Iodine and Thyroid Cancer Risk among Women in a Multiethnic Population: The Bay Area Thyroid Cancer Study[1]

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Abstract

Research on the relationship between iodine exposure and thyroid cancer risk is limited, and the findings are inconclusive. In most studies, fish/shellfish consumption has been used as a proxy measure of iodine exposure. The present study extends this research by quantifying dietary iodine exposure as well as incorporating a biomarker of long-term (1 year) exposure, *i.e.,* from toenail clippings. This study is conducted in a multiethnic population with a wide variation in thyroid cancer incidence rates and substantial diversity in exposure. Women, ages 20–74, residing in the San Francisco Bay Area and diagnosed with thyroid cancer between 1995 and 1998 (1992–1998 for Asian women) were compared with women selected from the general population via random digit dialing. Interviews were conducted in six languages with 608 cases and 558 controls. The established risk factors for thyroid cancer were found to increase risk in this population: radiation to the head/ neck [odds ratio (OR), 2.3; 95% confidence interval (CI), 0.97–5.5]; history of goiter/nodules (OR, 3.7; 95% CI, 2.5–5.6); and a family history of proliferative thyroid disease (OR, 2.5; 95% CI, 1.6–3.8). Contrary to our hypothesis, increased dietary iodine, most likely related to the use of multivitamin pills, was associated with a reduced risk of papillary thyroid cancer. This risk reduction was observed in "low-risk" women (*i.e.,* women without any of the three established risk factors noted above; OR, 0.53; 95% CI, 0.33–0.85) but not in "high-risk" women, among whom a slight elevation in risk was seen (OR, 1.4; 95% CI, 0.56–3.4). However, no association with risk was observed in either group when the biomarker of exposure was evaluated. In addition, no ethnic differences in risk were observed. The authors conclude that iodine exposure appears to have, at most, a weak effect on the risk of papillary thyroid cancer.

Introduction

In the United States population as a whole, thyroid cancer is a rare malignancy with an age-adjusted incidence rate of 6.5/ 100,000/year in women and 2.5/100,000/year in men (1). It is, however, one of the five most common cancers occurring among young women (ages 15–44) and among Filipina and Southeast Asian women residing in the United States (1). Among United States Filipina and Vietnamese women, the thyroid cancer incidence rates are 2- and 4-fold higher than are observed among women in the Philippines or Vietnam, respectively, or among white United States women (2). Futhermore, Rossing *et al.* (3) have shown that among Filipina and Japanese women residing in the United States, thyroid cancer incidence rates were elevated among women born in Asia but not among those born in the United States. This unusual incidence pattern suggests that environmental factors have an important influence on the development of thyroid cancer, that these factors act at a later stage in the carcinogenic process, and that these factors are changeable within a population. Nutritionally related factors are prime candidates for such exposures.

Iodine is a trace element that is essential in the synthesis of thyroid hormones (4). Both chronic iodine deficiency and chronically high iodine intake have been associated with the development of goiter (*i.e.,* hypertrophy and hyperplasia of the thyroid cells) and attributed to excessive secretion of TSH[3] by the pituitary. In turn, goiter has been associated with thyroid cancer risk, particularly in women (5–13). In general, chronic iodine deficiency and residence in an endemic goiter area are associated with an increased risk of the follicular histological type of thyroid cancer, whereas chronically high iodine intake may increase the risk of the more common papillary histological type of thyroid cancer. In most epidemiological studies, fish/shellfish consumption has been used as a proxy measure of iodine exposure. However, associations between fish consumption and thyroid cancer risk have been mixed with no discernable pattern and often inconsistent within a given study (5, 7, 8, 13–17). Only the study by Kolonel *et al.* (5) has quantified iodine intake. These investigators found a statistically nonsig-

[3] The abbreviations used are: TSH, thyroid-stimulating hormone; SEER, Surveillance, Epidemiology, and End Results; NAA, neutron activation analysis; OR, odds ratio; CI, confidence interval; USRDA, United States recommended daily allowance.

nificant 60% elevation in thyroid cancer risk associated with the highest quartile of iodine consumption and a significant elevated risk among a subgroup of women who had possible indications of subclinical thyroid dysfunction (5).

The present study expands this body of research by: (*a*) quantifying dietary iodine exposure in the diverse multicultural population under study; (*b*) including a long-term (1 year) biomarker of iodine exposure from nail clippings as part of its assessment; and (*c*) specifically hypothesizing that the detrimental effects of excess iodine exposure are limited to the development of papillary thyroid cancer among "high-risk" women, defined as those with a personal history of goiter or thyroid nodules, radiation exposure to the head/neck, or a family history of proliferative thyroid disease.

