (22). The observed associations varied by tumor size (≤1 cm vs. >1 cm). Our study results also suggest that moderate genistein intake is associated with a decreased risk of thyroid cancer with larger tumor size among females.

There is only one previous study, by Horn-Ross and colleagues in San Francisco, that has investigated coumestrol intake and thyroid cancer risk (7). They did not find an association between coumestrol intake and thyroid cancer risk. The inconsistency could be due to the different cutoffs of coumestrol consumption. Their reference level was less than 81.3 μg/day, which contained both our reference (<40 μg/day) and low-exposure (40–80 μg/day) groups. When our analysis was performed applying the same cutoffs as the San Francisco study (<81.3, 81.4–123.1, 123.2–167.7, 167.8–270.4, ≥270.5 μg/day), we found no significant association between coumestrol intake and thyroid cancer risk, which is consistent with their findings. The paradoxical results could be due to the reference group in the Horn-Ross' study incorporating that which was the exposure group (40–80 μg/day) in our study, which showed more than two times the risk of thyroid cancer.

Coumestrol is the most estrogenic compound and has the highest receptor binding affinity to both ER-α and ER-β, followed by genistein (36). The proliferation of thyroid cancer cells is positively stimulated by ER-α agonists and inhibited by ER-β agonists (37) in particular ER-β1 (38, 39). Moreover, in a prior experimental study including subjects with small well-differentiated thyroid cancers (average tumor size 9.4 mm), there was a greater expression of ER-α among tumor tissues than normal tissues (40). It has also been suggested that there are fewer ER-β1 receptors in smaller tumors (<2 cm) compared with larger tumors (38). Therefore, it is possible that coumestrol increases microcarcinoma risk by agonizing overexpressed ER-α in smaller tumors, in addition to lessening the protective effect from ER-β, thus leading to microcarcinoma proliferation.

Notably, we did not observe a linear relationship between coumestrol intake and thyroid cancer risk. The possible explanations include: (i) some agents are carcinogenic at low-exposure levels, but their carcinogenic potential does not increase with higher exposure such as radiation to the thyroid (41); (ii) a higher dose exposure could paradoxically be protective, as the mutagenic rate is overwhelmed by apoptosis; (iii) the sample size in each category is insufficient to demonstrate small differences.

In addition, thyroid microcarcinomas have shown the fastest increase in incidence and approximately half of all newly diagnosed thyroid cancers were microcarcinomas (4). An observational study of papillary microcarcinomas from Japan demonstrated that patients with papillary microcarcinomas that showed enlargement of 3 mm or more constituted 6.4% and 15.9% of patients at 5-year and 10-year follow-ups, respectively, and that the enlargement process was unrelated to patient background or clinical features (42). Thus, thyroid microcarcinoma appears to be a distinct entity with pathophysiologic features that are distinct from macrocarcinomas.

The anticarcinogenic effect of genistein on thyroid cancer has been demonstrated by previous studies (24, 43, 44). Evidence has shown that genistein could function as an anticarcinogen due to its higher binding affinity to ER-β than to ER-α (36), thereby leading to a more antiproliferative effect, inducing apoptosis and inhibiting angiogenesis (43, 44). Although it has been suggested that increased TSH levels are associated with an increase in thyroid cancer risk by causing less differentiation and more malignant cell transformation (45–47), multiple randomized controlled trials (RCT) have consistently shown that genistein supplementation did not change TSH levels with various doses (25, 48–51), suggesting that the protective effect of genistein was not through a TSH pathway. The San Francisco study (7), though not statistically significant, showed a 30% thyroid cancer risk reduction in the highest genistein intake group (OR = 0.70; 95% CI, 0.44–1.1). Among our female population, low-to-moderate genistein intake was associated with a 56% decrease in papillary thyroid cancer risk. When the analyses were stratified by tumor size, decreased risk was observed mainly among larger tumors. The amount of ER-α expression in macrocarcinomas is about 1.3 times the amount in microcarcinomas (52), whereas the binding capacity of genistein to ER-β is five to seven times higher than to ER-α (36). Therefore, it is possible that the binding capacity of ER-β overcomes the number of ER-α and thus leads to a greater anticarcinogenic effect on macrocarcinomas (40). Again, this suggests that microcarcinomas and macrocarcinomas possess different pathophysiologies.

Support for an association between total intake of isoflavones and thyroid cancer risk has been inconsistent (7, 15, 18). Two case–control studies have suggested that high isoflavone intake has a protective effect against thyroid cancer (7, 15). One prospective cohort study (18) found no association, which is consistent with our findings. Previous

Published OnlineFirst December 11, 2019; DOI: 10.1158/1055-9965.EPI-19-0456

Table 2. Risk of thyroid cancer associated with PE intake among all cases and by histology subtypes.

