Thyroid Function and Cancer Risk: A Prospective Population Study

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Abstract

Background: **It has been hypothesized that thyroid function may influence cancer risk, but few studies with adequate statistical power have investigated this question, and the results have not been consistent.**
Methods: **In a prospective study of 29,691 people (19,710 women and 9,981 men) without previously known thyroid disease, thyrotropin was measured at baseline, and cancer incidence was recorded during 9 years of follow-up. Using Cox regression analysis, we studied the associations (hazard ratios) of thyrotropin categories with total cancer risk, and specifically, with risk of lung, colon, prostate, and breast cancer adjusted for age, sex, and smoking status.**
Results: **Low thyrotropin levels (<0.50 mU/L) were associated with increased cancer risk [adjusted hazard ratio (HR), 1.34; 95% confidence interval (CI), 1.06-1.69] compared with the euthyroid reference group. The higher risk was driven by lung cancer (adjusted HR, 2.34; 95% CI, 1.24-4.40) and prostate cancer (adjusted HR, 1.97; 95% CI, 1.04-3.76). After excluding the first 2 years of follow-up, the associations were strengthened to 2.91 (1.49-5.70) for lung cancer and 2.60 (1.36-4.99) for prostate cancer.**
Conclusion: **Thyrotropin levels suggestive of hyperthyroid function are associated with increased cancer risk, and specifically, with increased risk of lung and prostate cancer, whereas hypothyroid function does not seem to be associated with cancer risk.** (Cancer Epidemiol Biomarkers Prev 2009;18(2): 570–4)

Introduction

Thyroid hormones play a major role in physiologic processes crucial to growth, maturation, and metabolism. It has therefore been suggested that thyroid function might influence cancer development (1). According to this hypothesis, thyroid hormones could stimulate tumor growth (2, 3) and thus be associated with increased risk, whereas hypothyroid function could lead to a reduced risk and a more favorable prognosis in patients with cancer (1, 3).

The results of observational studies in humans have not been consistent, but one study has reported lower risk of breast cancer associated with hypothyroidism (4). Previous follow-up studies have emphasized effects of hyperthyroid function or effects related to treatment for hyperthyroidism, but these studies have shown no clear association with cancer risk (5) or mortality (5-7). However, it has been reported that hyperthyroid patients treated with radioactive iodine may be at increased risk of cancer (8). It has also been suggested that patients with thyroid adenoma (7) or toxic nodular goiter (6) could be at increased risk.

In relation to the prognosis of patients with cancer, patients with head and neck cancer who develop hypothyroidism may experience longer survival (3). In patients with breast cancer, it has been suggested that the presence of thyroid peroxidase antibodies, indicating autoimmune thyroid disease, may be associated with improved survival (9).

In animal experiments, it has been shown that thyroxine stimulates tumor growth and metastasis (10), whereas the induction of hypothyroidism seems to slow down tumor growth, reduce the tendency to metastasize, and improve survival (10-13).

In this population-based study of nearly 30,000 individuals without previously known thyroid disease, the aim was to assess if thyroid function is associated with subsequent risk of total cancer, and more specifically, with risk of four frequent cancer types: lung, colon, prostate, and breast cancer.

Materials and Methods

Study Population. Between 1995 and 1997, all inhabitants 20 years and older in Nord-Trøndelag County in Norway were invited to participate in the Nord-Trøndelag Health Study. A total of 92,936 individuals were invited and 66,140 (71.2%) attended. The study has been described in detail elsewhere (14). Briefly, the participants were asked to complete a self-administered questionnaire which included a range of health-related questions, including history of thyroid disease (15). The

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survey also included various clinical measurements, such as height, weight, waist circumference, and blood pressure.

A nonfasting venous blood sample was drawn from each participant, and thyrotropin concentrations were measured in subsamples of the population. These samples included all women older than 40 years of age and a 50% random sample of men older than 40 years. In addition, thyrotropin was measured in 5% random samples of men and women 20 to 40 years of age. In total, thyrotropin was measured in 34,200 individuals (23,496 women and 10,704 men) from these samples. In individuals whose thyrotropin levels were <0.20 mU/L, suggesting possible manifest hyperthyroidism, free thyroxine and total triiodothyronine were also measured.

