Association Between Thyroid Cancer and Cardiovascular Disease Risk: A Nationwide Observation Study

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Abstract

Background

Research findings on the long-term cardiovascular risk associated with thyroid cancer and treatment are unclear. This study aimed to investigate the standardized incidence rate (SIR) of coronary heart disease (CHD), ischemic stroke (IS), and atrial fibrillation (AF) among thyroid cancer patients in comparison with the general population across different age groups.

Methods

Design, setting, and participants

This observational cohort study enrolled patients between January 1, 2011 and December 31, 2016 with follow-up until December 31, 2018. This study analyzed the data of Taiwanese thyroid cancer patients registered on the National Taiwan Cancer Registry Database, with CHD and IS.

Main outcomes and measures

SIR models were used to evaluate the association between thyroid cancer and CHD, IS, AF, and cardiovascular disease outcome, stratified by age and sex. SIR analyses were also conducted for both sexes, age groups (<60, ≥60 years), and different follow-up years.

Results

After excluding 128 individuals <20 years or >85 years and with missing index data, 4274 eligible thyroid cancer patients without CHD history, 4343 patients without IS history, and 4247 patients without AF history were included for analysis. During the median follow-up of 3.5 (1.2) years, CHD incidence was 70; IS, 30; and AF, 20. Compared with the general population, thyroid cancer patients had higher CHD risk throughout the age spectrum (SIR, 1.33; 95% confidence interval [CI], 1.02 to 1.65). The overall CHD risk gradually declined, but it was persistent for more than 5 years after thyroid cancer diagnosis. CHD risk was observed in both males and females, especially in young thyroid cancer patients <65 years. However, lower SIRs for IS (SIR, 0.74; 95% CI, 0.47 to 1), AF (SIR, 0.74; 95% CI, 0.42 to 1.06), and cardiovascular disease (SIR, 0.88; 95% CI, 0.7 to 1.05) were observed among thyroid cancer patients (not significant).

Conclusions

Thyroid cancer survivors have a substantial CHD risk even at long-term follow-up, especially in those patients <65 years. Further research on the association between thyroid cancer and CHD risk is warranted.

Introduction

Thyroid cancer was the fifth most common cancer among women and the ninth most common cancer among both sexes in 2018. The incidence has dramatically increased worldwide over recent decades¹ with an 211% increase in the United States between 1975 and 2013² (2) and 490% in South Korea between 1995 and 2005³, although thyroid cancer-related mortality rates have not changed substantially⁴. Initial thyroid cancer treatment comprises total thyroidectomy, radioactive iodine therapy, and administration of exogenous thyroxine to facilitate thyroid stimulating hormone suppressive.⁴Angus, et al. ⁵.

Radioactive iodine and thyroid stimulating hormone suppressive therapies can lead to short-term adverse events, such as thyroiditis, hypothyroidism and hyperthyroidism related palpitation and progressive atherosclerosis in the carotid intima⁶. Although several studies had consistently the short-term cardiovascular effect, the long-term risk of coronary heart disease (CHD), ischemic stroke (IS), and atrial fibrillation (AF) in individuals with thyroid cancer remains controversial.

For example, some studies have demonstrated that thyroid cancer patients had higher odds (ranging from 1.05 to 1.28) of developing cardiovascular disease^{7,8}. However, another research failed to find an association between thyroid cancer and the risk of cardiovascular disease⁹. Furthermore, some researcher found an increased risk (ranging from 1.06 to 3.95) of AF among thyroid cancer patients^{7,10}, while another study did not find any such association¹¹. Using a nationwide population-based cohort, we aimed to examine the following hypotheses: (1) CHD and IS are more frequent in thyroid cancer patients than in the general reference population, (2) AF is as frequent in thyroid cancer patients as in the general reference population, and (3) the risk of cardiovascular disease among thyroid cancer patients was the same across different ages.

