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Thyroxin Use Is Associated With Increased Risk of Thyroid Cancer in Patients With Hypothyroidism

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Abstract

Despite evidence linking thyroxin use and breast cancer, little is known regarding the risk of other cancers with thyroxin use. The purpose of this case-control study was to evaluate the association of thyroid cancer with primary hypothyroidism based on a population-based database. The data for this case-control study were retrieved from the Taiwan Longitudinal Health Insurance Database 2005. We included 1285 patients with thyroid cancer as cases and 3855 sex- and age-matched subjects as controls. We used conditional logistic regression to examine the association of thyroid cancer with previously diagnosed hypothyroidism. We found that a prior hypothyroidism diagnosis was found among 37 cases (2.88%) and 33 controls (0.86%). Conditional logistic regression analysis revealed that the cases were more likely to have been previously diagnosed with hypothyroidism than controls (adjusted OR, 3.01; 95%CI, 1.85–4.89). We also found that thyroid cancer was significantly associated with hypothyroidism patients who were regular thyroxin users (adjusted OR, 8.68; 95%CI, 4.34–17.34). However, we failed to observe a significant association between thyroid cancer and hypothyroidism patients who were irregular thyroxin users. This investigation detected a novel association between thyroid cancer and thyroxin use in patients with primary hypothyroidism.

Keywords

thyroxin, hypothyroidism, thyroidectomy, epidemiology

Thyroxin is a synthetic hormone commonly used to manage hypothyroidism.[1] It is also used in suppressive therapy for thyroid nodules and benign goiter and may be used to prevent goiter recurrence after partial thyroidectomy.[2–4] It is believed that the suppression of thyroid-stimulating hormone (TSH) secretion in normal subjects by the administration of thyroid hormone results in thyroid atrophy, and as the risk of thyroid cancer in patients with thyroid nodules increases with increasing serum TSH concentrations, the risk of thyroid cancer is potentially reduced under suppressive therapy.[5] Thyrotropin suppression might also benefit patients with differentiated thyroid cancers.[6,7] However, studies have also reported that thyroid hormone is associated with the development of cancers.[8] Women with primary hypothyroidism had a 61% lower risk of developing invasive breast cancer, and women newly diagnosed with breast cancer were 57% less likely to have an under-active thyroid gland condition compared with a control group of healthy women.[9] Despite evidence linking thyroxin use and breast cancer, little is known regarding the risk of other cancers with thyroxin use.

The purpose of this study was to evaluate the potential association of thyroid cancer with primary hypothyroidism based on a population-based coverage database.

Methods

Database

This study was exempt from full review by the Institutional Review Board of Taipei Medical University (TMU-JIRB 201612024) because the LHID2005 consists of deidentified secondary data released to the public for research purposes.

We retrieved the data for this case-control study from the Longitudinal Health Insurance Database (LHID2005). The LHID2005, compiled by the Taiwan

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National Health Research Institute, includes medical claims data and registry files for 1 000 000 enrollees randomly sampled from all enrollees in the Taiwan National Health Insurance (NHI) program in 2005 (n = 23.72 million, with an enrollment rate of approximately 98.5% in 2000). Data in the LHID2005 include a registry of contracted medical facilities, a registry of board-certified physicians, a registry of catastrophic illness patients, a monthly claims summary for inpatient claims, a monthly claims summary for ambulatory care claims, details of inpatient orders, details of ambulatory care orders, and expenditures for prescriptions dispensed at contracted pharmacies. The Taiwan National Health Research Institute has validated the representativeness of the LHID2005 and confirmed that it corresponds with the whole population of NHI beneficiaries on sex ad age distribution. The LHID2005 is released to academic institutions in Taiwan for research purposes.

Study Sample

We selected cases for this case-control study by identifying 1301 patients who had received a first-time diagnosis of thyroid cancer (ICD-9-CM code 193, malignant neoplasm of the thyroid gland) at an ambulatory care center (including clinics and outpatient departments of hospitals) from January 1, 2001, to December 31, 2013. We only included patients who had received a first-time diagnosis of thyroid cancer to limit the study group to new-onset thyroid cancer cases. We defined the first ambulatory care visit for thyroid cancer as the index date for the cases. We further excluded patients younger than 18 years (n = 16) to limit the study sample to the adult population. As a result, 1285 patients with thyroid cancer were included as cases.