PE intake	Controls ($n = 433$)	All cases ($n = 387$)		Papillary ($n = 328$)		Well differentiated ($n = 377$)	
		Cases	OR[a] (95% CI)	Cases	OR[a] (95% CI)	Cases	OR[a] (95% CI)
Genistein (μg/day)							
<760	88	81	1.00 (—)	70	1.00 (—)	78	1.00 (—)
760–1,260	85	66	0.93 (0.51–1.68)	55	0.73 (0.39–1.37)	66	0.95 (0.52–1.72)
1,260–1,860	86	74	1.06 (0.60–1.88)	66	1.09 (0.61–1.96)	73	1.10 (0.62–1.94)
1,860–3,110	87	83	0.97 (0.54–1.71)	69	0.74 (0.40–1.36)	80	0.93 (0.52–1.67)
>3,110	87	83	1.21 (0.69–2.12)	68	0.98 (0.54–1.76)	80	1.18 (0.67–2.07)
P for linear trend			0.25		0.44		0.31
Daidzein (μg/day)							
<530	88	73	1.00 (—)	62	1.00 (—)	70	1.00 (—)
530–910	85	72	1.31 (0.72–2.36)	62	1.08 (0.58–2.01)	72	1.35 (0.74–2.45)
910–1,310	86	76	1.30 (0.73–2.32)	69	1.35 (0.75–2.43)	75	1.34 (0.75–2.40)
1,310–2,240	87	86	1.26 (0.70–2.24)	71	0.98 (0.53–1.81)	82	1.20 (0.67–2.16)
>2,240	87	80	1.35 (0.76–2.39)	64	1.12 (0.61–2.05)	78	1.35 (0.75–2.41)
P for linear trend			0.26		0.45		0.32
Biochanin A (μg/day)							
<30	108	136	1.00 (—)	105	1.00 (—)	126	1.00 (—)
30–50	81	70	0.74 (0.43–1.27)	63	0.78 (0.44–1.37)	70	0.81 (0.47–1.39)
50–70	77	62	0.79 (0.45–1.36)	53	0.84 (0.47–1.50)	62	0.86 (0.49–1.49)
70–120	91	67	0.70 (0.41–1.21)	61	0.83 (0.47–1.47)	67	0.76 (0.44–1.32)
>120	76	52	0.60 (0.33–1.08)	46	0.67 (0.36–1.25)	52	0.64 (0.35–1.15)
P for linear trend			0.64		0.97		0.74
Formononetin (μg/day)							
0	93	101	1.00 (—)	82	1.00 (—)	96	1.00 (—)
0–10	153	133	1.05 (0.64–1.71)	118	1.21 (0.72–2.02)	129	1.09 (0.66–1.79)
10–20	81	50	0.80 (0.44–1.43)	39	0.87 (0.46–1.63)	50	0.85 (0.47–1.54)
20–30	27	33	0.87 (0.39–1.92)	30	1.11 (0.49–2.51)	33	0.93 (0.42–2.06)
>30	79	70	0.98 (0.55–1.73)	59	1.02 (0.56–1.89)	69	1.00 (0.56–1.79)
P for linear trend			0.79		0.77		0.85
Glycitein (μg/day)							
<100	94	82	1.00 (—)	69	1.00 (—)	79	1.00 (—)
100–170	81	69	1.34 (0.75–2.39)	59	1.22 (0.66–2.25)	69	1.40 (0.78–2.50)
170–260	89	78	1.21 (0.69–2.14)	69	1.20 (0.67–2.16)	77	1.24 (0.70–2.20)
260–430	86	76	1.07 (0.60–1.92)	64	0.93 (0.50–1.72)	73	1.05 (0.58–1.89)
>430	83	82	1.45 (0.83–2.53)	67	1.26 (0.70–2.28)	79	1.41 (0.80–2.48)
P for linear trend			0.26		0.45		0.33
Total isoflavones (μg/day)							
<1,410	88	81	1.00 (—)	69	1.00 (—)	78	1.00 (—)
1,410–2,240	85	62	0.90 (0.50–1.64)	53	0.71 (0.38–1.34)	62	0.92 (0.50–1.68)
2,240–3,280	89	82	1.16 (0.66–2.03)	74	1.21 (0.68–2.14)	81	1.19 (0.68–2.09)
3,280–5,440	84	79	1.00 (0.56–1.80)	65	0.76 (0.41–1.42)	76	0.97 (0.54–1.75)
>5,440	87	83	1.25 (0.72–2.18)	67	1.01 (0.56–1.83)	80	1.21 (0.69–2.13)
P for linear trend			0.25		0.44		0.31
Coumestrol (μg/day)							
<40	94	76	1.00 (—)	63	1.00 (—)	71	1.00 (—)
40–80	85	117	2.48 (1.39–4.43)	103	2.80 (1.51–5.19)	115	2.53 (1.41–4.57)
80–130	88	74	2.41 (1.32–4.40)	59	2.50 (1.31–4.78)	73	2.49 (1.35–4.59)
130–200	88	54	1.45 (0.77–2.73)	48	1.60 (0.82–3.14)	54	1.53 (0.81–2.91)
>200	78	66	2.38 (1.26–4.50)	55	2.56 (1.30–5.06)	64	2.43 (1.27–4.65)
P for linear trend			0.25		0.18		0.26
Total PEs (μg/day)							
<1,510	87	81	1.00 (—)	69	1.00 (—)	78	1.00 (—)
1,510–2,470	86	77	1.15 (0.64–2.05)	67	0.97 (0.53–1.77)	77	1.19 (0.66–2.13)
2,470–3,400	86	65	1.18 (0.67–2.10)	57	1.21 (0.67–2.19)	64	1.22 (0.68–2.18)
3,400–5,560	87	79	0.94 (0.52–1.70)	66	0.74 (0.40–1.39)	76	0.92 (0.50–1.66)
>5,560	87	85	1.36 (0.78–2.37)	69	1.13 (0.63–2.04)	82	1.32 (0.75–2.33)
P for linear trend			0.25		0.44		0.31

[a]Adjusted for age, gender, race, family history of any cancer, education, BMI, history of benign thyroid disease, and previous alcohol consumption.

Published OnlineFirst December 11, 2019; DOI: 10.1158/1055-9965.EPI-19-0456

Table 3. Risk of thyroid cancer associated with PE intake for thyroid cancer among papillary carcinomas by tumor size.

