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A Prospective Study of Iodine Status, Thyroid Function, and Prostate Cancer Risk: Follow-up of the First National Health and Nutrition Examination Survey

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Abstract: *Few studies have investigated the association between iodine status, thyroid disease, and cancer risk despite evidence that thyroid function impacts many organs, including the prostate. We investigated iodine status and prostate cancer risk prospectively using data from the NHANES I Epidemiologic Follow-up Study. Participants were stratified into tertiles according to the urinary iodine/creatinine ratio, as a marker of iodine exposure. As iodine is an integral constituent of thyroid hormones, we also examined the relationship between thyroid disease and prostate cancer risk. Relative to the group with low urinary iodine, the age-adjusted hazard ratio was higher (although marginally insignificant) in the moderate group, hazard ratio 1.33 (95% confidence interval 1.00–1.78), and significantly lower in the high group, 0.71 (0.51–0.99). Thyroid disease was associated with an increased prostate cancer risk, 2.34 (1.24–4.43). Similarly, >10 yr since thyroid disease diagnosis was associated with an elevated risk, 3.38 (1.66–6.87). After adjusting for other confounding factors, only a history of thyroid disease, 2.16 (1.13–4.14), and >10 yr since diagnosis of thyroid disease, 3.17 (1.54–6.51) remained significant. Although the role of dietary iodine remains speculative, a role for thyroid disease and/or factors contributing to thyroid disease as a risk factor for prostate carcinogenesis warrants additional investigation.*

Introduction

An increasing number of in vitro and in vivo studies have shown that thyroid hormones may influence the proliferation and metabolic activity of prostate cells. Animal studies have shown that reciprocal interactions occur between the thyroid and prostate (1,2). In rats, prostatectomy has been shown to cause significant reductions in triiodothyronine (T3) and thyroxine (T4) levels in vivo; while prostatic secretions may enhance T3 and T4 production in thyroid cells cultured in vitro (2). In vitro studies have shown that T3 enhances cellular proliferation in prostatic LNCaP carcinoma cells (3–5).

Recent human studies by Lehrer et al. (6,7) have demonstrated men with prostatic hyperplasia and prostate cancer have elevated serum T3 levels in comparison to normal controls. Although there can be various causes for raised T3 levels, in regions of iodine deficiency (<100 μg iodine per L in urine) preferential synthesis and secretion of T3 has been observed (8). In this respect, a case-control study by Key et al. (9) found an inverse trend between iodine intake and prostate cancer risk. Thus, there could be an intriguing yet largely unstudied link between prostate cancer development and iodine and/or iodine-containing thyroid hormones.

To examine a possible protective role for iodine on prostate cancer risk, we used prospective data from a follow-up study of the First National Health and Nutrition Examination Survey (NHANES I). As iodine is of primary importance in the formation of thyroid hormones, we also examined the relationship between thyroid disease, goiter, and prostate cancer risk.

Methods

Study Design

The First National Health and Nutrition Examination Survey (NHANES I) was a multistage, national probability sample of the US civilian noninstitutionalized population conducted from 1971 to 1975 (10,11). Baseline data collection included demographics, medical history, standardized medical examination, dietary history, laboratory tests, and anthropometric measurements. The NHANES Epidemiologic Follow-up Study (NHEFS) was a prospective cohort study of NHANES I participants who were aged 25–74 yr when the original survey was conducted, which included 5,811 males (12–15). For the NHEFS study, subjects (or proxy respondents if deceased) were traced and interviewed again in

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1982–1984, 1986, 1987, and 1992. Data were also collected from hospital records, including pathology reports, and if deceased, death certificates. This tracing accounted for 90% of the original cohort 25–74 yr of age.

Exposure Variables

From the laboratory tests, medical history interview, and medical examination, the following exposure variables were derived.

Iodine Status

Urinary iodine concentrations were determined by the Iodine Research Laboratory, University of Massachusetts Medical Center (Worcester, MA). Spot urine samples were collected from fasting participants (10–16 h before the morning examination or for 6 h before the afternoon or evening examination). Urinary iodine concentrations (UIC) were determined using the Sandell-Kolthoff reaction as modified by Benotti et al. (16), a catalytic reaction of iodide on the oxidation of arsenic (III) by cerium (IV). For the measure of iodine concentration, a creatinine adjustment was used to correct for volume fluctuations between samples. Measurement of the urinary iodine/creatinine ratio is one of the most widely used methods of estimating iodine intake and was used as the surrogate measure of iodine status in cohort participants at baseline.