Materials and Methods

Study Participants

This population-based case-control study was conducted in the San Francisco Bay Area. All participants were women between 20 and 74 years of age, residents of one of the five counties comprising the area, who spoke sufficient English, Spanish, Tagalog, Cantonese, Mandarin, or Vietnamese to complete the interview; and who had no prior history of cancer of the thyroid. Patients were identified through the Greater Bay Area Cancer Registry, a population-based cancer registry which is part of the SEER program and the California Cancer Registry. All 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. Seventeen (2%) patients had died, one physician indicated contraindications to contacting a particular patient (<1%), 106 (13%) declined to participate, 27 (3%) did not speak one of the six languages in which we were interviewing, and 58 (7%) were not interviewed for other reasons (*e.g.,* illness or the inability to locate them or interview them before the end of the study).

Controls were identified through random-digit dialing and were matched to cases on 5-year age group and broad racial/ethnic group (*i.e.,* white, African American, Latina, Asian, or Native American). We called 9756 phone numbers to identify controls. Of these, 3898 were not residential numbers, and the status of 856 numbers could not be determined because they were never answered despite 10 attempts calling on a specified variety of days and times. On the basis of anecdotal information from the phone company, many of these 856 numbers may represent those that are in flux at any given time (*i.e.,* have been unassigned from one user but not yet reassigned to another and thus, will simply ring). Of the 5002 known residences, 3928 (79%) were successfully enumerated. From these enumerated residences, 793 eligible controls were selected for participation in the study and 558 (70%) were interviewed. One hundred and fifty-four (19%) declined to participate, 23 (3%) did not speak one of the six languages in which we were interviewing, and 57 (7%) were not interviewed for other reasons.

Data Collection

Interviewing. The study protocol and instruments were reviewed and approved annually by the Northern California Cancer Center's Institutional Review Board. In-person interviews were conducted using a standardized structured questionnaire. Asian and Latina women were interviewed by bilingual, bicultural interviewers. Whenever possible, phrasing of questions was drawn from established and validated instruments. Stand-

ard translation methodology, including forward and backward translation and review for colloquial phrasing, was used in translating all subject materials (18, 19) into the five non-English languages. The interview included questions on a wide variety of topics including demographics; birthplace of self, parents, and grandparents; language spoken; height, weight, and body shape; residential history; menstrual and reproductive histories; use of birth control pills and hormone replacement therapy; medical history including history of benign thyroid conditions and medical radiation exposure; family history of thyroid disease; and cigarette smoking.

Dietary intake, including alcohol consumption and vitamin and mineral supplement use, during the year before diagnosis or interview for cases and controls, respectively, was assessed using a food-frequency questionnaire designed to capture the diverse diet of the ethnically and culturally heterogeneous Bay Area population and to quantify iodine intake. Portion size was determined using visual aids including food models, three-dimensional abstract models, glasses, dishes, and measuring cups and spoons. Our nutrient database was based on the work by Dr. Gladys Block (20) and updated from other sources (21–29).[4],[5]

Histological Review. Pathology materials from cases were reviewed to provide a uniform histological classification of the thyroid tumors. We received permission to review pathology materials from 603 (99%) of the 608 patients interviewed. Slides were available for 543 (90%) patients, review was based solely on pathology reports for 55 (9%), slides and reports were unavailable for three (<1%), and, for the remaining two (<1%), pathological materials were not released. For the 598 cases for whom histological material (slides or reports) was available, 544 (91%) were classified as papillary histological type (including both papillary and mixed papillary/follicular histologies), 28 (5%) as follicular histology, 11 (2%) as Hurtle cell tumors, five (1%) as medullary carcinomas, and 10 (2%) were of other histological type. Agreement on histological type between our expert review and the original hospital classification (as reported to the cancer registry) was 94%. For cases classified as papillary cancer by the hospital, our expert review concurred in 99%; for follicular cancer, agreement was 65%, and for other histological types, agreement was 88%.

Toenail Collection. Trace elements, such as iodine, are incorporated into the base of the finger and toenails as they are formed. Neutron activation analysis of nail clippings from the large toe provides an integrated measure of iodine exposure over a 2–4-week period approximately 1 year prior to clipping (30). Participants were asked to clip their own toenails at the time of interview or as soon afterward as was feasible. Of the 608 cases interviewed, 556 (91%) provided toenail clippings for the analysis of iodine exposure. Of the 558 controls interviewed, 526 (94%) provided clippings. Clippings were stored in small paper coin envelopes at room temperature before being transferred to the University of Missouri for analysis.

Neutron Activation Analysis

Toenail specimens were clipped into 1–2-mm pieces, washed in deionized water with sonication, collected on a filter mem-

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brane, and oven-dried at 50°C. The clippings were then examined using low-power magnification, and any extraneous debris was removed. Approximately 50 milligrams of nail was weighed into a small, precleaned, high-density polyethylene vial having a volume of ~0.5 ml. Samples were irradiated with neutrons (produced from a U-235 fission reactor), then transferred to a high-resolution γ-ray spectrometer and counted for a preselected period. NAA was done instrumentally (without chemical processing) using the full fission-neutron spectrum for analyzing scandium (to access soil contamination, none of which was observed) and the ε-boron spectrum for analyzing iodine.