For the selection of controls, we first excluded all enrollees who had a medical history of thyroid cancer since the beginning of the NHI program in 1995. We then retrieved 3855 controls (3 controls per thyroid cancer patient) from the remaining enrollees and matched them to the cases according to age, sex, and index year using the SAS Proc SurveySelect program (SAS Institute, Cary, North Carolina). For the cases, the index year was the year in which they received their first-time thyroid cancer diagnosis, whereas for the controls, the index year was simply a matched year in which the controls visited a physician. We further assigned the first medical service utilization during the index year as the index date for controls.

Exposure Assessment

This study attempted to evaluate the odds of having been previously diagnosed with hypothyroidism for the cases and controls. We identified hypothyroidism cases based on ICD-9-CM diagnosis code 244 (n = 82). We included hypothyroidism patients who had received at least a hypothyroidism diagnosis made by an endocrinologist to increase the diagnostic validity of the hypothyroidism group. In this study, we found all hypothyroidism diagnoses were made by endocrinologists. Furthermore, we excluded hypothyroidism patients who had undergone operations on the thyroid and parathyroid glands (ICD-9-CM procedure code 06) before their first diagnosis of hypothyroidism (n = 8). Finally, we only included hypothyroidism patients if they had received at least 1 hypothyroidism diagnosis prior to the index date (n = 70).

Statistical Analysis

We performed all the statistical analyses using the SAS system (SAS System for Windows, version 8.2; SAS Institute Inc., Cary, North Carolina). We used chi-square tests to compare the distributions of sociodemographic characteristics and medical comorbidities (including hypertension, diabetes, coronary heart disease [CHD], hyperlipidemia, stroke, osteoporosis, obesity, and tobacco use disorder) between the cases and the controls. The data on sociodemographic characteristics were retrieved from the Registry for Beneficiaries. They included monthly income (NT$0–NT$15 840, NT$15 841–NT$25 000, ≥NT$25 001; the average exchange rate in 2008 was US$1.00 = New Taiwan [NT]$29), geographical location (northern, central, southern, and eastern), and urbanization level of the patient's residence. The urbanization level of the residence was classified as 1 of 5 levels (5 levels, with 1 the most urbanized and 5 the least urbanized) according to the standards published by the Taiwanese National Health Research Institute. We further used conditional logistic regression (conditioned on age, sex, and index year) to examine the association of thyroid cancer with previously diagnosed hypothyroidism after adjusting for monthly income, geographical location, and urbanization level of the patient's residence, hypertension, diabetes, CHD, hyperlipidemia, stroke, osteoporosis, obesity, and tobacco use disorder . The conventional $P \leq .05$ was used to assess statistical significance.

Results

Table 1 presents the distribution of demographic characteristics and medical comorbidities between the cases and the controls. After matching for age, sex, and index date, the thyroid cancer patients had a greater tendency than controls to have the following comorbidities: hypertension (30.5% vs 19.7%, $P < 0.001$), diabetes (14.6% vs 9.3% $P < .001$), CHD (13.2% vs 7.8%, $P < .001$), osteoporosis (9.2% vs 5.2%, $P < .001$), and hyperlipidemia (23.7% vs 15.5%, $P < .001$). However,

Table 1. Demographic Characteristics and Comorbid Medical Conditions of Patients With Thyroid Cancer and Comparison Subjects (n = 5140)