Thyroid Disease

In the medical history interview, participants were asked about their history of thyroid disease (without specifying subtype) and time since diagnosis ($<$10 yr or $\geq$10 yr). This was split into a history (past or present) of thyroid disease or no history. An examination of risk according to a history of hypothyroidism or hyperthyroidism could not be undertaken as this was only determined in a small subset of the cohort.

In the medical examination, a physical assessment of thyroid size was performed and classified according to World Health Organization (WHO) criteria used for grading goiters (i.e., grade 0 = no goiter; grade 1 = palpable goiter; grade 2 = visible goiter; grade 3 = very large goiter). This was categorized as goiter (grades 1–3) or no goiter (grade 0).

Prostate Cancer Risk Factors

Information about other possible prostate cancer risk factors including race (white vs. nonwhite), marital status (yes vs. no), income (high vs. low-middle), and alcohol consumption (yes vs. no), and region (northeast, midwest, south, west) as strata were obtained from baseline data.

Study Population

Of the 5,811 men of the NHEFS study, 252 cases of prostate cancer were identified from diagnoses of prostate cancer at follow-up interviews (1982–1984, 1986, 1987, and 1992), discharge diagnoses from hospital stays, and/or death certificates. We excluded 1,577 men without a measurement of urinary iodine at baseline. Of this remaining cohort, there were 197 cases of prostate cancer of which a further 10 subjects were excluded due to prostate cancer at baseline. Thus, the final analytical cohort consisted of 4,234 men, including 187 cases of prostate cancer.

Prostate Cancer Incidence

Incident events were based on documentation of an event occurring during the period between the participant's baseline examination and last follow-up interview. The date of record for incident events were identified by date of first hospital admission with an established study event or date of death from a study event in the absence of hospital or nursing home documentation of such an event. Only invasive prostate cancer diagnoses International Classification of Diseases, Ninth Revision (ICD-9) code of 185 were categorized as cases. Subjects who self reported a baseline history of prostate cancer without other confirmatory documentation were included with noncases.

Statistical Analyses

Noncases were censored on the last date known to be alive and without prostate cancer. For each baseline characteristic, the frequencies of potential risk factors mean value or percentage of study participants were separately calculated by tertile of iodine intake (i.e., low, moderate, high). The χ^2 test was used to identify those potential confounding factors. Cox proportional hazard regression analyses were performed to explore the relationship between iodine status, thyroid disease, goiter, and the subsequent development of prostate cancer. The Statistical Analysis Software (SAS) was used to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals (CI). Age was used as the time scale for all time-to-event analyses (17).

Ethical Considerations

The study protocol was approved by the Clinical Research Ethics Board of the University of British Columbia.

Results

In Table 1, a comparison of the frequencies of potential risk factors at baseline per category of iodine/creatinine ratio (i.e., low, moderate, high) is presented. The mean age of men at examination in our study sample was 52.7 yr old, approximately 16.5% of the participants were non-white. The majority of subjects reported high (36.6%) or low (32.9%) household incomes, with a minority of middle income earners (26.4%). Most subjects reported alcohol use at baseline (77.2%). Significant associations were observed between the

Table 1. Baseline (1971–74) Characteristics of Study Population by Tertile of Iodine/Creatinine Ratio

Demographic variables	Iodine/creatinine categories (μg/g) <201, $n = 1452$ n (%)	201–345, $n = 1554$ n (%)	>345, $n = 1228$ n (%)	P-value[a]
Age				**<0.001**
25–44	537 (38.5)	503 (36.0)	356 (25.5)	
45–64	406 (31.5)	492 (38.2)	391 (30.3)	
65–74	509 (32.9)	559 (36.1)	481 (31.1)	
Race				**<0.001**
White	1100 (31.1)	1319 (37.3)	1115 (31.6)	
Other	352 (50.3)	235 (33.6)	113 (16.1)	
Married at baseline	1168 (33.5)	1304 (37.4)	1014 (29.1)	**0.043**
Family income				0.075
Low	491 (35.3)	496 (35.6)	405 (29.1)	
Middle	347 (31.1)	422 (37.8)	348 (31.2)	
High	560 (36.2)	559 (36.1)	429 (27.7)	
Alcohol at baseline	1165 (35.6)	1201 (36.7)	904 (27.6)	**<0.001**
Region				**<0.001**
Northeast	379 (41.6)	322 (35.3)	211 (23.1)	
Midwest	334 (33.1)	385 (38.2)	289 (28.7)	
South	379 (33.4)	404 (35.6)	353 (31.1)	
West	360 (30.6)	443 (37.6)	375 (31.8)	

[a]The P-values from χ^2 test.

adjustment variables (with family income approaching significance) and the categorized iodine/creatinine ratios by the χ^2 test, as seen in Table 1.