Materials And Methods

This retrospective cohort study used data from the National Taiwan Cancer Registry Database (NTCRD). The data analysis was conducted for the period from January 1, 2011 to December 31, 2016 and followed up until December 31, 2018. The NTCRD was set up in 1979 to collect data of all confirmed cancer diagnoses among Taiwanese citizens since 2002, and it has been revised for the third time to date. The NTCRD contains cancer characteristics including staging; first-time surgical treatment; chemo-, radiation, hormone, and target therapy; and lifestyle habits such as smoking and alcohol and betel nut consumption. Additionally, the NTCRD was merged with the National Health Insurance Research Database (NHIRD) and national death records. The NHIRD incorporated longitudinal information of 99% citizens' demographic, medical, and pharmaceutical data based on the International Classification of Disease, 9th revision (ICD-9), medical procedure data, hospitalization and outpatient clinic records, and drug prescriptions. The national death records list the specific causes of death based on the ICD-9/ICD-10 codes. Additional details on the cohort protocol are available in a previously published study¹². The protocol was reviewed and approved by the Research Ethics Committee of Mackay Memorial Hospital.

For the present analysis, baseline was defined as the day when the thyroid cancer patients received thyroidectomy in the period from January 1, 2011 to December 31, 2016. From all the patients who underwent thyroidectomy, we excluded those participants who were <20 or >85 years old, had cancers other than thyroid cancer, and had history of CHD, IS, or AF before index date (362 with cancers other than thyroid cancer, 101 with CHD, 32 with IS, and 128 with AF) (Supplementary Figure 1).

Assessment of coronary heart disease, ischemic stroke, atrial fibrillation, and cardiovascular diseases

After thyroid cancer diagnosis, patients were followed up until December 31, 2018. The endpoint of primary interest among thyroid cancer patients and the general reference population was hospitalization for CHD, defined as fatal and non-fatal CHD (including non-fatal myocardial infarction and coronary artery bypass graft surgery) after thyroid cancer diagnosis in NHIRD claim records based on ICD-9 (Table 1). Fatal CHD was defined as death caused by CHD as listed in the death certificate on the national death records. Secondary interest included IS defined by one hospitalization diagnosis and AF defined by one hospitalization or two outpatient clinic diagnoses after thyroid cancer was diagnosed by ICD-9. The definition of cardiovascular diseases was CHD or IS.

Table 1
Baseline characteristics of Taiwan thyroid cancer cohort patients without coronary heart disease at baseline

	N	%
All	4274	100
Mean age (SD)	49	13.1
Sex		
Men	1041	24.4
Women	3233	75.6
BMI (kg/m ²)		
<18.5	156	3.8
18.5-23.9	1874	46
24.0-26.9	1074	26.4
≥ 27.0	971	23.8
Urbanization		
Urban	3267	76.4
Non-urban	1007	23.6
Current smoking or quit < 15 years	366	8.6
TNM staging		
Stage I	2865	68.6
Stage II	248	5.9
Stage III	754	18
Stage IV	312	7.5
Hypertension	1814	42.4
Diabetes	473	11.1
Hyperlipidemia	820	19.2
Aspirin used	423	9.9

Statistical Analyses

We compared the CHD incidence of Taiwanese thyroid cancer patients with that of the general population using the standardized incidence ratio (SIR), computed as the ratio of observed to expected CHD cases, stratified by age and sex. The incidences of CHD, IS, and AF were compared with the age- and sex-specific disease incidence rates in the Taiwanese population, accounting for person-years of observation. CHD, IS, and AF incidence data from the NHIRD were used as a reference.

We computed SIRs separately among thyroid cancer patients for both sexes, each age group (20–39, 40–59, ≥60 years), and different follow-up year and compared them with that of the reference population. The change in trends of SIRs for both sexes and age <65 or ≥65 years old in different follow-up years was analyzed. SAS version 9.4 (SAS Institute, Cary, NC, USA) and Stata version 12 (Stata Corporation, College Station, TX, USA) were used for statistical analyses.

Results

Sample characteristics

After excluding 128 individuals who were <20 or >85 years old or had missing index data, 4375 thyroid cancer patients were eligible for the study. Further, 4274 patients without CHD history, 4343 patients without IS history, and 4247 patients without AF history were included for CHD, IS, and AF analysis, respectively. The mean age was 49 (standard deviation, 13.1) years and mean follow-up was 3.5 (standard deviation, 1.2) years. The basic characteristics of the thyroid cancer patients in the study are shown in Table 2.