	Cases, n = 1285		Controls, n = 3855		
Variable	Total Number	Column %	Total Number	Column %	*P*
Age (years), mean (SD)			46.8 (15.0)		
Male	282	22.0	846	22.0	> .999
Hyperlipidemia	304	23.7	596	15.5	< .001
Hypertension	392	30.5	760	19.7	< .001
Diabetes	187	14.6	359	9.3	< .001
Coronary heart disease	169	13.2	301	7.8	< .001
Osteoporosis	118	9.2	199	5.2	< .001
Stroke	84	6.5	202	5.2	.079
Obesity	31	2.4	63	1.6	.071
Tobacco use disorder	51	3.9	174	4.5	.408
Urbanization level					.696
1 (most urbanized)	442	34.4	1311	34.0	
2	389	30.3	1143	29.6	
3	156	12.1	529	13.8	
4	175	13.6	521	13.5	
5 (least urbanized)	123	9.6	351	9.1	
Geographic region					.411
Northern	665	51.7	1908	49.5	
Central	276	21.5	910	23.6	
Southern	317	24.7	955	24.8	
Eastern	27	2.1	82	2.1	
Monthly income					.594
NT$0–NT$15 840	473	36.8	1447	37.5	
NT$15 841–NT$25 000	457	35.6	1399	36.3	
≥NT$25 001	355	27.6	1009	26.2	

The average exchange rate in 2009 was US$1.00 = New Taiwan (NT)$30. SD, standard deviation.

Table 2. Crude and Adjusted Odds Ratios (ORs) for Thyroid Cancer Among Sampled Patients

	Total Sample, n = 5140	Patients With Thyroid Cancer, n = 1285	Controls, n = 3855
Variable		n (%)	
Presence of hypothyroidism			
Yes	70 (1.36)	37 (2.88)	33 (0.86)
Crude OR (95%CI)		3.43[b] (2.14-5.55)	1.00
Adjusted[a] OR (95%CI)		3.01[b] (1.85-4.89)	1.00

OR was calculated by conditional logistic regression, which was conditioned on age and the year of index date.

[a]Adjustments are made for patient's hypertension, hyperlipidemia, diabetes, coronary heart disease, osteoporosis, obesity, and tobacco use disorder.

[b]$P < .001$.

we did not observe any significant differences between the cases and controls regarding the distributions of monthly income ($P = .594$) and the urbanization level ($P = .696$) and geographic location ($P = .411$) of the patient's residence.

Table 2 shows the distribution of prior hypothyroidism between cases and controls. Of 5140 sampled patients, 70 (1.36%) were found to have had received a hypothyroidism diagnosis before the index date. Specifically, a prior hypothyroidism diagnosis was found among 37 cases (2.88%) and 33 controls (0.86%); $P < .001$. Furthermore, conditional logistic regression analysis (conditioned on age, sex, and index year) revealed that the cases were more likely to have been previously diagnosed with hypothyroidism compared with the controls (OR, 3.43; 95%CI, 2.14–5.55; $P < .001$). Regression analysis also suggested that the OR for prior hypothyroidism among the cases compared with the controls was 3.01 (95%CI, 1.85–4.89; $P < .001$) after adjusting for hypertension, diabetes, CHD, hyperlipidemia, osteoporosis, obesity, and tobacco use disorder.

Furthermore, Table 3 presents the association between thyroid cancer and regular/irregular thyroxin use. In this study, we defined hypothyroidism patients who had received continuous thyroxin prescriptions for ≥60 days within 6 months before the index date as regular thyroxin users. All other patients who had been prescribed thyroxin for <60 days within the 6 months before the index date were defined as irregular thyroxin users. We found that thyroid cancer was significantly associated with hypothyroidism with regular thyroxin use (adjusted OR, 8.68; 95%CI, 4.34–17.34). However, we failed to observe a significant association

Table 3. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Thyroid Cancer Among Sampled Patients According to Use of Thyroxin

	Patients With Thyroid Cancer, n = 1285	Controls, n = 3855
Use of Thyroxin	n (%)	
Patients with prior hypothyroidism and regular thyroxin user	34 (2.65)	11 (0.29)
Patients with prior hypothyroidism and irregular thyroxin user	3 (0.23)	22 (0.57)
Patients without prior hypothyroidism	1248 (97.12)	3822 (99.14)
OR (95%CI)		
Patients with prior hypothyroidism and regular thyroxin user		
Crude OR (95%CI)	9.45[b] (4.78–18.71)	1.00
Adjusted[a] OR (95%CI)	8.68[b] (4.34–17.34)	1.00
Patients with prior hypothyroidism and irregular thyroxin user		
Crude OR (95%CI)	0.42 (0.13–1.40)	1.00
Adjusted[a] OR (95%CI)	0.32 (0.09–1.10)	1.00

OR was calculated by conditional logistic regression, which was conditioned on age sex, and year of index date.