The majority of cases had a low to moderate iodine status (Table 2). In the Cox regression model, moderate iodine/creatinine levels were associated with a borderline increased risk of disease relative to low levels, HR = 1.33 (95% CI 1.00–1.78). However, in the multivariate model the risk was no longer significant, HR = 1.31 (95% CI 0.98–1.75). In contrast, high intake was significantly associated with a reduced risk of prostate cancer, HR = 0.71 (95% CI 0.51–0.99); and following multivariate adjustment it remained reduced, but was no longer significant, HR = 0.75(95% CI 0.53–1.05). There was no association between use of table salt and prostate cancer risk. A reported history of thyroid disease was associated with a greater than two fold increase in risk, HR = 2.34 (95% CI 1.24–4.43), which remained significant following the multivariate adjustment, HR = 2.16 (95% CI 1.13–4.14). Similar to having a history of thyroid disease, use of thyroid medication at baseline tended to be associated with an increased risk, but this was not significant whether adjusted for age or multivariate analysis 1.35 (95% CI 0.43–4.22). An increasing time since first diagnosis of thyroid disease ($\geq$10 years) also was associated with elevated hazards in both the age, HR = 3.38 (95% CI 1.66–6.87), and multivariate models, HR = 3.17 (95% CI 1.54–6.51). The presence of a goiter (WHO grades 1–3) as determined by physical exam was not associated with prostate cancer risk HR = 0.94 (95% CI 0.30–2.95), although goiter was uncommon among cases, with only three having signs of an enlarged thyroid upon physical exam.

Discussion

The association between dietary iodine intake and incidence of prostate cancer remains unclear. In the group with the highest iodine status, there was a decreased risk of prostate cancer, but it lost significance following multivariate adjustment. A previous case-control study by Key et al. (9) found a non-significant reduced risk for prostate cancer in subjects with the highest iodine intake (OR = 0.75, 95% CI 0.51–1.11, P-value for trend 0.077), where iodine intake was estimated from a dietary questionnaire. It may be that an iodine intake higher than the recommended daily allowance (RDA) could afford protection against prostate cancer, but this cannot be conclusively determined from the present study. The mean iodine level in our cohort was 50 μg/L. In contrast, the Japanese have a comparatively high iodine intake as shown in a study by Nagata et al. (18) where the mean UIC in four different regions ranged from 810 to 1,620 μg/L. A large study in Sapporo, a city in Northern Japan, observed a mean iodine level of 3,400 μg/L (19). Low rates of prostate cancer are seen in Japan where iodine intake is commonly above the RDA of 150 μg/day (20). In fact, in the developed world Japan has one of the lowest age-adjusted prostate cancer incidence rates, 12.6 per 100,000; in the United States by comparison, the rate is 124.8 per 100,000 (21). However, Japanese immigrants to the United States, and their successive generations, have incidence rates that gradually increase to that of Caucasian men in the United States (22). A chronological correlation study by Tominaga and Kurioshi (23) examined the association between cancer mortality in Japan and changing dietary patterns over time.

Table 2. Prostate Cancer Risk According to Markers of Iodine Status and Thyroid Function

Study variables	Cases (%)	Hazard Ratios (HR)	
		Age-adjusted[a] HR (95% CI)	Multivariate-adjusted[b,c] HR (95% CI)
Iodine/creatinine (μg/g)			
Low (<201)	61 (32.6%)	1.00	1.00
Moderate (201–345)	81 (43.3%)	1.33 (1.00–1.78)[e]	1.31 (0.98–1.75)
High (>345)	45 (24.1%)	**0.71** (0.51–0.99)	0.75 (0.53–1.05)
P-value for trend[d]		0.405	0.460
Use of salt shaker			
Rarely/occasionally	128 (68.4%)	1.00	1.00
Frequently	59 (31.6%)	1.05 (0.77–1.42)	0.99 (0.73–1.36)
Thyroid disease			
Never	177 (94.7%)	1.00	1.00
Ever	10 (5.3%)	**2.34** (1.24–4.43)	**2.16** (1.13–4.14)
Thyroid medication use			
No	184 (98.4%)	1.00	1.00
Yes	3 (1.6%)	1.35 (0.43–4.22)	1.27 (0.40–4.00)
Years since 1st diagnosis			
No diagnosis	178 (95.2%)	1.00	1.00
<10 yr	1 (0.5%)	0.64 (0.09–4.59)	0.54 (0.08–3.89)
$\geq$10 yr	8 (4.3%)	**3.38** (1.66–6.87)	**3.17** (1.54–6.51)
Goiter at baseline			
No	184 (98.4%)	1.00	1.00
Yes	3 (1.6%)	0.94 (0.30–2.95)	0.93 (0.30–2.92)

