Actual causes of death in thyroid cancer patients in Korea: A Nationwide Case Control Cohort Study

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Abstract

Objective: Thyroid cancer (TC) incidence has increased robustly in Korea. However, the actual cause of death, overall mortality risk, and cause-specific mortality risk in TC patients have not been clearly elucidated.

Design: Retrospective cohort study.

Methods: We analyzed 4082 TC patients from the Korean National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS, 2002–2013) with a median of 48-month follow-up. We compared these patients with 12 246 controls matched for age, sex, and histories of major cardiovascular disease (CVD) to investigate the cause of death and risks of overall and cause-specific mortality.

Results: Overall, 61 deaths (1.5%) occurred in the TC group. The most common cause of death was TC-specific mortality (32.8%), followed by other malignancy-related mortality (31.1%) and CVD mortality (13.1%). The overall mortality risk was comparable between the TC and control groups (unadjusted hazard ratio (HR): 1.17; 95% confidence interval (CI): 0.87–1.58); the adjusted HR remained at 1.25 (95% CI: 0.90–1.74) after multivariate adjustment for body mass index (BMI), socioeconomic status (SES), smoking, alcohol consumption, and histories of hypertension, diabetes mellitus, and dyslipidemia. In addition, there was not enough evidence against the surmise that the CVD mortality risk was similar between the TC and control groups, with an HR of 0.50 (95% CI: 0.22–1.16) after adjustment for CVD risk factors.

Conclusions: Excellent overall survival was observed in TC patients. The most common cause of death was TC-specific mortality, suggesting the importance of thyroid cancer treatment. The overall and cause-specific mortality risks, particularly CVD mortality risk, did not differ between TC patients and the general population.

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Introduction

Thyroid cancer (TC) is the most common and curable malignancy in the endocrine system, and its rapid increase in incidence has been reported worldwide (1, 2, 3, 4). Particularly in South Korea, the incidence of TC has increased sharply, and it has been the most common cancer among Korean women since 2005 (5, 6, 7). Despite this sharp increase, TC-related mortality is relatively low compared

to that of other cancer types (4, 8). The American Cancer Society reported that the 5-year relative survival rate of TC was 99.7% between 2006 and 2012 (4). Moreover, recent studies have shown that the trend for survival in TC patients has either improved (9, 10, 11) or remained steady (12).

The increasing incidence and high survival rate inevitably raise important questions about the actual

causes of death in TC patients; another question is whether TC patients have higher or comparable mortality risks than the general population. More than 10 years ago, Eustatia-Rutten *et al.* investigated the actual causes of death in differentiated TC (DTC) patients and reported that more than 60% of DTC patients died of a DTC-related cause; other malignancies and cardiovascular disease (CVD) were other common causes of death (13). Thereafter, further studies have been performed on the risks of cardiovascular mortality and overall mortality in TC patients and their comparison with the general population. One study identified increased risks of overall mortality and cardiovascular mortality in DTC patients, compared to the general population (14), while another study did not (15). These inconsistent results can be explained by differences in sample size, proportion of high-risk TC patients, length of follow-up, and statistical methods, leaving this issue open to debate. Moreover, these previous studies had important limitations, such as small sample size of TC patients, relatively high disease-specific mortality rates (up to 65%; compared to the generally known 10-year mortality rate) (1, 3, 9), and discrepancies in CVD history between TC patients and the general population.

Given these data, we compared the actual causes of death and risk of overall mortality, including cause-specific mortality, between TC patients and a general population matched for age, sex, and CVD history using the Korean National Health Insurance Service-Health Screening Cohort data (NHIS-HEALS, 2002–2013).

Subjects and methods

Data source and study population

The Korean NHIS is the sole mandatory public medical insurance system for all citizens of South Korea and is managed by the Korean government. Recently, the NHIS released the NHIS-HEALS database (2002–2013), including 514 866 randomly selected Koreans (approximately 10% of all health screening participants) aged 40–79 years who were eligible for the National Health Screening Program. The database incorporated longitudinal information of participants' demographic, medical, and pharmaceutical records based on the International Classification of Disease, 10th revision (ICD-10); data of medical procedures; hospitalization; biochemical laboratory test results, such as those of blood pressure, fasting glucose, and lipid profiles; and drug prescriptions were recorded.

In addition, the database was merged with death records including the specific causes of death based on the ICD-10 codes, managed by the Korean National Statistical Office. A more detailed cohort protocol is already published elsewhere (16, 17, 18).