[a]Adjustments are made for patient's hypertension, hyperlipidemia, diabetes, coronary heart disease, osteoporosis, obesity, and tobacco use disorder.

[b]$P < .001$.

between thyroid cancer and hypothyroidism with irregular thyroxin use.

Discussion

In this study, we found that in patients with primary hypothyroidism, regular use of thyroxin is associated with an elevated risk of thyroid cancer. Our findings were in light of the observation that thyroxin is associated with cancer development and imply that under certain conditions, this effect might surpass the negative feedback resulting from TSH suppression.

Traditionally, the adverse effects of thyroxin therapy have been regarded as primarily cardiovascular changes and bone changes.[10] Little is known regarding the association between thyroxin use and carcinogenesis. As mentioned above, thyroid hormone use is reported to be associated with the development of cancers.[8] Most of these reports focused on the association between thyroxin use and the development of breast cancers. It has been reported that the incidence of breast cancer was twice as high in women with hypothyroidism who were taking thyroid hormone than in women with hypothyroidism who were not taking thyroid supplements.[11] In 1 study, the incidence of breast cancer almost doubled in women who had taken thyroid hormone for more than 15 years (19.48%) compared with those who had taken thyroid hormones for only 5 years (10%). As thyroxin is used in suppressive therapy for thyroid goiter and to prevent goiter recurrence after partial thyroidectomy, it seems logical that through the suppression of TSH, the risk of developing thyroid cancer should be lowered with thyroxin use.[2–5] To our surprise, however, our study the results appear to indicate the opposite.

To date, there seem to be no studies reporting the possible mechanisms of thyroxin-related carcinogenesis. Nevertheless, the phenomenon might be explained in 2 possible ways. First, the thyroxin might act as an enhancing agent in the normal carcinogenesis pathways. Lishi et al first reported that thyroxin enhances the carcinogenesis effect of azoxymethane in inducing rat colon adenocarcinoma.[12] Later, the same group determined that thyroxin also enhances the gastric carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine in Wistar rats.[13] Second, thyroxin on its own might stimulate the growth of thyroid cancer cells. Lin et al reported that thyroid hormone is a MAPK-dependent growth factor for thyroid cancer cells and is antiapoptotic.[14] The researchers treated human papillary and follicular thyroid cancer cell lines with L-thyroxin (T4) or 3,5,3'-triiodo-L-thyronine (T3), and enhanced cell proliferation resulted. They also revealed that thyroid hormone induces activation of the Ras/MAPK (ERK1/2) signal transduction pathway, which promotes papillary and follicular thyroid cancer cell proliferation in vitro.

The strength of this study is that through our national health insurance database with a large number of cases, we were able to enroll a relatively large number of cases with hypothyroidism after excluding those who had developed thyroid cancer before the index date and those that had undergone any type of thyroid operation. This allowed us to avoid some selection bias, as patients who are taking thyroid hormone after thyroidectomy, whether for hyperthyroidism or nodular goiter, might be more likely to develop thyroid cancers.[15–17] Moreover, by further separating the cases into regular and irregular thyroxin users, an indirect dose-dependent phenomenon was observed. However, there are several limitations. The major limitation of this study is that based on this health insurance database study, the exact cause of hypothyroidism cannot be accurately addressed, even with the exclusion of surgical cases and confirmed thyroid cancer cases. Therefore, there might still be some selection bias, as thyroiditis has been reported to be associated with thyroid cancer development.[18] Second, because of the health insurance database study design, in our study the definition of regular or irregular thyroxin use was based on continuous thyroxin prescriptions for ≥ 60 or <60 days, respectively, within 6 months before the index date; this distinction remained rather questionable

and may not have reflected the patients' actual drug intake.

However, it should be emphasized that although the findings suggest an association between thyroid cancer and regular thyroxin use, additional studies are needed to further evaluate and validate these findings.

In conclusion, this investigation found an association between thyroxin use and the development of thyroid cancer in patients with primary hypothyroidism. Although the true role of thyroxin in thyroid cancer development remains to be investigated, physicians might consider this association when treating patients with subclinical hypothyroidism.

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Declaration of Conflicting Interests

None

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