Laboratory Measurements. Concentrations of thyrotropin (thyroid-stimulating hormone), free thyroxine, and total triiodothyronine were measured at the Hormone Laboratory, Aker University Hospital, Oslo, using DELFIA hTSH Ultra (sensitivity, 0.03 mU/L; and total analytic variation, <5%), DELFIA FT_4 (total analytic variation, <7%), and AutoDELFIA T_3 (total analytic variation, <5%), respectively, all from Wallac Oy. Reference ranges for thyrotropin in this population have been published previously (15), and based on these results, the reference range for clinically normal thyrotropin in this study was defined as 0.50 to 3.5 mU/L. The laboratory reference ranges were 8 to 20 pmol/L for free thyroxine and 1.2 to 2.7 nmol/L for total triiodothyronine. The Norwegian population is generally considered to have sufficient iodine intake (16).

Cancer Risk. The unique 11-digit identification number of every Norwegian citizen enabled linkage to incidence data recorded at the Cancer Registry of Norway. Information from the Cancer Registry includes date and diagnosis of cancer, histopathologic type, and clinical stage at diagnosis.[6] Date of death or migration is supplied by continuously updated information from the National Registry. In this study, we assessed the association of thyrotropin with total cancer (excluding basal cell carcinoma) and specifically, with lung, colon, prostate, and breast cancer.

Statistical Analysis. Among 34,200 individuals with thyrotropin measurements, 4,509 were excluded from follow-up. The exclusion criteria included known thyroid disease (n = 2,873), previously diagnosed cancer (n = 1,171), missing information on smoking habits (n = 459), or invalid linkage with the National Registry (n = 6). Thus, a total of 29,691 people (19,710 women and 9,981 men) were eligible for follow-up in this study. Each participant contributed person-time from baseline (between August 1995 and June 1997) until a cancer was diagnosed, or until migration or death, or until the end of follow-up (December 31, 2005), whichever occurred first.

The participants were placed in five categories according to thyrotropin level: three categories within the clinical reference range (0.50-1.4, 1.5-2.4, and 2.5-3.5 mU/L); one category below the reference range (<0.50 mU/L), indicating hyperthyroid function; and one category above the reference range (≥3.6 mU/L), indicating hypothyroid function. Hazard ratios (HR) of cancer were estimated using a Cox proportional hazards model, in which cancer rates within each of the thyrotropin categories were compared with the rate in the reference group, defined as the lower third of the clinical reference range (0.50-1.4 mU/L). We estimated HRs of total cancer (excluding basal cell carcinoma), in addition to specific analyses of four major cancers; colon (ICD-7; 153), lung (ICD-7; 162), breast (ICD-7; 170), and prostate (ICD-7; 177) cancer. In a separate analysis, we attempted to reduce the potential bias from effects that a preclinical cancer could have on thyrotropin levels by starting follow-up 2 years after the baseline.

Furthermore, people with thyrotropin levels below the clinical reference range (<0.50 mU/L) were subdivided into a group with biochemically overt hyperthyroid function (defined as thyrotropin <0.20 mU/L combined with free thyroxine >20.0 pmol/L and/or total triiodothyronine >2.7 nmol/L) and a group with probable subclinical hyperthyroid function (thyrotropin 0.20-0.49 mU/L, or thyrotropin <0.20 mU/L and neither free thyroxine nor total triiodothyronine above the reference range). This classification of overt and subclinical hyperthyroidism was possible due to the free thyroxine and total triiodothyronine measurements that were done in people whose thyrotropin levels were <0.20 mU/L.

The HRs were age-adjusted by using attained age as the time variable in the analyses. Because results did not substantially differ between men and women, we present the combined results with adjustment for sex. In addition, we adjusted for smoking status at baseline (17) using two different models. In the first model, we adjusted for never, former, or current smoking. In the second model, we further adjusted for the average number of cigarettes smoked per day (reported in 90% of former or current smokers) if this information was available, and for years since smoking cessation (reported in 95% of former smokers). We report the results from the second model, although the estimates did not differ substantially between the two models. Additional adjustment for body mass index did not influence the results. All data analyses were conducted using Stata (version 9.0, StataCorp LP).

The study was approved by the regional committee for medical research ethics and by the Norwegian Data Inspectorate. The Nord-Trøndelag Health Study is a collaborative effort of the Faculty of Medicine, Norwegian University of Science and Technology; the Norwegian Institute of Public Health; and the Nord-Trøndelag County Council.