For iodine analysis, the nail sample was irradiated under a boron (as boron nitride) shield, which effectively eliminates the thermal neutrons. The irradiation protocol consisted of 5–25 irradiations of 10 s each separated by a 30–90 s "cooling period" for each cycle. The number of cycles largely depended on the sample size, larger samples having fewer cycles. The I-127 (n,γ)I-128 nuclear reaction has nearly equal contributions from thermal and ε-boron neutron capture. Consequently, substantially reducing the thermal component reduced the I-128 signal ~50%, whereas the common interferences in biological samples were correspondingly reduced by 98% or more. This allowed the signal:noise ratio to be greatly increased, which substantially improved the accuracy, precision, and sensitivity of the measurement. One to 5 min after the final irradiation cycle, the sample was real-time counted for 5–50 min using the γ-ray spectrometer described above. The concentration of iodine was determined via standard comparison using the 442.9 KeV γ-ray from the decay of I-128 ($t_{1/2}$ = 24.99 min).

Data Analysis

ORs and 95% CIs were estimated using unconditional logistic regression analyses, controlling for age, race/ethnicity, and other potentially confounding factors as noted in the footnotes of the tables (including education, radiation to the head or neck, history of goiter or thyroid nodules, a family history of proliferative thyroid disease, daily caloric intake, smoking, and alcohol consumption; Refs. 31 and 32). Dietary analyses excluded 18 (3%) cases and 14 (3%) controls who substantially over- or underreported their intake, *i.e.,* reported a usual diet which consisted of >5000 or <600 calories/day. Analyses of iodine exposure based on toenail clippings were limited to 325 cases and 459 controls; excluded from these analyses were 128 (23%) cases and 31 (6%) controls whose clippings did not represent the prediagnostic period (*i.e.,* were collected >12 months after diagnosis/selection; the higher exclusion rate among cases reflects the retrospective ascertainment of half of the Asian cases); 40 (7%) cases of nonpapillary thyroid cancer; 52 (9%) cases and 27 (5%) controls who in the past 2 years had received CT scans or other medical procedures where a large single dose of iodine is administered as part of the procedure; and 11 (2%) cases and 9 (2%) controls who had used Mercurochrome or other antiseptics on their nails, which may have caused external contamination of the nail with iodine. The average time between diagnosis/selection and collection of toenail specimens was 4.6 and 3.4 months for cases and controls, respectively.

Results

The average age at diagnosis/selection, for interviewed cases and controls, was similar: 42.3 ± 12.7 years and 43.2 ± 13.4 years, respectively. Participants were predominantly white

Table 1 Established thyroid cancer risk factors and thyroid cancer risk among participants in the multiethnic Bay Area Thyroid Cancer Study

Risk factor	Cases	Controls	OR[a]	95% CI
Medical radiation[b,c]				
Head or neck	20	8	2.7	1.2–6.2
Another area	4	7	0.57	0.16–2.0
None	580	543	1.0	
Benign thyroid disease[d,e]				
Goiter or nodules	134	36	4.7	3.1–7.2
Hyperthyroidism	19	17	0.55	0.26–1.2
Hypothyroidism	34	35	0.65	0.38–1.1
None of the above	455	485	1.0	
Family history of thyroid disease				
Thyroid cancer	16	3	6.1	1.8–21.3
Goiter or nodules	66	28	2.6	1.7–4.2
Hyper- or hypothyroidism	74	53	1.5	1.0–2.3
Other or unknown type	39	41	1.0	0.65–1.6
None of the above	406	429	1.0	

[a] Adjusted for age, race/ethnicity, and education.
[b] More than 5 years before diagnosis/selection.
[c] One control reported radiation to the head/neck and another area.
[d] More than 2 years before diagnosis/selection.
[e] Thirty-three cases and 15 controls reported having been diagnosed with two or more types of benign thyroid disease during their lifetime.

(51%) and Asian (35%); 11% were Latina; and 3% were African American, Native American, or of mixed race/ethnicity. This racial/ethnic distribution did not differ significantly between cases and controls. Among Asians there were no case-control differences in the Asian subgroups represented; 33% were Filipina, 30% were Chinese, 11% were Vietnamese, 7% were Japanese, and 19% were of other or mixed subgroups. Among Latinas, 59% were of Mexican heritage and 24% were from Central America; cases were more likely to be Mexican, whereas controls were more likely to be Central American. Eighty-three percent of participants were interviewed in English. Forty-five percent of Latinas were interviewed in Spanish, 89% of Vietnamese in Vietnamese, 33% of Chinese in Cantonese and 25% in Mandarin, and 18% of Filipinas in Tagalog. Eighty-five percent of Asians and 63% of Latinas were born outside the United States; these distributions did not differ significantly between cases and controls. Cases were more likely than controls to have received a high school diploma (93% *versus* 88%; OR, 1.9; 95% CI, 1.2–2.9, adjusting for established thyroid cancer risk factors, *i.e.,* a history of goiter or thyroid nodules, radiation to the head or neck, and a family history of proliferative thyroid disease).