This study initially included 6828 newly diagnosed patients with TC of all types (TC group) (ICD-10 C73) registered from January 1, 2004 to December 31, 2013. A total of 4082 TC patients were finally analyzed, after excluding subjects who met the following criteria: (1) patients who did not undergo thyroidectomy after TC diagnosis or had already undergone thyroidectomy 6 months before diagnosis; (2) prior diagnosis of other malignancy (C00–C97, except C73); or (3) history of levothyroxine prescription or radioactive iodine treatments. For selecting individuals for the control group, we excluded the following subjects: (1) patients with a prior diagnosis of any cancer type and (2) those with a history of thyroid disease, thyroidectomy, levothyroxine prescription, or radioactive iodine treatment during the entire study period. We selected control individuals matched for age, sex, and histories of ischemic heart disease (IHD), ischemic stroke (IS), and hemorrhagic stroke (HS) in triplicate. The national insurance claims data inevitably has a limitation for detection of false-positive cases because diagnostic data are based on ICD-10 codes. To minimize this constraint, we performed matching for IHD, IS, and HS, which are the most common and important subcategories of CVD and defined each category in specific detail. IHD was defined as hospitalization due to I20–I25 combined with a procedure of coronary artery angiography. IS was defined as hospitalization owing to I63 with brain imaging study. HS was defined as hospitalization owing to I60–I62 or I64 with brain imaging study. Figure 1 illustrates a schematic diagram of this study.

This study was approved by the Institutional Review Board of the Korea University Anam Hospital (IRB number: ED16255). Informed consent was not required because this study was based on the NHIS database, which are fully anonymized and de-identified for analysis.

Study definition and outcomes

The causes of death were classified according to the ICD-10 codes: TC-specific mortality (C73), CVD mortality (I00–I99), IHD mortality (I20–I25), IS mortality (I63), HS mortality (I60–I62 or I64), other malignancy mortality (C00–C97, except C73), respiratory disease (J00–J99), digestive disease (K00–K95), endocrine disease (E00–E99),

Figure 1

Schematic representation of the study design.

injury/trauma (S00–T98), and unknown/not otherwise specified (NOS).

In TC patients, follow-up time was defined as the time from the date of TC claim to the date of death from any cause or the last date of data collection in this cohort (December 31, 2013). In the control group, follow-up time was defined as the time from the date of the first insurance claim in the same year of the matched TC patient's diagnosis to the date of identical criteria in the matched TC patients.

We also used specific criteria for reducing the possibility of false positive diagnoses. Hypertension was defined as I10–I15 with concurrent hypertension medication prescription or I10–I15 with a systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Diabetes mellitus (DM) was defined as E10–E14 with concurrent diabetes medication prescription or a fasting glucose level ≥ 126 mg/dL, and dyslipidemia was defined as E78 with a total cholesterol level > 240 mg/dL. Socioeconomic status (SES) at baseline was categorized into three groups depending on the individual's income level: lower, 30%; middle, 40%; and upper, 30%.

Statistical analysis

We presented continuous data as mean and standard deviation (s.d.) for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. Categorical data were presented as frequencies and percentages. A generalized estimating equation (GEE) method were used for our matched data to compare personal and clinical demographics between the TC and control groups. The Kaplan–Meier survival

analyses with stratified log-rank tests were performed to compare survival curves between the cohort groups. Independent risk factors associated with patient mortality were evaluated using a stratified Cox regression analysis model with hazard ratios (HRs) and 95% confidence intervals (CIs). All reported *P* values were two-sided, and $P < 0.05$ was considered significant. All statistical analyses were performed using the SAS software, version 9.4 (SAS Institute Inc.), STATA 11.0 (STATA), and GraphPad Prism, version 8 (GraphPad Software).

Results

Baseline characteristics of the study population

The present study included 4082 TC patients (3207 women and 875 men), with a median age of 55 years (IQR: 50–61 years) (Table 1). Histories of IHD, IS, and HS were observed in 1.8% (75/4082), 1.1% (43/4082), and 0.3% (13/4082) of TC patients, respectively, and history of each CVD category was exactly matched between the TC and control groups. Median follow-up time was 48 months (IQR: 25–76 months) in the TC group. Most TC patients underwent total or subtotal thyroidectomy (3475/4082; 85.1%), and half of the patients received radioactive iodine treatment (2145/4082; 52.5%). The previous histories of hypertension (42.8% vs 31.4%), DM (10.3% vs 8.7%) and dyslipidemia (8.9% vs 6.6%) were more frequent in the TC group than in the control group, although no statistical significance was observed. Upper SES levels (52.9% vs 31.4%) were more frequent in the TC group than in the control group. Meanwhile, high alcohol

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Table 1 Baseline demographics of the study population.