Table 2
Cardiovascular incidence, displayed as standardized incidence ratios (SIR) and 95% confidence intervals subdivided by three cardiovascular endpoints and atrial fibrillation

Primary Endpoints	Events	SIR	95% CI	
			Lower	Upper
CHD	70	1.57	1.2	1.93
IS	30	0.74	0.47	1
AF	20	0.74	0.42	1.06
CVD	96	0.88	0.7	1.05
Abbreviations: CHD, coronary heart disease; IS, ischemic stroke; CVD, cardiovascular disease; Af, atrial fibrillation; SIR, standardized incidence ratios; CI, confidence interval.				

Observed and expected coronary heart disease and ischemic stroke events

SIR was significantly high for CHD (SIR, 1.57; 95% confidence interval [CI], 1.2 to 1.93) and low (not significantly) for IS (SIR, 0.74; 95% CI, 0.47 to 1), AF (SIR, 0.74; 95% CI, 0.42 to 1.06), and cardiovascular diseases (SIR, 0.88; 95% CI, 0.7 to 1.05) (Table 2 and Figure 1). The overall CHD SIRs gradually declined,

but they were persistent for more than 5 years after the diagnosis of thyroid cancer (Table 3). Although SIRs of CHD were significantly high for both sexes, patients with thyroid cancer at a younger age had higher SIRs than patients with thyroid cancer at >65 years of age. Patients <65 years of age had a 1.5- to 2.66-fold significantly higher CHD SIR, while those >65 years of age had 0.57- to 1.42-fold odds of CHD SIRs, which remained high, although not significantly (Table 3). The difference in the risk of CHD between the two age groups remained up to 5 years after thyroid cancer diagnosis (Table 4 and Figure 2).

Table 3
Standardized incidence ratio by potential explanatory factors for
coronary heart disease

(A)				
Subgroup	Incidence events	SIR	95% CI	
			Lower	Upper
All	70	1.57	1.2	1.93
Age at diagnosis				
< 65	49	2.08	1.5	2.66
≥ 65	21	1	0.57	1.42
Sex				
Men	28	1.63	1.03	2.24
Men: 20~39	2	1.25	0	3.7
Men: 40~64	20	1.62	0.93	2.32
Men: ≥ 65	6	0.78	0.1	1.47
Women	42	1.53	1.06	1.99
Women: 20~39	1	1.8	0	5.33
Women: 40~64	26	1.59	0.98	2.2
Women: ≥ 65	15	1.01	0.5	1.53
Follow-up (years)				
1	27	2.05	1.28	2.83
2	42	1.65	1.15	2.15
3	53	1.5	1.09	1.9
4	67	1.6	1.22	1.99
5	70	1.57	1.2	1.93

Table 4

Standardized incidence for coronary heart disease at different follow up years stratified by age younger than 65 years old and older than 65

Follow-up (years)	Age < 65 years old				Age ≥ 65 years old			
	Incidence events	SIR	95% CI		Incidence events	SIR	95% CI	
			Lower	Upper			Lower	Upper
1	16	2.54	1.3	3.79	11	1.6	0.66	2.55
2	28	2.23	1.4	3.05	14	1.09	0.52	1.66
3	36	1.99	1.34	2.64	17	0.98	0.51	1.45
4	47	2.17	1.55	2.79	20	1	0.56	1.43
5	49	2.08	1.5	2.66	21	1	0.57	1.42

Observed And Expected Ischemic Stroke And Atrial Fibrillation Events

Patients with thyroid cancer had lower risk (not significant) of IS and AF than the general reference population. The SIR for IS was lower (not significant) than expected (SIR, 0.74; 95% CI, 0.47 to 1) (Table 3), while IS risk was significantly lower among those with thyroid cancer at >65 years of age (SIR, 0.6; 95% CI, 0.27 to 0.92) (Table 4). SIR was lower (not significant) for AF up to 5 years of follow-up based on the data of 20 participants (SIR, 0.74; 95% CI, 0.42 to 1.06) (Table 2).