Established Risk Factors for Thyroid Cancer. Table 1 presents the associations between thyroid cancer risk and medical radiation (occurring 5 or more years before diagnosis/selection), a personal history of benign thyroid conditions (diagnosed 2 or more years before diagnosis/selection), and a family history of proliferative thyroid disease. Examination of the three established risk factors (each defined as present or absent) in a single model (adjusting also for age, race/ethnicity, and education) showed that all were important independent predictors of risk in this study (OR, 2.3; 95% CI, 0.97–5.5 for radiation to the head/neck; OR, 3.7; 95% CI, 2.5–5.6 for a personal history of goiter or nodules; and OR, 2.5, 95% CI, 1.6–3.8 for a family history of proliferative thyroid disease, defined as thyroid cancer, goiter, or nodules).

Of the 28 cases with follicular tumors, none had received radiation to the head or neck, 10 (36% compared with 21% of papillary cases) had a history of goiter or nodules, and 8 (29%

Table 2 Fish consumption and the risk of papillary thyroid cancer among participants in the Bay Area Thyroid Cancer Study

Type of fish (g/d)	Cases	Controls	OR[a]	95% CI
Shellfish				
<1.0	136	122	1.0	
1.0–3.5	95	98	0.88	0.61–1.3
3.6–7.5	165	202	0.72	0.52–1.0
>7.5	131	122	0.93	0.64–1.3
Saltwater fish				
<1.0	130	129	1.0	
1.0–3.5	126	122	1.0	0.73–1.5
3.6–7.5	84	94	0.92	0.62–1.4
>7.5	187	199	0.96	0.69–1.3
Fresh-water fish				
<1.0	328	320	1.0	
1.0–3.5	81	110	0.71	0.51–1.0
3.6–7.5	39	47	0.80	0.49–1.3
>7.5	79	67	1.1	0.74–1.7
Canned tuna[b]				
<1.0	145	177	1.0	
1.0–3.5	87	85	1.3	0.88–1.8
3.6–7.5	98	84	1.5	1.0–2.1
>7.5	197	198	1.2	0.90–1.7
Total fish consumption[c]				
<7.8	109	110	1.0	
7.8–16.0	104	108	0.97	0.66–1.4
16.1–30.2	99	109	0.94	0.64–1.4
30.3–51.8	94	109	0.87	0.59–1.3
>51.8	121	108	1.1	0.74–1.6
Fish sauce/dried or salted fish[d]				
None	45	63	1.0	
<0.3	50	53	1.3	0.77–2.3
0.3–2.0	27	35	1.1	0.57–2.0
>2.0	61	37	2.3	1.3–4.0

[a] Adjusted for age, race/ethnicity, and daily caloric intake.
[b] Includes dishes made with canned tuna, *e.g.,* tuna fish sandwiches and tuna casserole.
[c] Defined as the sum of daily consumption of shellfish, saltwater fish, fresh water fish, and canned tuna.
[d] Among Asian women only.

Table 3 Iodine and the risk of papillary thyroid cancer among participants in the Bay Area Thyroid Cancer Study

Iodine	Cases	Controls	OR	95% CI
Dietary (µg/day)				
<273	120	108	1.0[a]	
273–348	92	109	0.68	0.45–1.0
349–422	94	109	0.68	0.44–1.0
423–537	117	109	0.71	0.45–1.1
>537	104	109	0.49	0.29–0.84
In nails (ppm)				
<0.08	74	92	1.0[b]	
0.08–0.11	60	92	0.69	0.43–1.1
0.12–0.17	69	92	1.0	0.63–1.6
0.18–0.35	64	92	0.76	0.48–1.2
>0.35	58	91	0.74	0.46–1.2
Among "high-risk" women[c]				
Dietary (µg/d)				
<324	54	25	1.0[d]	
324–457	52	16	1.5	0.68–3.2
>457	65	24	1.4	0.56–3.4
In nails (ppm)				
<0.10	35	15	1.0[e]	
0.10–0.20	29	18	0.87	0.35–2.1
>0.20	40	18	0.96	0.40–2.3
Among all other women				
Dietary (µg/d)				
<324	120	155	1.0[d]	
324–457	118	157	0.80	0.56–1.2
>457	106	156	0.53	0.33–0.85
In nails (ppm)				
<0.10	98	161	1.0[e]	
0.10–0.20	79	127	1.0	0.68–1.5
>0.20	72	139	0.79	0.51–1.2