		Papillary carcinoma			
	Controls	≤1 cm (n = 158)		>1 cm (n = 167)	
PE intake	(n = 433)	Cases	OR[a] (95% CI)	Cases	OR[a] (95% CI)
Genistein (μg/day)					
<760	88	37	1.00 (—)	31	1.00 (—)
760–1,260	85	25	0.54 (0.24–1.24)	30	0.86 (0.39–1.91)
1,260–1,860	86	33	1.12 (0.55–2.30)	33	1.06 (0.49–2.29)
1,860–3,110	87	34	0.61 (0.28–1.33)	34	0.75 (0.34–1.68)
>3,110	87	29	0.78 (0.36–1.67)	39	1.19 (0.56–2.53)
P for linear trend			0.71		0.15
Daidzein (μg/day)					
<530	88	32	1.00 (—)	28	1.00 (—)
530–910	85	31	0.93 (0.42–2.05)	31	1.07 (0.48–2.42)
910–1,310	86	33	1.38 (0.66–2.87)	36	1.39 (0.65–3.00)
1,310–2,240	87	35	0.84 (0.39–1.82)	35	0.87 (0.39–1.96)
>2,240	87	27	0.88 (0.40–1.94)	37	1.34 (0.61–2.92)
P for linear trend			0.70		0.15
Biochanin A (μg/day)					
<30	108	49	1.00 (—)	55	1.00 (—)
30–50	81	37	1.04 (0.51–2.12)	26	0.67 (0.32–1.41)
50–70	77	25	0.90 (0.42–1.92)	27	0.84 (0.40–1.76)
70–120	91	30	1.00 (0.49–2.07)	31	0.65 (0.31–1.37)
>120	76	17	0.60 (0.25–1.41)	28	0.68 (0.32–1.49)
P for linear trend			0.61		0.34
Formononetin (μg/day)					
0	93	41	1.00 (—)	41	1.00 (—)
0–10	153	54	1.11 (0.57–2.16)	63	1.13 (0.59–2.16)
10–20	81	22	0.89 (0.41–1.97)	17	0.74 (0.32–1.72)
20–30	27	15	1.22 (0.44–3.36)	14	0.96 (0.34–2.72)
>30	79	26	0.97 (0.45–2.11)	32	1.05 (0.48–2.28)
P for linear trend			0.76		0.59
Glycitein (μg/day)					
<100	94	36	1.00 (—)	32	1.00 (—)
100–170	81	31	1.34 (0.63–2.87)	27	1.10 (0.48–2.50)
170–260	89	33	1.14 (0.54–2.39)	36	1.30 (0.61–2.74)
260–430	86	33	0.92 (0.42–2.00)	31	0.87 (0.38–1.96)
>430	83	25	1.01 (0.46–2.20)	41	1.54 (0.73–3.25)
P for linear trend			0.69		0.15
Total isoflavones (μg/day)					
<1,410	88	36	1.00 (—)	31	1.00 (—)
1,410–2,240	85	24	0.69 (0.31–1.55)	29	0.64 (0.28–1.45)
2,240–3,280	89	37	1.25 (0.61–2.57)	37	1.15 (0.54–2.43)
3,280–5,440	84	33	0.73 (0.33–1.61)	31	0.65 (0.29–1.48)
>5,440	87	28	0.86 (0.40–1.87)	39	1.13 (0.53–2.38)
P for linear trend			0.70		0.15
Coumestrol (μg/day)					
<40	94	24	1.00 (—)	39	1.00 (—)
40–80	85	56	4.33 (1.86–10.07)	47	2.31 (1.09–4.86)
80–130	88	31	4.38 (1.79–10.71)	27	1.46 (0.64–3.30)
130–200	88	23	2.29 (0.91–5.78)	24	1.32 (0.57–3.08)
>200	78	24	3.11 (1.22–7.91)	30	2.17 (0.94–5.02)
P for linear trend			0.34		0.50
Total PEs (μg/day)					
<1,510	87	36	1.00 (—)	31	1.00 (—)
1,510–2,470	86	31	0.88 (0.40–1.92)	36	1.09 (0.50–2.37)
2,470–3,400	86	30	1.32 (0.63–2.76)	27	1.18 (0.54–2.59)
3,400–5,560	87	31	0.63 (0.28–1.42)	34	0.72 (0.32–1.65)
>5,560	87	30	1.00 (0.46–2.15)	39	1.30 (0.61–2.77)
P for linear trend			0.71		0.15

[a]Adjusted for age, gender, race, family history of any cancer, education, BMI, history of benign thyroid disease, and previous alcohol consumption.

Published OnlineFirst December 11, 2019; DOI: 10.1158/1055-9965.EPI-19-0456

Table 4. Risk of thyroid cancer associated with PE intake among female subjects.