Results

In this prospective study of 29,691 people, a total of 2,511 individuals developed cancer during a median follow-up of 9.0 years (Table 1). For total cancer, people with thyrotropin levels lower than the clinical reference range (<0.50 mU/L), suggesting hyperthyroid function, were at higher risk than people in any of the other categories, including people in the highest category, indicating hypothyroid function. Thus, people with thyrotropin levels <0.50 mU/L had a 34% (adjusted HR, 1.34; 95% CI,

[6] http://www.kreftregisteret.no/

Table 1. HRs for total cancer and specifically, for cancer of the colon, lung, breast, and prostate, by categories of thyrotropin measured at baseline

Thyrotropin (mU/L)	Persons (*n*)	Cancers (*n*)	HR*	HR (95% CI)†
Total cancer				
<0.50	674	76	1.36	1.34 (1.06-1.69)
0.50-1.4	12,389	1,010	1.0 (Reference)	1.0 (Reference)
1.5-2.4	10,882	914	0.95	0.98 (0.90-1.08)
2.5-3.5	3,597	313	0.89	0.95 (0.83-1.08)
>3.5	2,149	198	0.90	0.96 (0.82-1.12)
Colon cancer				
<0.50	674	9	1.42	1.38 (0.70-2.73)
0.50-1.4	12,389	106	1.0 (Reference)	1.0 (Reference)
1.5-2.4	10,882	119	1.15	1.18 (0.90-1.53)
2.5-3.5	3,597	46	1.18	1.23 (0.86-1.74)
>3.5	2,149	23	0.91	0.95 (0.60-1.50)
Lung cancer				
<0.50	674	11	2.60	2.34 (1.24-4.40)
0.50-1.4	12,389	84	1.0 (Reference)	1.0 (Reference)
1.5-2.4	10,882	64	0.81	0.99 (0.71-1.37)
2.5-3.5	3,597	24	0.87	1.25 (0.79-1.98)
>3.5	2,149	9	0.54	0.87 (0.43-1.74)
Breast cancer				
<0.50	503	12	1.20	1.20 (0.67-2.16)
0.50-1.4	8,027	164	1.0 (Reference)	1.0 (Reference)
1.5-2.4	7,118	118	0.79	0.78 (0.61-0.99)
2.5-3.5	2,476	46	0.86	0.85 (0.61-1.18)
>3.5	1,586	30	0.86	0.85 (0.57-1.25)
Prostate cancer				
<0.50	171	10	1.96	1.97 (1.04-3.76)
0.50-1.4	4,362	135	1.0 (Reference)	1.0 (Reference)
1.5-2.4	3,764	121	0.94	0.93 (0.73-1.20)
2.5-3.5	1,121	37	0.79	0.78 (0.54-1.13)
>3.5	563	23	0.87	0.86 (0.55-1.35)

*HRs adjusted for age and sex.
†HRs adjusted for age, sex, and smoking status.

1.06-1.69) higher cancer risk, compared with people within the reference group (0.50-1.4 mU/L).

For colon cancer, the results showed a similar pattern, but the number of cases among people in the lowest category of thyrotropin was too low to yield precise estimates (adjusted HR, 1.38; 95% CI, 0.70-2.73). For lung cancer, however, people with thyrotropin levels lower than the clinical reference range (<0.50 mU/L) had a substantially higher risk compared with people within the other thyrotropin groups. Compared with the reference group, the adjusted HR for lung cancer was 2.34 (95% CI, 1.24-4.40). Adjustment for smoking only moderately attenuated the association (HR, 2.60 unadjusted and 2.34 adjusted).

In relation to breast cancer risk, thyrotropin levels showed no clear pattern, and the number of cases in the suggested hyperthyroid or hypothyroid function groups was too low to yield precise estimates. For prostate cancer, however, men with thyrotropin levels suggesting hyperthyroid function were at higher risk compared with men in any of the other thyrotropin categories. Compared with the reference group, the adjusted HR for prostate cancer among men with hyperthyroid function was 1.97 (95% CI, 1.04-3.76). For the other categories of thyrotropin, prostate cancer risk did not substantially differ from that of the reference group.