	Patients with TC (n = 4082)	Control individuals (n = 12 246)	cOR (95% CI)	P value
Age, median (years, IQR)	55 (50–61)	55 (50–61)	–	–
Female, n (%)	3207 (78.6)	9621 (78.6)	–	–
History of cardiovascular disease, n (%)			–	–
IHD	75 (1.8)	225 (1.8)		
IS	43 (1.1)	129 (1.1)		
HS	13 (0.3)	39 (0.3)		
Follow-up, median (months, IQR)	48 (25–76)	48 (31–82)	–	–
Thyroidectomy, n (%)	4082 (100.0)		–	–
Total + subtotal thyroidectomy	3475 (85.1)	–		
Hemithyroidectomy	607 (14.9)	–		
Levothyroxine, n (%)	3904 (95.6)	–	–	–
Levothyroxine prescription period (days, IQR)	1578 (797.5–2584.5)	–	–	–
Levothyroxine median dosage (IQR)	107.1 (86.9–150.0)	–	–	–
RAI treatment, n (%)	2145 (52.5)	–	–	–
Median cumulative RAI dosage, median (mCi, IQR)	120 (40–150)	–	–	–
BMI, median (kg/m ² , IQR)	24.03 (22.2–26.0)	23.72 (21.9–25.8)	1.00 (1.00–1.00)	0.941
SES, n (%)				
Upper (30%)	2160 (52.9)	4959 (40.5)	1.86 (1.70–2.04)	<0.001
Mid (40%)	1204 (29.5)	4219 (34.5)	1.22 (1.10–1.35)	<0.001
Lower (30%)	718 (17.6)	3068 (25.1)	1 (reference)	
Smoking, n (%)				
Never	3503 (85.8)	10 185 (83.2)	1 (reference)	
Ex-smoker	284 (7.0)	735 (6.0)	1.12 (1.00–1.27)	0.059
Current	211 (5.2)	1054 (8.6)	0.58 (0.51–0.67)	<0.001
Unknown	84 (2.0)	272 (2.2)	–	–
Alcohol consumption, n (%)				
Never	3090 (75.7)	8774 (71.7)	1 (reference)	
≤2 times a week	765 (18.7)	2531 (20.7)	0.86 (0.80–0.93)	<0.001
≥3 times a week	181 (4.4)	801 (6.5)	0.64 (0.55–0.75)	<0.001
Unknown	46 (1.2)	140 (1.1)	–	–
Hypertension, n (%)	1746 (42.8)	3844 (31.4)	1.00 (1.00–1.00)	0.188
DM, n (%)	419 (10.3)	1068 (8.7)	1.00 (1.00–1.01)	0.807
Dyslipidemia, n (%)	362 (8.9)	806 (6.6)	1.00 (1.00–1.01)	0.279

All P values were calculated by generalized estimating equation (GEE) method.

CI, confidential interval; cOR, crude odd ratio; DM, diabetes mellitus; HS, hemorrhagic stroke; IHD, ischemic heart disease; IQR, interquartile range; IS, ischemic stroke; RAI, radioactive iodine; TC, thyroid cancer.

consumption (≥3 times a week) (4.4% vs 6.5%) and current smoking (5.2% vs 8.6%) were less frequent in the TC group than in the control group. BMI was comparable between the TC and control groups.

Cause of death and overall mortality risk in the TC and control groups

During 2004–2013, a total of 61 deaths occurred in the TC group, along with 178 deaths in the control group. The specific causes of death are summarized in Table 2. The most frequent cause of death in the TC group was TC-related mortality (20/61, 32.8%), followed by other malignancies (19/61, 31.1%), CVD (8/61, 13.1%), injury/trauma (8/61, 13.1%), and unknown/NOS (5/61, 8.2%).

No deaths were caused by respiratory or digestive disease. In the control group, the most frequent cause of death was malignancies other than TC (59/178, 33.1%), followed by CVD (51/178, 28.7%), injury/trauma (30/178, 16.9%), respiratory disease (7/178, 3.9%), and unknown/NOS (27/178, 15.2%).