PE intake	Controls ($n = 306$)	Cases ($n = 317$)	OR[a] (95% CI)
Genistein (μg/day)			
<760	64	71	1.00 (—)
760–1,260	62	55	0.59 (0.28–1.23)
1,260–1,860	66	63	0.95 (0.48–1.90)
1,860–3,110	55	65	0.88 (0.43–1.81)
>3,110	59	63	0.82 (0.40–1.68)
P for linear trend			0.37
Daidzein (μg/day)			
<530	65	64	1.00 (—)
530–910	60	60	1.09 (0.53–2.25)
910–1,310	64	62	1.36 (0.67–2.77)
1,310–2,240	58	71	1.16 (0.57–2.35)
>2,240	59	60	1.03 (0.50–2.12)
P for linear trend			0.38
Biochanin A (μg/day)			
<30	86	123	1.00 (—)
30–50	62	59	0.68 (0.34–1.35)
50–70	59	52	0.71 (0.35–1.43)
70–120	57	52	0.59 (0.29–1.21)
>120	42	31	0.56 (0.27–1.28)
P for linear trend			0.82
Formononetin (μg/day)			
0	61	82	1.00 (—)
0–10	101	106	1.09 (0.57–2.07)
10–20	62	43	0.77 (0.37–1.58)
20–30	20	29	0.62 (0.22–1.75)
>30	62	57	0.82 (0.39–1.72)
P for linear trend			0.38
Glycitein (μg/day)			
<100	68	71	1.00 (—)
100–170	62	60	0.89 (0.44–1.79)
170–260	66	66	1.17 (0.58–2.35)
260–430	52	60	0.96 (0.46–2.01)
>430	58	60	0.94 (0.46–1.89)
P for linear trend			0.42
Total isoflavones (μg/day)			
<1,410	65	70	1.00 (—)
1,410–2,240	63	53	0.74 (0.36–1.52)
2,240–3,280	66	68	1.15 (0.57–2.30)
3,280–5,440	54	63	1.01 (0.49–2.09)
>5,440	58	63	0.94 (0.46–1.92)
P for linear trend			0.37
Coumestrol (μg/day)			
<40	67	65	1.00 (—)
40–80	62	104	2.08 (1.01–4.29)
80–130	60	59	1.56 (0.73–3.35)
130–200	68	48	1.35 (0.63–2.88)
>200	49	41	1.50 (0.64–3.54)
P for linear trend			0.94
Total PEs (μg/day)			
<1,510	63	69	1.00 (—)
1,510–2,470	65	67	0.94 (0.47–1.91)
2,470–3,400	64	54	1.21 (0.59–2.49)
3,400–5,560	56	63	0.89 (0.42–1.87)
>5,560	58	64	1.04 (0.51–2.12)
P for linear trend			0.37

[a]Adjusted for age, race, family history of any cancer, education, BMI, history of benign thyroid disease, age at menarche, use of oral contraceptives, age at first full-term pregnancy, menopausal status, estrogen use, and previous alcohol consumption.

RCTs have concluded that isoflavone soy protein supplements do not affect serum TSH levels (25, 50, 53). Therefore, it is unlikely that total isoflavone intake affects thyroid cancer risk by influencing TSH levels.

Historically, the major consumers of soy foods were Asian countries such as China, Korean, and Japan (54). The estimated daily soy consumption was found to be higher in China, Korean, and Japan (soy and soy foods: 23.5–135.4 g/day, 21.07 g/day, and 50.7–102.1 g/day, respectively; soy protein: 2.5–10.3 g/day, 7.4–8.5 g/day, and 6–11.3 g/day, respectively; ref. 55) than in the USA with one previous study showing an average soy protein intake of 9.25 g/day, with higher consumption found among vegetarians (55, 56). The concentrations of genistein and coumestrol measured in various foods differed by area and population (35, 57, 58). In general, the genistein mainly comes from soy-based foods (such as soybeans, soymilk, tofu, soy protein, and black bean sauce) and foods with added soy flour or protein (such as doughnuts, "power"-type bars, etc.). The main sources of coumestrol include sprouts (such as alfalfa sprouts, clover sprouts, and mung bean sprouts), soy-based products (such as soybeans, soymilk and tofu), and foods with added soy flour or protein (such as canned tuna, doughnuts, pancakes and waffles). Overall, the level of genistein in the same food category is much higher than the level of coumestrol (35, 57).

Previous observational studies have shown inconsistent results regarding the effects of soy-based food consumption on thyroid cancer risk, with some studies suggesting a protective effect (7, 14, 15) and other studies reporting no associations (8, 13, 18). Our study found no statistically significant relationship between soy-based food consumption and thyroid cancer risk. Studies that reported a protective effect were mainly conducted in Asian populations (7, 14, 15), where soy food consumption was higher than in Western populations. This may suggest that soy-based food consumption, especially at a relatively higher amount, could be beneficial in the prevention of thyroid cancer, and genistein may play an important role in the anticarcinogenic process.

Our study, consistent with a study conducted in San Francisco, has shown no association between foods with added soy flour or protein and thyroid cancer risk (7). It has been suggested that there is a positive relationship between refined cereals and thyroid cancer (16, 17). Though foods with added soy flour, such as doughnuts, pancakes, and waffles, have a relatively high genistein content, the potential anticarcinogenic effects of genistein may be cancelled out by their high sugar components, which can cause glycemic overload, elevated insulin and insulin-like growth factor level, and can subsequently promote tumor cell growth (16, 59). It has been suggested that fresh fish consumption is a protective factor against thyroid cancer, but consumption of processed fish, such as canned tuna, has been linked to an increased risk of thyroid cancer (17, 60). The proposed mechanism is that the additives in processed foods may affect iodine absorption and potentially cause iodine deficiency (60). Iodine deficiency is associated with increased thyroid cancer risk (61). Therefore, foods with added soy flour or protein, due to their mixed components and other possible carcinogenic factors, may promote tumor proliferation.

To the best of our knowledge, this is the first study to investigate the effects of both specific phytoestrogenic compounds and soy-based foods on thyroid cancer risk by tumor size. Our study has several strengths. First, Diet*Calc Analysis Software was adopted to estimate PE compound levels. The accurate measurement of specific nutrients could decrease the possibility of exposure misclassification. Furthermore, carefully reviewed pathologic reports allowed for stratified analysis based on the pathologic information.