[a] Adjusted for age, race/ethnicity, daily caloric intake, radiation to the head/neck, history of goiter/nodules, family history of proliferative thyroid disease, education, smoking, and alcohol consumption.
[b] Adjusted for age, race/ethnicity, radiation to the head/neck, history of goiter/nodules, family history of proliferative thyroid disease, education, smoking, and alcohol consumption.
[c] Defined as radiation to the head or neck, a personal history of goiter or nodules, and/or a family history of proliferative thyroid disease.
[d] Adjusted for age, race/ethnicity, and daily caloric intake.
[e] Adjusted for age and race/ethnicity.

compared with 13% of papillary cases) had a family history of proliferative thyroid disease. ORs associated with goiter were, thus, higher for follicular than papillary thyroid cancer; however, all were statistically significant: OR, 8.2 (95% CI, 3.5–19.6) and 4.1 (95% CI, 2.7–6.1) for a history of goiter or nodules (yes/no) for follicular and papillary cancer, respectively, and OR, 6.7 (95% CI, 2.7–16.9) and 2.5 (95% CI, 1.6–3.9) for a family history of proliferative thyroid disease (yes/no) for follicular and papillary cancer, respectively.

Iodine. Analyses of the effects of iodine were conducted separately for papillary and follicular tumors, because it is believed the effects of iodine on the development of these two histological types of thyroid cancer may be in opposite directions. Table 2 presents the associations between papillary thyroid cancer risk and various types of fish. With the exception of fish sauce/dried or salted fish (condiments commonly used in Asian cuisine), consumption of fish/shellfish was not associated with thyroid cancer risk. Other foods which can be rich in iodine, including bread products (iodate may be added as a dough conditioner), dairy products (iodophors may be used in the dairy industry as a disinfectant), salt (defined qualitatively as how often salt was added to food at the table), and seaweed, were also examined. Only cooked seaweed was associated with thyroid cancer risk and not in the direction hypothesized (OR, 0.61; 95% CI, 0.44–0.84 for consumption of ≥0.33 g/day *versus* nonconsumers).

Iodine intake (µg/day) from dietary sources was calculated for each participant based on iodine values available from published sources (22, 23, 32). These values, however, do not include iodine from seaweed or fish sauce/dried or salted fish, because these were not available. On average, the primary sources of iodine in this study population were mixed dishes which are generally prepared with salt or salty foods, most notably rice and pasta dishes and pizza, accounting for 30% of average daily iodine intake; milk and other dairy products accounting for 13%; bread products accounting for 12%; multivitamin pills and iodine supplements (the latter taken by only a few women) accounting for 11%; and fish/shellfish accounting for 3%.

Although there were too few follicular cancers (*n* = 28 cases) to be able to accurately evaluate the association between iodine and follicular cancer risk, no differences in the mean intake of dietary iodine was observed for cases and controls. Average nail iodine levels in women with follicular cancer were significantly lower than in controls (0.19 *versus* 0.29 parts/million, respectively; *P* = 0.02), consistent with observations of iodine deficiency predisposing to this type of thyroid cancer.

Table 3 presents the association between papillary thyroid cancer risk and iodine exposure. Total dietary iodine consump-

tion was inversely related to papillary thyroid cancer risk (OR, 0.49; 95% CI, 0.29–0.84 for the highest quintile of intake). This effect was similar for white and Asian women. Iodine from food alone was not associated with risk, with ORs for the quintiles varying between 0.99 and 1.2 (OR, 1.0; 95% CI, 0.55–1.9 for the highest quintile), but supplemental iodine was (OR, 0.56; 95% CI, 0.37–0.85 and OR, 0.69; 95% CI, 0.50–0.95 for <150 and 150+ μg/day). Thus, the protective effect for total dietary iodine was largely attributable to the higher consumption of multivitamin pills (most brands contain 150 μg of iodine) by controls. Adjusting for β-carotene or vitamin C, antioxidant micronutrients found in multivitamin pills, did not affect these estimates of risk for total iodine consumption. Adjustment for vitamin E attenuated the estimates somewhat (OR, 0.63; 95% CI, 0.36–1.1 for the highest quintile of total dietary iodine).

Also presented in Table 3 are the effects for iodine as measured in toenail clippings. This measure presumably reflects both dietary and nondietary exposures. This is important because (*a*) dietary iodine databases have several limitations as discussed below; and (*b*) it has been estimated that living on the coast can provide up to 15% of the USRDA for iodine (33), and ingestion/absorption of salt/iodine from sea air cannot be quantified as part of dietary intake. Iodine as measured in toenail clippings suggested a nonsignificant decrease in risk associated with higher iodine exposure (OR, 0.77; 95% CI, 0.47–1.2 for the highest quintile) and did not differ by ethnicity.