In a separate analysis, we started follow-up 2 years after baseline in order to reduce potential bias due to preclinical effects of cancer on thyrotropin levels (Table 2). This analysis showed a moderately stronger association with total cancer for thyrotropin levels of <0.50 mU/L (HR increased from 1.34 to 1.52). In the site-specific analyses, the association with lung cancer was strengthened (HR, 2.34 to 2.91), and a similar strengthening was observed for prostate cancer (HR, 1.97 to 2.60).

Among people with thyrotropin levels <0.50 mU/L, suggestive of hyperthyroid function, we could distinguish between biochemically overt hyperthyroid function and probable subclinical hyperthyroid function (Table 3). Compared with the reference group (thyrotropin, 0.50-1.4 mU/L), the HR of total cancer in overtly hyperthyroid people was 1.96 (95% CI, 1.11-3.47). When follow-up started 2 years after baseline, the HR was strengthened to 2.35 (95% CI, 1.29-4.26). In people with subclinical hyperthyroid function, the HR for total cancer was 1.27 (95% CI, 0.98-1.63), and 1.42 (95% CI, 1.08-1.86) when follow-up started 2 years after baseline. The site-specific analyses, starting follow-up 2 years after baseline, showed that subclinically hyperthyroid people were at higher risk of lung cancer (HR, 2.55; 95% CI, 1.22-5.35) and prostate cancer (HR, 2.46; 95% CI, 1.24-4.87). For people with overt hyperthyroid function, the point estimates for lung and prostate cancer risk were stronger than for subclinical hyperthyroid function, but a low number of cancers precluded precise estimates (Table 3).

Discussion

In this prospective study of nearly 30,000 people without known thyroid disease at baseline, people with

Table 2. HRs of total cancer, and cancer of the lung and prostate, by categories of thyrotropin, with follow-up starting 2 y after baseline

Thyrotropin (mU/L)	Persons (*n*)	Cancers (*n*)	HR (95% CI)
Total cancer			
<0.50	648	67	1.52 (1.18-1.95)
0.50-1.4	12,050	806	1.0 (Reference)
1.5-2.4	10,581	764	1.04 (0.94-1.15)
2.5-3.5	3,483	258	0.99 (0.86-1.14)
>3.5	2,074	164	1.01 (0.86-1.20)
Lung cancer			
<0.50	648	10	2.91 (1.49-5.70)
0.50-1.4	12,050	62	1.0 (Reference)
1.5-2.4	10,581	48	1.00 (0.68-1.46)
2.5-3.5	3,483	23	1.60 (0.99-2.61)
>3.5	2,074	8	1.03 (0.49-2.17)
Prostate cancer			
<0.50	160	10	2.60 (1.36-4.99)
0.50-1.4	4,204	107	1.0 (Reference)
1.5-2.4	3,627	101	1.00 (0.76-1.31)
2.5-3.5	1,069	33	0.91 (0.61-1.35)
>3.5	530	19	0.95 (0.58-1.56)

NOTE: HRs adjusted for age, sex, and smoking status.

thyrotropin levels indicating hyperthyroid function were at higher risk of total cancer compared with other people, including those with suggested hypothyroid function. The higher risk in people with hyperthyroid function was mainly driven by effects on lung and prostate cancer. The risk was elevated both in people with probable subclinical hyperthyroid function, and more strongly, in people with biochemically overt hyperthyroid function.

Few previous studies have addressed the association of thyroid function with cancer risk. One small cohort study showed no association of thyrotropin with cancer mortality (18), and studies that examined cancer risk and mortality after treatment for hyperthyroidism have not reported consistent results. It has been suggested that patients treated with radioactive iodine may be at increased risk for cancer (8), but others have not confirmed any clear association of treatment against hyperthyroidism and cancer risk or mortality (5-7). However, these studies aimed to assess whether medical treatment could influence cancer development and did not specifically assess the association of thyroid function with cancer risk or mortality. One study has found that autoimmune hypothyroidism may be associated with reduced risk and severity of breast cancer (4), and it has been suggested that the presence of thyroid autoantibodies in patients with breast cancer, indicating autoimmune thyroiditis, may be associated with improved prognosis (9). However, increased breast cancer risk associated with autoimmune hypothyroidism has also been reported (4, 9).