Published OnlineFirst December 11, 2019; DOI: 10.1158/1055-9965.EPI-19-0456

Table 5. Risk of thyroid cancer associated with PE intake for thyroid cancer among papillary carcinomas by tumor size among female subjects.

		Papillary carcinoma			
	Controls	≤1 cm ($n = 142$)		>1 cm ($n = 126$)	
PE intake	($n = 306$)	Cases	OR[a] (95% CI)	Cases	OR[a] (95% CI)
Genistein (μg/day)					
<760	64	33	1.00 (—)	28	1.00 (—)
760–1,260	62	24	0.40 (0.15–1.07)	23	0.34 (0.12–0.98)
1,260–1,860	66	32	1.19 (0.51–2.75)	26	0.54 (0.19–1.51)
1,860–3,110	55	27	0.60 (0.24–1.53)	25	0.26 (0.08–0.85)
>3,110	59	26	0.48 (0.18–1.26)	24	0.53 (0.19–1.49)
P for linear trend			0.60		0.31
Daidzein (μg/day)					
<530	65	29	1.00 (—)	25	1.00 (—)
530–910	60	29	0.77 (0.30–1.97)	24	0.85 (0.30–2.42)
910–1,310	64	31	1.80 (0.76–4.27)	27	0.94 (0.33–2.64)
1,310–2,240	58	28	0.67 (0.26–1.74)	27	0.42 (0.13–1.33)
>2,240	59	25	0.63 (0.24–1.69)	23	0.84 (0.29–2.39)
P for linear trend			0.60		0.31
Biochanin A (μg/day)					
<30	86	48	1.00 (—)	46	1.00 (—)
30–50	62	35	0.77 (0.33–1.83)	20	0.86 (0.32–2.32)
50–70	59	22	0.79 (0.32–1.95)	22	0.81 (0.29–2.25)
70–120	57	27	0.79 (0.33–1.89)	21	0.41 (0.14–1.25)
>120	42	10	0.38 (0.12–1.18)	17	0.91 (0.30–2.71)
P for linear trend			0.59		0.63
Formononetin (μg/day)					
0	61	40	1.00 (—)	29	1.00 (—)
0–10	101	49	1.28 (0.57–2.86)	45	0.87 (0.34–2.24)
10–20	62	19	0.77 (0.30–1.93)	15	0.74 (0.25–2.19)
20–30	20	13	0.86 (0.24–3.04)	12	0.57 (0.13–2.47)
>30	62	21	0.59 (0.22–1.59)	25	0.76 (0.26–2.19)
P for linear trend			0.26		0.50
Glycitein (μg/day)					
<100	68	32	1.00 (—)	28	1.00 (—)
100–170	62	30	1.05 (0.43–2.55)	23	0.56 (0.20–1.60)
170–260	66	31	1.31 (0.55–3.11)	28	0.79 (0.29–2.16)
260–430	52	26	0.83 (0.32–2.17)	23	0.44 (0.14–1.40)
>430	58	23	0.66 (0.25–1.73)	24	0.68 (0.25–1.88)
P for linear trend			0.54		0.35
Total isoflavones (μg/day)					
<1,410	65	32	1.00 (—)	28	1.00 (—)
1,410–2,240	63	23	0.62 (0.24–1.62)	23	0.32 (0.11–0.95)
2,240–3,280	66	36	1.53 (0.66–3.57)	27	0.66 (0.24–1.83)
3,280–5,440	54	25	0.75 (0.29–1.92)	24	0.25 (0.07–0.83)
>5,440	58	26	0.61 (0.23–1.59)	24	0.56 (0.20–1.58)
P for linear trend			0.60		0.31
Coumestrol (μg/day)					
<40	67	22	1.00 (—)	32	1.00 (—)
40–80	62	55	2.94 (1.12–7.73)	38	2.16 (0.80–5.86)
80–130	60	29	2.55 (0.91–7.14)	18	0.65 (0.19–2.20)
130–200	68	21	1.57 (0.56–4.38)	22	1.28 (0.43–3.79)
>200	49	15	1.41 (0.44–4.56)	16	1.02 (0.29–3.68)
P for linear trend			0.93		0.41
Total PEs (μg/day)					
<1,510	63	32	1.00 (—)	27	1.00 (—)
1,510–2,470	65	30	0.85 (0.34–2.13)	30	0.65 (0.24–1.78)
2,470–3,400	64	29	1.60 (0.66–3.85)	19	0.72 (0.25–2.12)
3,400–5,560	56	24	0.64 (0.24–1.70)	26	0.27 (0.08–0.91)
>5,560	58	27	0.72 (0.28–1.88)	24	0.69 (0.24–1.97)
P for linear trend			0.60		0.31

[a]Adjusted for age, race, family history of any cancer, education, BMI, history of benign thyroid disease, age at menarche, use of oral contraceptives, age at first full-term pregnancy, menopausal status, estrogen use, and previous alcohol consumption.

However, the present study also has limitations. Dietary intake was self-reported and thus might lead to potential recall bias. Because the relationship between PE intake and thyroid cancer risk has not been well established, potential recall bias is likely to be nondifferential and result in an underestimation of the true association. Due to limited sample size, the study was unable to investigate the association between PE intake and rare histologic subtypes, such as medullary and anaplastic thyroid cancer. The subgroup analyses, which were stratified by histology, gender, and tumor size, might yield unstable results. The FFQ in our study captured the vast majority of previously validated PE-rich food; however, certain food items, mainly Asian-style bean products and sprouts, that contain high levels of genistein [such as Chinese black bean sauce, Natto (fermented Japanese beans), and soybean sprouts] and coumestrol (such as clover sprouts, soybean sprouts, alfalfa sprouts and mung bean sprouts) were not included (https://data.nal.usda.gov/dataset/usda-database-isoflavone-content-selected-foods-release-21-november-2015/resource/1de757af). Nevertheless, according to a Centers for Disease Control and Prevention (CDC) population survey (62), among the Connecticut respondents (with 88.6% being of white race), only 3.9% of them reported consuming alfalfa sprouts, 6.0% bean sprouts and 8.7% other sprouts, which included clover sprouts. The consumption was significantly lower than in Asian countries, where sprouts have been common foods since ancient times (63). Hence, the uncaptured PE-rich food items were unlikely to make a significant contribution to our final results. Lastly, our study did not include lignans, the quantities of which were undetected or of trace amounts in most foods (35), which could potentially result in an underestimation of total PE exposure.