On the basis of our hypotheses, we also examined the effects of dietary iodine and nail iodine levels on the risk of papillary thyroid cancer stratified by a "risk" indicator reflecting prior proliferative benign thyroid disease (*i.e.,* a personal history of goiter or thyroid nodules), possible underlying thyroid damage (*i.e.,* radiation exposure to the head or neck), or possible genetic susceptibility (*i.e.,* a family history of proliferative thyroid disease, including cancer). As can be seen in Table 3, dietary iodine exposure was associated with a reduction in papillary thyroid cancer risk among low-risk women (OR, 0.53; 95% CI, 0.33–0.85 for the highest tertile) but with a slight nonsignificant increase in risk among high-risk women (OR, 1.4; 95% CI, 0.56–3.4 for the highest tertile). This interaction, however, was not statistically significant (X^2_2 = 1.34; P = 0.51). When nail iodine levels were used as the measure of exposure, no such pattern was observed (Table 3).

Discussion

Consistent with previous studies of thyroid cancer risk (5, 9, 11, 12, 17), the present study found positive associations between thyroid cancer risk and medical radiation to the head or neck, a personal history of goiter or nodules, and a family history of proliferative thyroid disease. As in previous studies, the results for the effects of iodine (using various measures) on thyroid cancer risk were mixed. There was some evidence that a high level of dietary iodine, at more than three times the USRDA and related to intake of multivitamin pills, was associated with reduced thyroid cancer risk. This effect, however, was not evident among the high-risk subgroup of women who may be particularly susceptible to thyroid carcinogenesis.

The multiethnic, multicultural nature of the present population provided a wide range of iodine exposure, similar to the equally diverse group previously studied by Kolonel *et al.* (5) in Hawaii. Although these two studies are the only ones to quantify iodine exposure and neither showed strong associations, their results differ in a some ways. Overall, Kolonel *et al.* (5) found a statistically nonsignificant elevation in risk (OR,

1.6; 95% CI, 1.2–3.2) associated with the highest quartile of dietary iodine consumption among women. The present study found a reduction in risk (OR, 0.53; 95% CI, 0.31–0.90) for the highest quintile of exposure. The measures of iodine intake in both studies included the use of supplements but not the use of table salt. Although both studies found some evidence that excess iodine during the previous year was detrimental in small subgroups of women who may be particularly susceptible to developing thyroid cancer, which women were included in these subgroups differed. In the Hawaii study, the high-risk groups were defined as women who had used fertility drugs (4% of the study population) or whose first pregnancy outcome was a miscarriage or stillbirth (5% of the study population), because these women were found to be at elevated risk of thyroid cancer, and these conditions have been associated with a hormonal imbalance which may be characterized by increased levels of TSH. The high-risk subgroups in the Hawaii study were at a >4-fold increased risk when iodine consumption was twice the USRDA compared with women without these conditions who consumed lower levels of iodine. In the present study, these findings were not replicated (data not shown). In the present study, the high-risk subgroup was defined as women with previous benign thyroid disease, possible underlying thyroid damage, or possible genetic susceptibility (*i.e.,* a personal history of goiter or nodules, radiation to the head or neck, and/or a family history of proliferative thyroid disease; 23% of the population). In this subgroup, iodine consumption at twice the USRDA was associated with only a 50% increased risk. This point estimate was not statistically significant but was in contrast with the 50% reduction in risk seen for low-risk women consuming similar amounts of iodine. In a study in Shanghai, miscarriage, benign thyroid disease, or a family history of thyroid cancer did not modify the association between weekly consumption of fish/shellfish and thyroid cancer risk (13); however, the levels of iodine consumption in the high-intake group in that study may have been too low to impact risk in susceptible subgroups, because these levels were about one-half that of the high-intake groups defined by Kolonel *et al.* (5) and in the present study. Nonetheless, although the hypothesis is intriguing, there is little current evidence that definable subgroups of women are particularly susceptible to any carcinogenic effects of iodine.

In addition to measuring dietary intake, we included the use of a long-term (1 year) biomarker of iodine exposure, *i.e.,* iodine measured via NAA in clippings from the large toenails collected within 12 months of diagnosis. Clippings from this period should reflect exposure ~6–12 months before diagnosis, because it takes the large toenail about 10 to 16 months to grow out after it is formed at the nail base. Because not all iodine exposure comes from food intake (for example, living in coastal areas can provide up to 15% of the USRDA for iodine (33), and quantitative measures of iodine were not available for all potentially important food stuffs (*e.g.,* iodized as well as non-iodized salt, fish sauce, and seaweed), we incorporated this biomarker of exposure into the analyses. In preliminary studies, we found reasonable associations between iodine supplementation and nail iodine levels in Malawi children and between "high iodine consumption" (defined as daily use of multivitamins and the usual addition of salt to food during both cooking and at the table) and nail iodine levels in Utah men (34). In the present study, however, correlations between dietary iodine and nail levels of iodine were minimal (Pearson correlation; r = 0.07), suggesting either a substantial influence of nondietary or nonquantifiable dietary exposures in this population, and/or that this biomarker may simply not be a good reflection of dietary