All-cause mortality was comparable between the TC and control groups (1.49 vs 1.45%), with an unadjusted HR of 1.17 (95% CI, 0.87–1.58), which remained at 1.25 (95% CI, 0.90–1.74) after adjustment for BMI, SES, smoking, alcohol consumption, and histories of hypertension, DM, and dyslipidemia (Table 3). Other malignancy-related mortality was also similar between the TC and control groups (31.1 vs 33.1%), with an unadjusted HR of 1.04 (95% CI, 0.61–1.75),

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Table 2 Specific causes of deaths in the thyroid cancer and control groups.

	TC, n (%)	Control, n (%)	P value
Total, n	4082	12 246	
Overall mortality, n	61	178	0.815
TC-specific mortality	20 (32.8)	0 (0.0)	–
CVD	8 (13.1)	51 (28.7)	0.044
IHD	1 (1.6)	13 (7.3)	0.157
IS	2 (3.3)	3 (1.7)	0.447
HS	2 (3.3)	16 (9.0)	0.190
Other malignancies	19 (31.1)	59 (33.1)	0.874
Respiratory disease	0 (0.0)	7 (3.9)	–
Digestive disease	0 (0.0)	2 (1.1)	–
Endocrine disease	1 (1.6)	2 (1.1)	0.741
Injury/trauma	8 (13.1)	30 (16.9)	0.580
Unknown/NOS	5 (8.2)	27 (15.2)	0.227

All P values were calculated by generalized estimating equation (GEE) method.

CVD, cardiovascular disease; HS, hemorrhagic stroke; IHD, ischemic heart disease; IS, ischemic stroke; NOS, not otherwise specified; TC, thyroid cancer.

which remained at 1.09 (95% CI, 0.61–1.97) after adjustment for BMI, SES, smoking, and alcohol consumption history. Regarding CVD mortality, the absolute mortality rate was lower in the TC group than in the control group (13.1 vs 28.7%); however, there was not enough evidence against the surmise that the CVD mortality risk was similar between two groups, with an HR of 0.50 (95% CI, 0.22–1.16) after adjustment for BMI, SES, smoking, alcohol consumption, and histories of hypertension, DM, and dyslipidemia. The Kaplan–Meier survival curves for each end-point are depicted in Fig. 2. No significant differences were observed in all-cause mortality (log-rank $P=0.292$; Fig. 2A), other malignancy-related mortality (log-rank $P=0.140$; Fig. 2B), and CVD mortality (log-rank $P=0.893$; Fig. 2C) between the TC and control groups.

Table 3 Comparison between overall, cardiovascular, and other malignancy mortalities.

	Mortality, n (%)	Unadjusted		Adjusted	
		HR (95% CI)	P value [‡]	HR (95% CI)	P value [‡]
Overall mortality					
Control	178/12 246 (1.45)	1 (reference)		1 (reference)	
TC	61/4082 (1.49)	1.17 (0.87–1.58)	0.293	1.25 (0.90–1.74)*	0.182
CVD mortality					
Control	51/12 246 (0.42)	1 (reference)		1 (reference)	
TC	8/4082 (0.20)	0.57 (0.27–1.22)	0.145	0.50 (0.22–1.16)*	0.106
Other malignancy mortality					
Control	59/12 246 (0.48)	1 (reference)		1 (reference)	
TC	19/4082 (0.47)	1.04 (0.61–1.75)	0.893	1.09 (0.61–1.97) [†]	0.763

*Adjusted for body mass index (BMI), socioeconomic status (SES), smoking, alcohol consumption, and previous history of hypertension, diabetes mellitus, and dyslipidemia. [†]Adjusted for BMI, SES, smoking, and alcohol consumption. [‡]Stratified Cox's PH regression analysis were performed to obtain the hazard ratio (HR) and 95% confidence.

95% CI, confidence interval; CVD, cardiovascular disease; TC, thyroid cancer.

Discussion

Over the past several decades, numerous studies have been reported on TC, particularly on the TC-specific mortality rate and its trends. Although many of the related aspects remain controversial, it has been accepted that the TC-related mortality rate is relatively low (1, 4, 9, 19). However, the actual causes of death in TC patients have not been clearly elucidated. In this context, we present the largest study to date that investigates the causes of death and risks of overall and cause-specific mortality in TC patients, compared to that in the general population. The most common cause of death in TC patients was TC-specific mortality, followed by other malignancy-related mortality and CVD mortality. Notably, the major causes of death, particularly CVD mortality, were not significantly higher in TC patients than in the general population matched for age, sex, and CVD history.