Conclusion

This population-based case–control study supports the hypothesis that coumestrol is associated with an increased risk of thyroid cancer with small tumor size and that genistein is associated with a decreased risk of thyroid cancer with larger tumor size among females. The novel finding that risks varied by tumor size warrants further investigation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Q. Wang, X. Ni, R. Udelsman, Y. Zhang
Development of methodology: R. Udelsman, Y. Zhang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Q. Wang, N. Zhao
Writing, review, and/or revision of the manuscript: Q. Wang, N. Zhao, X. Ni, R. Udelsman, Y. Zhang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Q. Wang, H. Huang
Study supervision: X. Ni, Y. Zhang

Acknowledgments

This study was supported by American Cancer Society (ACS) grant RSGM-10-038-01-CCE (Y. Zhang) and NIH grant R01ES020361 (Y. Zhang). Certain data used in this study were obtained from the Connecticut Tumor Registry located in the Connecticut Department of Public Health. The authors assume full responsibility for the analyses and interpretation of these data. The cooperation of the Connecticut hospitals, including Charlotte Hungerford Hospital, Bridgeport Hospital, Danbury Hospital, Hartford Hospital, Middlesex Hospital, Hospital of Central Connecticut, Yale/New Haven Hospital, St. Francis Hospital and Medical Center, St. Mary's Hospital, Hospital of St. Raphael, St. Vincent's Medical Center, Stamford Hospital, William W. Backus Hospital, Windham Hospital, Eastern Connecticut Health Network, Griffin Hospital, Bristol Hospital, Johnson Memorial Hospital, Greenwich Hospital, Lawrence and Memorial Hospital, New Milford Hospital, Norwalk Hospital, MidState Medical Center, John Dempsey Hospital, and Waterbury Hospital, in allowing patient access, is gratefully acknowledged. Rajni Mehta from the Yale Comprehensive Cancer Center's RCA provided great help in both Institutional Review Board (IRB) approvals and field implementation of the study. Helen Sayward, Anna Florczak, and Renee Capasso from the Yale School of Public Health did exceptional work in study subject recruitment.

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.

Received May 5, 2019; revised July 28, 2019; accepted December 3, 2019; published first December 11, 2019.

References

1. Cronin KA, Lake AJ, Scott S, Sherman RL, Noone AM, Howlader N, et al. Annual report to the nation on the status of cancer, part I: National cancer statistics. Cancer 2018;124:2785–800.
2. U.S. Cancer Statistics Working Group. U.S. cancer statistics data visualizations tool, based on November 2017 submission data (1999–2015). Bethesda, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2018.
3. Zhu C, Zheng T, Kilfoy BA, Han X, Ma S, Ba Y, et al. A birth cohort analysis of the incidence of papillary thyroid cancer in the United States, 1973–2004. Thyroid 2009;19:1061–6.
4. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. JAMA 2017; 317:1338–48.
5. Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. Thyroid 2013;23: 885–91.
6. Udelsman R, Zhang Y. The epidemic of thyroid cancer in the United States: the role of endocrinologists and ultrasounds. Thyroid 2014;24:472–9.
7. Horn-Ross PL, Hoggatt KJ, Lee MM. Phytoestrogens and thyroid cancer risk: the San Francisco Bay Area thyroid cancer study. Cancer Epidemiol Biomarkers Prev 2002;11:43–9.
8. Takezaki T, Hirose K, Inoue M, Hamajima N, Kuroishi T, Nakamura S, et al. Risk factors of thyroid cancer among women in Tokai, Japan. J Epidemiol 1996;6: 140–7.
9. Rinaldi S, Lise M, Clavel-Chapelon F, Boutron-Ruault MC, Guillas G, Overvad K, et al. Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. Int J Cancer 2012;131:E1004–14.
10. Kitahara CM, Platz EA, Freeman LE, Hsing AW, Linet MS, Park Y, et al. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. Cancer Epidemiol Biomarkers Prev 2011;20:464–72.
11. Greenlee H, White E, Patterson RE, Kristal AR; Vitamins and Lifestyle (VITAL) Study Cohort. Supplement use among cancer survivors in the Vitamins and Lifestyle (VITAL) study cohort. J Altern Complement Med 2004;10:660–6.
12. D'Adamo CR, Sahin A. Soy foods and supplementation: a review of commonly perceived health benefits and risks. Altern Ther Health Med 2014;20 Suppl 1: 39–51.
13. Przybylik-Mazurek E, Hubalewska-Dydejczyk A, Kuzniarz-Rymarz S, Kiec-Klimczak M, Skalniak A, Sowa-Staszczak A, et al. Dietary patterns as risk factors of differentiated thyroid carcinoma. Postepy Hig Med Dosw 2012;66:11–5.
14. Zhu QX, Bian JC, Shen Q, Tang HW, Zhang HW, Wu Y. [A matched case-control study of papillary thyroid carcinoma]. Zhonghua Liu Xing Bing Xue Za Zhi 2006;27:416–9. [Article in Chinese].
15. Haselkorn T, Stewart SL, Horn-Ross PL. Why are thyroid cancer rates so high in southeast Asian women living in the United States? The Bay Area thyroid cancer study. Cancer Epidemiol Biomarkers Prev 2003;12:144–50.
16. Chatenoud L, La Vecchia C, Franceschi S, Tavani A, Jacobs DR Jr, Parpinel MT, et al. Refined-cereal intake and risk of selected cancers in Italy. Am J Clin Nutr 1999;70:1107–10.