Discussion

The analysis of the nationally representative cohort showed that patients with thyroid cancer had higher risk of developing CHD than the general population, although the results were not significant for IS and AF. The CHD risk was highest in young thyroid cancer patients <65 years of age, which persisted more than 5 years after cancer diagnosis, while it was the same in patients >65 years and the general population.

The results of the present study are in accordance with the findings from a previous study⁸ that showed the risk of CHD events in patients with thyroid cancer is higher than that in the general population. To the best of our knowledge, no study has conducted SIR analysis for CHD risk among different age groups of thyroid cancer patients. A cohort study of 182419 patients found increased incidence in CHD in thyroid cancer patients without a subgroup analysis of different age stratification⁸. A cohort study of 3706 thyroid cancer patients conducted subgroup analysis of CHD risk in cancer patients of <40 and ≥40 years of age and a healthy control. Although higher incidence of CHD was observed among the thyroid cancer patients, the odds were higher in the younger group (<40 years) than those in older population (≥40 years) during the 1 to 5 year and 5 to 10 year follow-up periods, and it was not observed in the >10 year follow-up¹¹. Another cohort study of 6900 patients that conducted age-based subgroup analysis of

AF instead of CHD reported that AF risk was higher among younger patients than that in older patients. The SIRs of AF was 2.67 (95% CI, 1.61 to 4.41) in patients <45 years old and 1.03 (95% CI, 0.75 to 1.41) in patients ≥ 75 years old⁹. These findings suggest that there is a higher long-term risk of CHD in younger patients than in older patients. In addition, our results demonstrated that the incidence of AF in thyroid cancer patients was similar to that in the general population, which is consistent with a previously published population-based study¹¹ and an over-all meta-analysis result. However, in contrast to our findings, a previous study reported a significant 1.66-fold higher risk of hospitalization for AF^{9,10}. The discrepancy between the results of the current study and the previous study may be attributed to several reasons. First, in our study, 90% of the participants were <60 years old, while in the previous study one-third of the patients were >60 years old. Young patients might be able to tolerate the effect of subclinical thyrotoxicosis, especially after thyroid stimulating hormone suppression therapy. Second, the period of study inclusions was different in the two cohorts. In our study, thyroid cancer patients diagnosed after 2011 were included, while in the previous study, those diagnosed from 1987 to 2013 were included. Decades ago, the prevalent guidelines suggested lifelong thyroid stimulating hormone suppression treatment for all thyroid cancer patients. However, according to the current recommendations, such as the American Thyroid Association guidelines, thyroid stimulating hormone suppression treatment is not indicated for management of low recurrent risk thyroid cancer¹³. Thus, the fewer number of patients with subclinical thyrotoxicosis status could have further reduced the incidence of AF in recent years. This suggests that the recent update of recommendations on long-term AF prevention during thyroid cancer treatment may have resulted in the inconsistent results between the two studies with different periods of inclusion.

Although the pathophysiological reason of increased CHD incidence in thyroid cancer patients remains unclear, several factors might contribute to the higher risk. First, during thyroid cancer treatment, such as thyroidectomy, radioactive iodine therapy, and thyroid stimulating hormone suppression therapy, adverse events of hypothyroidism and hyperthyroidism status may develop. These events are involved in the development of atherosclerosis, a direct link to ischemic heart disease. For example, studies have reported that subclinical hyperthyroidism might contribute to increased left ventricular size^{14,15} and elevated systolic pressure, which reduce arterial elasticity and aggravate diastolic dysfunction¹⁶. Furthermore, hypercoagulability, a consequence of the pro-thrombotic effects of subclinical hyperthyroidism can also lead to atherosclerosis development. Second, radioactive iodine exposure might induce arterial atherosclerosis. Animal studies have demonstrated that radioactive iodine can cause atherosclerotic-like plaque formation through endothelial proliferation, chronic fibrosis of the intima and media, and occlusive changes in the vasa vasorum¹⁷⁻¹⁹. Furthermore, the intima-media thickness increased significantly after radioactive iodine ablation in hyperthyroidism patients, indicating the association of progressive atherosclerosis with radioiodine exposure⁶. However, the discrepancy in the odds for CHD and IS incidence in our study, which showed that thyroid cancer patients had a significantly higher risk of fatal and non-fatal CHD but insignificant risk of IS, may be attributed to the different etiologies of the two conditions. In contrast to the homogenous pathophysiology of CHD, where atherosclerosis is the major cause of heart attack, the etiology of IS is more complex. Besides