[a] Age used as time scale for all time-to-event analyses.
[b] Adjusted for age as mentioned previously, race (white vs. other), marital status (yes vs. no), income (high vs. middle to low)[d], and alcohol consumption (yes vs. no), and region (northeast, Midwest, south, west) as strata.
[c] High income had significant effect within each strata (region): HR = 1.57, 95% CI 1.15-2.16, P-value = 0.005.
[d] The P-values in log-trend test using the continuous variable of iodine/creatinine.
[e] The HR was marginally insignificant: 95% CI = 0.999–1.782.

They found that westernization of Japanese dietary habits was significantly associated with increasing mortality rates for prostate, breast and other cancers. Although there are many dietary differences between Japan and the west, a diet rich in seafood is a prominent difference. In Japan, iodine intake can vary widely with dietary habits. Iodine rich foods such as saltwater fish, and seaweed in particular (24), explain why Japan probably has the highest national iodine consumption in the world (20). One Japanese case-control study (25) has suggested that iodine rich seaweed may protect against prostate cancer. In this study, a reduced relative risk (RR = 0.47, 95% CI 0.23–0.97) was observed for older men who had a high consumption of seaweed (25). Another Japanese study found a trend towards a reduced prostate cancer risk for moderate (RR = 0.74, 95% CI 0.53–1.03) to high (RR = 0.86, 95% CI 0.60–1.24) seaweed consumption vs. low (26). These associations, however, may be due to a protective effect of nutrient factors in seaweed other than iodine. Additionally, there are other dietary factors in Japan that may be protective against prostate cancer, the most prominent being omega-3 fatty acids from fish and other seafoods (27) and soy products (28,29).

Iodine is an essential trace element primarily known for its role in thyroid hormones. Emerging experimental evidence, however, has shown that iodine may have many alternative metabolic functions, including a broad range of anti-proliferative (20,30,31), anti-inflammatory (30), antioxidant (31,33), and anti-microbial properties (34–37). Two iodine transporters, the sodium-iodide symporter (NIS) and pendrin, have been cloned and molecularly characterized recently. These transport proteins are most prominently expressed in the thyroid, where iodine-containing thyroid hormones are produced. However, they have also been found in hormone-dependent ovarian, breast, testicular and prostatic tissues (38–40), suggesting some physiological role for iodine in these tissues, including the prostate.

Deficient iodine intake has been associated with an increased risk of other cancers including stomach (41) and aggressive thyroid malignancies (42). Venturi et al. (43) has reviewed both animal and human data to support the theory that deficient iodine intake may increase the risk of stomach and thyroid cancer. For example, in patients with stomach cancer, Behrouzian and Aghdami (41) recently observed that cases had significantly lower urinary iodine levels compared to controls. With respect to thyroid cancer, in comparison to adequate/high iodine intake areas (where mean urinary iodine levels are >100 μg/L), iodine deficient regions have a higher proportion of aggressive follicular and anaplastic carcinomas and a lower proportion of the less aggressive papillary cancers (42). Similarly, an increased development of thyroid tumors was seen in animals fed on a low iodine diet (44,45). The potential for a similar etiological relationship for both prostate and thyroid cancer has been suggested by a recent analysis of US Surveillance,

Epidemiology and End-Results (SEER) data (46). It was observed that there was a significant increased risk for prostate cancer following a diagnosis of thyroid cancer (expected/observed = 1.31, 95% CI 1.16–1.48). Conversely, a significant increased risk for thyroid cancer following a diagnosis of prostate cancer (expected/observed = 1.21, 95% CI 1.01–1.43). Studies in animals have suggested that iodine may also protect against the development of mammary cancer (20,31,47–49). Iodine deficiency in animals has been shown to lead to the development of mammary hyperplasia (48,50). In contrast, iodine supplementation in both animals (48) and humans (51–53) has been shown to reverse these proliferative abnormalities. A peroxidase-catalysed reaction between iodine and arachidonic acid leads to the formation of δ-iodolactone, which appears to be a key regulator of apoptosis (54) and cellular proliferation in the thyroid (55). Interestingly, δ-iodolactone could not be detected in human tissues when iodine deficiency was present, but was detected following increased iodide administration (56). Thus, production of anti-proliferative iodolipids tissues may only occur in individuals with a relatively high iodine intake. Whether these iodolipids have activity in extrathyroidal tissue remains to be determined.