17. Braganza MZ, Potischman N, Park Y, Thompson FE, Hollenbeck AR, Kitahara CM. Adolescent and mid-life diet and subsequent risk of thyroid cancer in the NIH-AARP Diet and Health Study. Int J Cancer 2015;137:2413–23.
18. Xiao Q, Park Y, Hollenbeck AR, Kitahara CM. Dietary flavonoid intake and thyroid cancer risk in the NIH-AARP Diet and Health Study. Cancer Epidemiol Biomarkers Prev 2014;23:1102–8.
19. Dixon RA. Phytoestrogens. Annu Rev Plant Biol 2004;55:225–61.
20. Messina M. Soy and health update: evaluation of the clinical and epidemiologic literature. Nutrients 2016;8. doi: 10.3390/nu8120754.
21. Kurzer MS, Xu X. Dietary phytoestrogens. Annu Rev Nutr 1997;17:353–81.
22. Hedelin M, Löf M, Olsson M, Adlercreutz H, Sandin S, Weiderpass E. Dietary phytoestrogens are not associated with risk of overall breast cancer but diets rich in coumestrol are inversely associated with risk of estrogen receptor and progesterone receptor negative breast tumors in Swedish women. J Nutr 2008;138:938–45.
23. Yin F, Giuliano AE, Van Herle AJ. Growth inhibitory effects of flavonoids in human thyroid cancer cell lines. Thyroid 1999;9:369–76.
24. Long M, Kruger T, Ghisari M, Bonefeld-Jorgensen EC. Effects of selected phytoestrogens and their mixtures on the function of the thyroid hormone and the aryl hydrocarbon receptor. Nutr Cancer 2012;64:1008–19.
25. Dillingham BL, McVeigh BL, Lampe JW, Duncan AM. Soy protein isolates of varied isoflavone content do not influence serum thyroid hormones in healthy young men. Thyroid 2007;17:131–7.
26. Tiosano D, Paris F, Grimaldi M, Georgescu V, Servant N, Hochberg Z, et al. Evidence of ERalpha and ERbeta selectivity and partial estrogen agonism in traditional Chinese medicine. Reprod Biol Endocrinol 2014;12:97.
27. Kang HJ, Youn YK, Hong MK, Kim LS. Antiproliferation and redifferentiation in thyroid cancer cell lines by polyphenol phytochemicals. J Korean Med Sci 2011; 26:893–9.
28. Vivacqua A, Bonofiglio D, Albanito L, Madeo A, Rago V, Carpino A, et al. 17beta-estradiol, genistein, and 4-hydroxytamoxifen induce the proliferation of thyroid cancer cells through the g protein-coupled receptor GPR30. Mol Pharmacol 2006;70:1414–23.
29. Zhang Y, Chen Y, Huang H, Sandler J, Dai M, Ma S, et al. Diagnostic radiography exposure increases the risk for thyroid microcarcinoma: a population-based case-control study. Eur J Cancer Prev 2015;24:439–46.
30. Zeng F, Lerro C, Lavoue J, Huang H, Siemiatycki J, Zhao N, et al. Occupational exposure to pesticides and other biocides and risk of thyroid cancer. Occup Environ Med 2017;74:502–10.
31. Sandler JE, Huang H, Zhao N, Wu W, Liu F, Ma S, et al. Germline variants in DNA repair genes, diagnostic radiation, and risk of thyroid cancer. Cancer Epidemiol Biomarkers Prev 2018;27:285–94.
32. Luo J, Deziel NC, Huang H, Chen Y, Ni X, Ma S, et al. Cell phone use and risk of thyroid cancer: a population-based case-control study in Connecticut. Ann Epidemiol 2019;29:39–45.
33. Huang H, Zhao N, Chen Y, Deziel N, Dai M, Li N, et al. Alcohol consumption and risk of thyroid cancer: a population based case-control study in Connecticut. Adv Exp Med Biol 2018;1032:1–14.
34. Ba Y, Huang H, Lerro CC, Li S, Zhao N, Li A, et al. Occupation and thyroid cancer: a population-based, case-control study in Connecticut. J Occup Environ Med 2016;58:299–305.
35. Horn-Ross PL, Barnes S, Lee M, Coward L, Mandel JE, Koo J, et al. Assessing phytoestrogen exposure in epidemiologic studies: development of a database (United States). Cancer Causes Control 2000;11:289–98.
36. Choi SY, Ha TY, Ahn JY, Kim SR, Kang KS, Hwang IK, et al. Estrogenic activities of isoflavones and flavones and their structure-activity relationships. Planta Med 2008;74:25–32.
37. Magri F, Capelli V, Gaiti M, Villani L, Zerbini F, La Manna L, et al. ER-alpha and ER-beta expression in differentiated thyroid cancer: relation with tumor phenotype across the TNM staging and peri-tumor inflammation. Endocrine 2015; 49:429–35.
38. Huang Y, Dong W, Li J, Zhang H, Shan Z, Teng W. Differential expression patterns and clinical significance of estrogen receptor-α and β in papillary thyroid carcinoma. BMC Cancer 2014;14:383.
39. Dong W, Li J, Zhang H, Huang Y, He L, Wang Z, et al. Altered expression of estrogen receptor β2 is associated with different biological markers and clinicopathological factors in papillary thyroid cancer. Int J Clin Exp Pathol 2015;8: 7149–56.
40. Magri F, Capelli V, Rotondi M, Leporati P, La Manna L, Ruggiero R, et al. Expression of estrogen and androgen receptors in differentiated thyroid cancer: an additional criterion to assess the patient's risk. Endocr Relat Cancer 2012;19: 463–71.