atherosclerosis, research showed that cardio-embolism, small-vessel occlusion, non-atherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders could lead to IS events²⁰. The heterogeneous etiology results in a more complex association between thyroid cancer and IS.

Our results support the recent recommendations¹³ and have important implications in cardiotoxicity prevention. From a public health perspective, considering cancer as a chronic disease with safe long-term treatment rather than a fatal disease with aggressive intervention may provide pragmatic benefits to cancer patients. Further evidence of the association between radioactive iodine and thyroid stimulating hormone suppression therapies and CHD should be obtained by epidemiology studies.

Limitations

This study has several limitations. First, the relatively short follow-up period limited our ability to detect cardiovascular events and their association with thyroid cancer. However, the inclusion period of thyroid cancer diagnosis allowed the inclusion of the recent recommendations for thyroid cancer management rather than the recommendations prevalent decades ago. Second, although we conducted SIR analysis using age and sex stratification, residual confounding could have been present in our study, such as smoking and history of hypertension, diabetes, and hyperlipidemia. To deal with this, we conducted subgroup-stratified analyses of SIR and the percentage of basic characteristics in our inclusion population. Third, generalizing our results to other ethnic populations or countries should be treated with caution due to the potential differences in the health care systems and resources. Finally, the study findings are observational and cannot be used to establish causality, and further research is warranted.

Conclusion

In conclusion, while there were no significant risks for IS and AF, thyroid cancer survivors, especially young patients, have a significant risk of developing CHD that persists even at long-term follow-up. Further research on the association between thyroid cancer and the odds of CHD, including factors such as diagnosed age, cancer characteristics, and management, should be conducted.

Declarations

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The datasets generated and/or analysed during the current study are not publicly available due to the terms of consent to which the participants agreed but data are however available from the authors upon reasonable request and with permission of the Taiwanese National Health Insurance Research Database of Ministry of Health and Welfare (NHIRD_MOHW), Taiwan Cancer Registry Center and Ministry of Science and Technology (MOST 110-2314-B-195-004)..

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Author Contribution

M.-C.T., W.-C.L., C.-J.C., P.-J.T. and K.-L.C. designed the study. M.-C.T., W.-H.T., P.-J.T. and K.-L.C. contributed to writing of the manuscript. M.-C.T., C.-T. H., H.-Y. H. and T.-L. Y. contributed software and formal analysis. W.-C.L., C.-J.C. and K.-L.C. had project administration and data resources. W.-C.L., B.-Y.H., J.-R.J, and C.-J.C. contributed to collection and/or assembly of data. M.-C.T., W.-H.T., S.-P.C., C.-L.C., C.C.L., S.-C.L. and P.-J.T. contributed to interpretation. M.-C.T. and K.-L.C. had revisions and final approval of the manuscript. K.-L.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Disclosure Statement

All other authors have no potential conflicts of interest relevant to this article.

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Ethics approval and consent to participate:

The Mackay Memorial Hospital Committee Review Board approved the study protocol (IRB 20MMHIS475e approved with exempt review). The authors confirm that all of the research meets the ethics guidelines, including adherence to the legal requirements of the country where the study was performed.

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Figures

Figure 1

Cardiovascular and atrial fibrillation incidence, displayed as standardized incidence ratios (SIR) and 95% confidence intervals subdivided by five cardiovascular and atrial fibrillation endpoints. The blue line crossing SIR 1.0 equals the incidence rate of the general population

Figure 2

Standardized incidence for coronary heart disease at different follow up years stratified by age younger than 65 years old and older than 65

Supplementary Files

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