We also examined the association between salt shaker usage and prostate cancer risk, but no association was found. One case-control study in Poland found that a history of frequent table salt usage was associated with a significantly decreased risk of breast cancer (OR = 0.36, 95% CI 0.23–0.58) (57). It was proposed that the protective effect may have been due to the iodine content of the iodized salt (57). Table salt can be an important source of iodine intake, although only about 50–60% of table salt sold in the United States is iodized (58). In the NHANES I study, quantitative data on sodium intake from table salt was not collected and the data on salt shaker usage did not provide information on its use in cooking. There was no correlation between the urinary iodine/creatinine ratio and salt shaker usage.

A history of thyroid disease was associated with a more than two-fold higher HR even after the multivariate adjustment. A similar trend was seen in subjects who were using thyroid medication at baseline and in subjects who were at $\geq$10 yr since a diagnosis of the condition. To our knowledge, no previous study has examined the association between thyroid disease and prostate cancer risk. Animal studies have shown that reciprocal interactions occur between the thyroid and prostate, where thyroid hormones regulate a wide range of prostatic metabolic functions, and in turn, the prostate can influence T3 and T4 production. In rats, prostatectomy has been shown to cause significant reductions in T3 and T4 levels in vivo; whereas prostatic secretions have been show to enhance T3 and T4 production in thyroid cells cultured in vitro (2). In vitro studies have shown that T3 enhances androgen-stimulated cellular proliferation in prostatic LNCaP carcinoma cells at lower, but not at the higher androgen levels ($>10^{-10}$ M) studied (3). Zhang et al. (4) and Hsieh and Juang (5) also showed that T3 had a proliferative effect on LNCaP cells, which was attenuated by androgens only in the former study. Hsieh and Juang (5) did not observe any influence of T3 on the proliferation of other prostatic cell lines (PZ-HPV-7, CA-HPV-10, PC-3, PC-3). In contrast, for rabbits receiving long-term T4 injections prostatic weight was lowered, while prostatic glandular epithelial secretions remained unchanged (59). We did not have information on the original diagnosis (i.e., hyperthyroidism or hypothyroidism) for subjects reporting thyroid disease; however, hyperthyroidism is often treated with surgery or radioiodine ablation therapy, both of which commonly result in hypothyroidism. Thus, the eventual therapy for both hyperthyroidism and hypothyroidism is often the same, replacement hormone therapy with T4.

Many studies have examined the association between thyroid disease and breast cancer (20), however, thyroid diseases such as Graves' disease and autoimmune thyroiditis are much more common in females than males (60). This may be one reason for the lack of studies in this area for prostate cancer. The association between breast cancer and thyroid disease remains controversial (61,62). Two recent epidemiological investigations, a cohort study China (60) and a case-control study in Turkey (64), found the incidence of goiter to be significantly higher in subjects with gastric cancer in comparison to those without cancer; however, no conclusions could be drawn with respect to goiter in our cohort as it was not frequently observed. In Japan, despite the higher iodine intake, the overall prevalence of hyperthyroidism and hypothyroidism is similar to that of the United States (65).

Limitations of our study include the measure of iodine status, which was derived from spot fasting urine samples taken at baseline. No measurements of iodine status were made during the follow-up period, therefore we were not able to measure any potential changes in dietary iodine intake over the follow-up period. Using a single spot urine sample to estimate the usual dietary iodine intake among individuals would produce random measurement error, which tends to bias relative risk estimates toward one (effect to null) in follow-up studies. This is a conservative bias as it would induce false-negative results. Similarly, other measures were determined at baseline such as marital status, income, alcohol consumption, and region of residence, and may be expected to change over time. While urinary iodine measurements were made for the majority of the analytical cohort (72.9%), 1,577 men were excluded who did not have such a measurement, leading to a loss of 55 subjects with prostate cancer. The history of thyroid disease obtained during the medical interview was based upon a self-reported and not a clinically verified history.

In conclusion, a role for iodine in the development of prostate cancer remains unclear. Perhaps, epidemiological studies carried out in Japan, where there is a broader range of iodine intake, would provide a more conclusive answer to this question. Recently, there has been increasing interest in the use of radioiodine therapy for prostate and other cancers through enhanced expression of the NIS gene in malignant tissues (66,67). Considering the innate

anti-proliferative capabilities of non-radioactive iodine (20,68), it is unfortunate in little investigative attention has been directed in this area. Further investigations into the role of thyroid disease in the etiology of prostate cancer are warranted, particularly in light of the reciprocal influence of that these two organs have upon one another.

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