Recently, there has been a growing interest in determining whether an increase in CVD mortality risk is related to TC treatments (such as thyroid hormone suppression therapy). Klein Hesselink *et al.* reported that DTC patients had a 3.3-fold-higher CVD mortality risk and a 4.4-fold-higher all-cause mortality risk than age- and sex-matched control subjects (14). In this study, the all-cause mortality in DTC patients, during a median follow-up time of 8.5 years, was reported to be approximately 20%, which is relatively high compared to that in other studies (11, 20). The EUROcare-5 study, which included 29 European countries, reported that the observed 5-year survival rate in the Netherlands was the lowest among Central European countries, both in women and men. Another study from Finland, analyzing 901 DTC patients with a median follow-up time of 18.8 years, showed that all-cause mortality was 27.7% in DTC patients and that no

Figure 2

Kaplan-Meier survival curves for (A) overall, (B) cardiovascular disease, and (C) other malignancy mortality in patients with thyroid cancer compared with controls.

significant differences were observed in overall mortality between the DTC and control groups. Moreover, CVD mortality was significantly lower in DTC patients than in control subjects (15). Our study also showed that absolute IHD (1.6 vs 7.3%) and HS (3.3 vs 9.0%) deaths as well as total CVD death (13.1 vs 28.7%) were lower in TC patients than in the general population (13.1 vs 28.7%). These lower mortalities can be explained by early detection of severe CVD and related risk management during the follow-up period after thyroidectomy. Taken together, these results highlight the fact that differences in population parameters and study designs, including distinct follow-up periods, may lead to inconsistent conclusions; this warrants larger and better-standardized international studies to arrive at definite conclusions.

Regarding the other malignancy-related deaths, the second most common cause of death in the TC group was comparable between the TC and control groups. We also performed subgroup analysis on the association between TC treatment, such as radioactive iodine (RAI) treatment, and other malignancy-related mortality risks in the TC group. However, no significant relationship was observed due to the short-term follow-up period and low absolute event number.

Unlike previous studies, this study performed matching for histories of IHD, IS, and HS, in addition to age and sex, between the TC and control groups. Moreover, we used a more precise definition of CVD to minimize the inclusion of false-positive cases. Since CVD history is a well-known risk factor for CVD mortality (21), our study design had a significant strength in detecting the differences in CVD mortality between the two groups. Another strength of our study is a stringent death registration process, mandatorily administrated by the Korean National Statistical Office.

Nevertheless, several limitations of this study need to be mentioned. The NHIS-HEALS cohort only included participants aged between 40 and 79 years, limiting the generalization of these results to patients aged <40 and ≥80 years. However, the incidence of newly diagnosed TC increases sharply after the age of 45 years (22), and the majority of adverse clinical outcomes, including cancer-specific death, occur in patients aged between 40 and 80 years (23). Another major limitation of this study is the relatively short follow-up time, which does not completely cover the natural course of overall TC mortality. Therefore, a more careful interpretation is needed for forming definite conclusions due to possibly insufficient statistical power by relatively short-term follow-up period and small number of events (24, 25). Third, we did not include information of clinicopathological characteristics, such as pathological

subtype and stage, that affect TC prognosis. Several reports have revealed that the vast majority of TC cases in Korea involve DTC, particularly papillary TC, accounting for up to 97% of the total TC patient population (5, 6, 26). However, this fact has two facets. One is that the TC group in this study may predominantly consist of PTC, however, the proportion of TC patients with low-risk tumors having excellent prognoses and low disease-specific mortality is also very high. Therefore, it can be a challenging task to generalize our results to other populations, which present relatively high-risk clinicopathological characteristics. Lastly, we did not demonstrate the association between TSH suppression therapy and mortality risk due to the lack of information on TSH levels. This limitation gives us the potential pitfall of passing over the impact of long-term TSH suppression therapy on the mortality risk in high-risk and low-risk TC patients.

In conclusion, this study assesses the causes of death and risks of overall and cause-specific mortality in TC patients, compared with a general population matched for age, sex, and previous CVD history, using a nationwide database. Excellent overall survival was observed in TC patients. Nevertheless, the most common cause of death was TC-specific mortality, suggesting the importance of thyroid cancer treatment. The risks of other malignancy-related mortality and CVD mortality, the major causes of death in TC patients, were not significantly different between TC patients and the general population. Although the potential adverse clinical outcomes of TC patients on the overall and CVD mortalities are still debatable, our study, using a large study sample, contributes evidence that supports further investigation of long-term management in TC patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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