iodine. Although the absolute levels of iodine in the nail clippings from our study population were lower than might be expected on the basis of previous reports in other populations (34), the NAA procedures we used to measure nail iodine content were optimized for the present investigation, a technique not available in previous studies of this biomarker. As with dietary iodine, women with the lowest levels of nail iodine were at the highest risk of developing papillary thyroid cancer; however, a smooth trend of decreasing risk with increasing iodine levels was not observed, and differences between high- and low-risk subgroups were minimal, making the interpretation of the totality of the study findings less clear.

As discussed in various sections above, there are several limitations to the present study which should be kept in mind when interpreting study results. First, our measure of dietary iodine intake is not optimal. The accurate quantification of salt added at the table is very difficult to achieve and our qualitative estimate of use (*i.e.,* never/seldom, sometimes, often/always) was not associated with risk. Whether this lack of association is attributable to misclassification or to the true lack of an effect cannot be determined. In addition, the iodine content of seaweed and fish sauce/dried or salted fish was not available. Although neither of these items is usually consumed in large quantities, and they are routinely consumed only by a small portion of our study population, they are presumably very iodine-rich, and their omission from the iodine database could result in misclassification of iodine exposure; however, in opposite directions, as seaweed was associated with reduced thyroid cancer risk and fish sauce with an elevation in risk. It should also be noted that although iodine content was available for the majority of food items, iodine is not one of the most easily quantified nutrients, because the content of a given food item is dependent on the amount of salt added during preparation and/or the environment from which the food product comes (*e.g.,* the saline content of the water in which fish are raised, the iodine content of the soil, the addition of iodate to dough, or the use of iodophors as disinfectants), and the assays available for its quantification can produce somewhat variable results (22). All of these factors can lead to misclassification of total iodine exposure for any individual. Our iodine values were based primarily on those reported by Pennington *et al.* (22), the most comprehensive analysis of iodine levels in foods that we know of. However, this work was done primarily in the 1980s; and the use of iodine-containing dyes, iodate conditioners, and iodophors as disinfectants became less common during the 1990s, the period in which we assessed iodine exposure. Another caution that should be mentioned in relation to interpreting our findings includes the always-present possibility of nondifferential misclassification because of recall bias in case-control studies if cases were more acutely aware of hypotheses related to iodine exposure and thyroid cancer risk. To balance these limitations, we also included in our study a biomarker of iodine exposure, *i.e.,* in toenail clippings. However, it should be kept in mind that although, on average, the clipping from the large toe represents an integrated measure of iodine exposure over a several-week period ~1 year before clipping, the period represented varies from 10 to 16 months. Taking into account the ~4 months between diagnosis and nail clipping, the period of exposure represented by the samples we obtained from cases was usually 6–12 months before the diagnosis of these usually slow-growing tumors. Not enough information is known about the biology of thyroid tumorigenesis to determine whether this is the relevant period of exposure. Finally, the effects of iodine seem to be largely influenced by the use of multivitamin supplements. Although adjustment for the intake of antioxidant

vitamins (*e.g.,* vitamins C and E and carotene), which may be associated with reduced thyroid cancer risk and influenced by supplement intake, only slightly modified the association between dietary iodine and thyroid cancer risk, it cannot be ruled out that it is some unidentified factor associated with supplement use itself (and not accounted for by adjustment for factors such as antioxidant intake, education, smoking, or alcohol) that is responsible for the observed effect.

In conclusion, examination of the present findings and those of previous studies leads us to conclude that, for the majority of women, sufficient levels of dietary iodine are associated with either no alteration in risk or reduced risk of papillary thyroid cancer, possibly because of the effects of chronically "sufficient" iodine levels in maintaining normal thyroid levels of thyroxine and TSH. The corollary to this conclusion (*i.e.,* a possible reduced risk of thyroid cancer associated with sufficient iodine levels) is that lower iodine levels are associated with increased papillary thyroid cancer risk (as is observed for follicular thyroid cancer), presumably because of elevations in TSH. However, women in our lowest quintile of iodine consumption were consuming on average the USRDA of iodine. Although the possibility cannot be ruled out that among a subgroup(s) of high-risk women similar "sufficient" levels of dietary iodine may increase thyroid cancer risk to some extent, the width of our CIs preclude valid conclusions regarding such an effect. Thus, our original hypothesis (that excess iodine would increase the risk of papillary cancer) was not supported by the data. Despite some supporting evidence for this hypothesis from other epidemiological studies, the high levels of iodine consumption which have resulted in substantially increased rates of papillary cancer in specific populations (*i.e.,* Japanese consuming >200 mg/day of iodine from seaweed) are >20 times higher than the average consumption among women in our highest quintile of iodine intake. Finally, any conclusion suggesting altered cancer risk associated with dietary iodine is also tempered by the biomarker findings of iodine exposure in nail clippings, which presumably more closely reflect the totality of iodine exposure and provide less evidence that thyroid cancer risk is altered by iodine exposure.