The prospective design of this study makes it relatively immune to bias. However, nonthyroidal illness may alter thyrotropin and thyroid hormone levels (19). Thus, some people could have low thyrotropin levels not due to hyperthyroid function, but due to nonthyroidal disease such as a preclinical cancer. In a separate analysis, we attempted to reduce this potential problem by starting follow-up 2 years after thyrotropin was measured. Using this approach, the association of hyperthyroid function with cancer risk was strengthened, and not weakened as would be expected if the association was caused by cancer leading to low thyrotropin levels prior to diagnosis. Also, cancer risk was elevated in people with overt hyperthyroid function, defined as low thyrotropin levels combined with high levels of thyroid hormones. This suggests that the higher risk associated with hyperthyroid function is not likely to be inflated by preclinical effects of the malignancy on thyrotropin levels.

Adjustment for smoking status moderately attenuated the association of hyperthyroid function with lung cancer, but the higher risk persisted and remained strong. Potential confounding by other unmeasured factors cannot be excluded, but confounding of the association requires that these factors should by themselves be associated with thyrotropin level, and also with cancer risk. Based on prior knowledge, there are no obvious other factors that should be accounted for in the analyses of thyroid function and cancer risk.

Participants with previously known thyroid disease at baseline were excluded from follow-up. Nonetheless, some of the participants with thyrotropin levels suggesting hyperthyroid or hypothyroid function could have received medical treatment against thyroid disease during the follow-up period. It is a weakness of this

Table 3. HRs of total cancer and cancer of the lung and prostate among people with overt and subclinical hyperthyroid function, compared with the euthyroid reference group (0.50-1.4 mU/L)

	Overt hyperthyroid function*			Subclinical hyperthyroid function†		
	Cancers (*n*)	Persons (*n*)	HR (95% CI)‡	Cancers (*n*)	Persons (*n*)	HR (95% CI)‡
With follow-up starting at baseline						
Total cancer	12	75	1.96 (1.11-3.47)	64	599	1.27 (0.98-1.63)
Lung cancer	2	75	4.65 (1.14-19.04)	9	599	2.11 (1.06-4.20)
Prostate cancer	1	8	4.08 (0.57-29.36)	9	163	1.87 (0.95-3.68)
With follow-up starting 2 years after baseline						
Total cancer	11	70	2.35 (1.29-4.26)	56	578	1.42 (1.08-1.86)
Lung cancer	2	70	6.80 (1.65-28.09)	8	578	2.55 (1.22-5.35)
Prostate cancer	1	6	5.47 (0.76-39.55)	9	154	2.46 (1.24-4.87)

*Overt hyperthyroid function: thyrotropin <0.20 mU/L combined with free thyroxine and/or total triiodothyronine above the reference range.
†Subclinical hyperthyroid function: thyrotropin 0.20 to 0.49 mU/L, or thyrotropin <0.20 mU/L with neither free thyroxine nor total triiodithyronine above the reference range.
‡Adjusted for age, sex, and smoking status.

study that information was not available on possible thyroid treatment after the measurement at baseline, and we cannot exclude the possibility that such treatment could have influenced the reported results.

To assess the effects of thyroid function on cancer risk requires large population samples and long and reliable follow-up. Our study includes nearly 30,000 individuals without known thyroid disease at baseline, and thyroid function was measured up to many years prior to a cancer diagnosis. Nonetheless, this study does not have sufficient statistical power to assess the association of thyroid function with relatively rare cancers. We therefore restricted the analyses to total cancer and to four frequent cancers: colon, lung, breast, and prostate cancers. The higher risk of total cancer associated with hyperthyroid function was largely driven by effects on lung and prostate cancer, and there was no clear association for colon and breast cancer. Nonetheless, the moderate number of cancer cases in the site-specific analyses suggests that these estimates should be interpreted with caution and confirmed by other prospective studies.

Physiologically, thyroid function is important for metabolic processes and for growth and maturation of organ tissues. The biological mechanisms that could mediate the association of hyperthyroid function with the risk of certain cancers are not well understood. However, some possibilities have been suggested (1), including the modulation of autocrine and paracrine growth factors (1, 2, 20, 21).

In this prospective study of cancer risk among people without previously known thyroid disease, we found that thyrotropin levels suggestive of hyperthyroid function, measured years prior to diagnosis, were associated with increased risk of total cancer, and specifically, with higher risk of lung and prostate cancer.

Disclosure of Potential Conflicts of Interest

There is no conflict of interest related to this work.

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