41. de Vathaire F, Haddy N, Allodji RS, Hawkins M, Guibout C, El-Fayech C, et al. Thyroid radiation dose and other risk factors of thyroid carcinoma following childhood cancer. J Clin Endocrinol Metab 2015;100:4282–90.
42. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 2010;34:28–35.
43. Kuiper GG, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology 1997;138:863–70.
44. Jantan I, Ahmad W, Bukhari SN. Plant-derived immunomodulators: an insight on their preclinical evaluation and clinical trials. Front Plant Sci 2015;6:655.
45. Huang H, Rusiecki J, Zhao N, Chen Y, Ma S, Yu H, et al. Thyroid-stimulating hormone, thyroid hormones, and risk of papillary thyroid cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2017;26:1209–18.
46. Gudmundsson J, Sulem P, Gudbjartsson DF, Jonasson JG, Masson G, He H, et al. Discovery of common variants associated with low TSH levels and thyroid cancer risk. Nat Genet 2012;44:319–22.
47. Rinaldi S, Plummer M, Biessy C, Tsilidis KK, Ostergaard JN, Overvad K, et al. Thyroid-stimulating hormone, thyroglobulin, and thyroid hormones and risk of differentiated thyroid carcinoma: the EPIC study. J Natl Cancer Inst 2014;106: dju097.
48. Steinberg FM, Murray MJ, Lewis RD, Cramer MA, Amato P, Young RL, et al. Clinical outcomes of a 2-y soy isoflavone supplementation in menopausal women. Am J Clin Nutr 2011;93:356–67.
49. Bitto A, Polito F, Atteritano M, Altavilla D, Mazzaferro S, Marini H, et al. Genistein aglycone does not affect thyroid function: results from a three-year, randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2010;95:3067–72.
50. Bruce B, Messina M, Spiller GA. Isoflavone supplements do not affect thyroid function in iodine-replete postmenopausal women. J Med Food 2003;6:309–16.
51. Ham JO, Chapman KM, Essex-Sorlie D, Bakhit RM, Prabhudesai M, Winter L, et al. Endocrinological response to soy protein and fiber in mildly hypercholesterolemic men. Nutr Res 1993;13:873–84.
52. Vannucchi G, De Leo S, Perrino M, Rossi S, Tosi D, Cirello V, et al. Impact of estrogen and progesterone receptor expression on the clinical and molecular features of papillary thyroid cancer. Eur J Endocrinol 2015;173:29–36.
53. Persky VW, Turyk ME, Wang L, Freels S, Chatterton R Jr, Barnes S, et al. Effect of soy protein on endogenous hormones in postmenopausal women. Am J Clin Nutr 2002;75:145–53.
54. Huang H, Krishnan HB, Pham Q, Yu LL, Wang TT. Soy and gut microbiota: interaction and implication for human health. J Agric Food Chem 2016;64: 8695–709.
55. Rizzo G, Baroni L. Soy, soy foods and their role in vegetarian diets. Nutrients 2018;10:43.
56. Jaceldo-Siegl K, Fraser GE, Chan J, Franke A, Sabate J. Validation of soy protein estimates from a food-frequency questionnaire with repeated 24-h recalls and isoflavonoid excretion in overnight urine in a Western population with a wide range of soy intakes. Am J Clin Nutr 2008;87:1422–7.
57. Thompson LU, Boucher BA, Liu Z, Cotterchio M, Kreiger N. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestan. Nutr Cancer 2006;54:184–201.
58. Huang MH, Norris J, Han W, Block T, Gold E, Crawford S, et al. Development of an updated phytoestrogen database for use with the SWAN food frequency questionnaire: intakes and food sources in a community-based, multiethnic cohort study. Nutr Cancer 2012;64:228–44.
59. Malaguarnera R, Vella V, Nicolosi ML, Belfiore A. Insulin resistance: any role in the changing epidemiology of thyroid cancer? Front Endocrinol 2017;8:314.
60. Memon A, Varghese A, Suresh A. Benign thyroid disease and dietary factors in thyroid cancer: a case-control study in Kuwait. Br J Cancer 2002;86:1745–50.
61. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. Thyroid Res 2015;8:8.
62. Centers for Disease Control and Prevention. Foodborne Active Surveillance Network (FoodNet) Population Survey Atlas of Exposures. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2006–2007.
63. Tang D, Dong Y, Ren H, Li L, He C. A review of phytochemistry, metabolite changes, and medicinal uses of the common food mung bean and its sprouts (Vigna radiata). Chem Cent J 2014;8:4.

Published OnlineFirst December 11, 2019; DOI: 10.1158/1055-9965.EPI-19-0456

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Phytoestrogens and Thyroid Cancer Risk: A Population-Based Case–Control Study in Connecticut

Qian Wang, Huang Huang, Nan Zhao, et al.

Cancer Epidemiol Biomarkers Prev 2020;29:500-508. Published OnlineFirst December 11, 2019.