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, pp 24, 240–244. 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. (eds.). Cancer Incidence in Five Continents, Vol. 7. IARC Scientific Publications No. 143. Lyon, France: IARC and International Association of Cancer Registries, 1997.

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

4. National Research Council. Diet and Health. Washington, DC: National Academy Press, 1989.

5. 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.

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. Ron, E., Kleinerman, R. A., Boice, J. D., Jr., LiVolsi, V. A., Flannery, J. T., and Fraumeni, J. F., Jr. A population-based case-control study of thyroid cancer. J. Natl. Cancer Inst. (Bethesda), *79:* 1–12, 1987.

8. Franceschi, S., Fassina, A., Talamini, R., Mazzolini, A., Vianello, S., Bidoli, E., Serraino, D., and La Vecchia, C. Risk factors for thyroid cancer in northern Italy. Int. J. Epidemiol., *18:* 578–584, 1989.

9. 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.

10. Levi, F., Franceschi, S., La Vecchia, C., Negri, E., Gulie, C., Duruz, G., and Scazziga, B. Previous thyroid disease and risk of thyroid cancer in Switzerland. Eur. J. Cancer, *27:* 85–88, 1991.

11. Mack, W. J., Preston-Martin, S., Bernstein, L., Qian, D., and Xiang, M. Reproductive and hormonal risk factors for thyroid cancer in Los Angeles County females. Cancer Epidemiol. Biomark. Prev., *8:* 991–997, 1999.

12. 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 Inst. (Bethesda), *73:* 575–581, 1984.

13. 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.

14. Franceschi, S., Levi, F., Negri, E., Fassina, A., and La Vacchia, C. Diet and thyroid cancer: a pooled analysis of four European case-control studies. Int. J. Cancer, *48:* 395–398, 1991.

15. 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.

16. 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.

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

18. Marin, G., Triandis, H. C., Bentancourt, H., and Kashima, Y. Ethnic affirmation *versus* social desirability: explaining discrepancies in bilingual responses to questionnaires. J. Cross-Cult. Psychol., *14:* 173–176, 1983.

19. Brislin, R. W., Lonnen, W. J., and Thorndike, E. M. Cross-cultural Research Methods. New York: John Wiley & Son, Inc., 1973.

20. 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.

21. 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.

22. Pennington, J., and Young, B. Iron, zinc, copper, manganese, selenium, and iodine in foods from the United States total diet study. J. Food Compos. Anal., *3:* 166–184, 1990.

23. Pennington, J. A. T., Schoen, S. A., Salmon, G. D., Young, B., Johnson, R. D., and Marts, R. W. Composition of core foods of the U. S. food supply, 1982–1991. J. Food Compos. Anal., *8:* 171–217, 1995.

24. USDA Provisional Table on the Selenium Content of Foods, 1992.

25. Pennington, J. A. T. Bowes' and Church's Food Values of Portions Commonly Used. Philadelphia: J. B. Lippincott Co., 1989.

26. Diet Analysis Plus, Version IV, 1997.

27. Food composition table (Mainland China). 1991.

28. Food composition tables—recommended for use in the Philippines. 1997.

29. Zhang, W., He, Q., and Wu, Q. Iodine contents of eighty-five kinds of food in Shanghai District. Acta Nutr. Sin., *18:* 492–494, 1996.

30. Morris, J. S., Stampfer, M. J., and Willet, W. Dietary selenium in humans: toenails as an indicator. Biol. Trace Elem. Res., *5:* 529–537, 1983.

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. Volume I: The Analysis of Case-Control Studies, IARC Scientific Publ. No. 32. Lyon, France: IARC, 1980.

33. Park, Y. K., Harland, B. F., Vanderveen, J. E., Shank, F. R., and Prosky, L. Estimation of dietary iodine intake of Americans in recent years. J. Am. Diet. Assoc., *79:* 17–24, 1981.

34. Spate, V. L., Morris, J. S., Chickos, S., Baskett, C. K., Mason, M. M., Cheng, T. P., Reams, C. L., West, C., Furnee, C., Willett, W., and Horn-Ross, P. Determination of iodine in human nails via epithermal neutron activation analysis. J. Radioanal. Nucl. Chem., *195:* 21–30, 1995.

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