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Risk of Osteoporotic Fractures among Patients with Thyroid Cancer: A Nationwide Population-Based Cohort Study

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Background: The associations between thyroid cancer and skeletal outcomes have not been thoroughly investigated. We aimed to investigate the risk of osteoporotic fractures in patients with thyroid cancer compared to that in a matched control group.

Methods: This retrospective cohort study included 2,514 patients with thyroid cancer and 75,420 matched controls from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC, 2006–2019). The rates of osteoporotic fractures were analyzed, and associations with the levothyroxine dose were evaluated.

Results: Patients with thyroid cancer had a significantly lower risk of fracture than did the control group (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.69 to 0.94; $P=0.006$). Patients diagnosed with thyroid cancer after the age of 50 years (older cancer group) had a significantly lower risk of fracture than did those in the control group (HR, 0.72; 95% CI, 0.6 to 0.85; $P<0.001$), especially those diagnosed with spinal fractures (HR, 0.66; 95% CI, 0.51 to 0.85; $P=0.001$). Patients in the older cancer group started osteoporosis treatment earlier than did those in the control group (65.5±7.5 years vs. 67.3±7.6 years, $P<0.001$). Additionally, a lower dose of levothyroxine was associated with a reduced risk of fractures.

Conclusion: In the clinical setting, the risk of fracture in women diagnosed with thyroid cancer after the age of 50 years was lower than that in the control group, which was caused by more proactive osteoporosis treatment in postmenopausal women with thyroid cancer.

Keywords: Thyroid neoplasm; Osteoporosis; Fractures

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INTRODUCTION

Until recently, the prevalence of thyroid cancer has been increasing worldwide [1,2]. Although the survival rate depends on factors such as the type and stage of cancer, the patient's age and overall health condition, and the type of treatment received, the overall 5-year survival rate for thyroid cancer patients is >95% [3]. The incidence of thyroid cancer is highest in young and middle-aged adults, with most cases occurring between the ages of 25 and 65 years [4]. Thyroid cancer is commonly diagnosed at a relatively young age, and its high survival rate has led to an increasing number of survivors. Therefore, patients with thyroid cancer could undergo longer follow-up and monitoring and may be at greater risk of long-term complications, including osteoporosis and cardiovascular disease, due to the need for thyroid-stimulating hormone (TSH) suppression therapy [5,6]. Accordingly, long-term management for thyroid cancer survivors is necessary not only to ensure the early detection of cancer recurrence but also to monitor various diseases that could be induced by cancer treatment [7,8].

Several meta-analyses have reported that TSH suppression in patients with thyroid cancer causes a reduction in bone mineral density (BMD) in postmenopausal women [7,9]. The results revealed that postmenopausal women showed a decrease in BMD at the lumbar spine and total hip, whereas premenopausal women with thyroid cancer exhibited an increase in BMD during TSH suppression therapy [7]. These findings suggest that estrogen-related differences may affect changes in BMD, as supported by other meta-analyses [10].

However, regarding the occurrence of osteoporotic fractures in patients with thyroid cancer, a few large cohort studies have found no significant difference in fracture rate when comparing fractures in patients with thyroid cancer and control groups [11-13]. Therefore, it is difficult to establish whether patients with thyroid cancer are at high risk for developing osteoporotic fractures.

The aim of this study was to investigate the risk of osteoporotic fractures in patients with thyroid cancer compared to that in a matched control group. We also sought to determine the association between levothyroxine dose and osteoporotic fractures in patients with thyroid cancer.

METHODS

Ethics approval

This study was conducted in accordance with the Helsinki Declaration and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting standards. The requirement for informed consent was waived because all National Health Insurance Service (NHIS) data were anonymized and deidentified before use (IRB No. DKUH 2021-10-029).

Data source

The NHIS-National Sample Cohort (NSC) was first established in 2006 and was followed up until 2019. Retrospective data from 1,137,861 individuals obtained from 2002 to 2005 were combined with the original data. A total of 364,274 subjects aged ≥40 years in 2006 who had undergone at least one health examination were selected [14].

Thyroid cancer group

All patients with an incident diagnosis of thyroid cancer were identified by the International Classification of Diseases, 10th revision (ICD-10) codes for thyroid cancer (C73) at least twice [15] between January 1, 2006, and December 31, 2019. The exclusion criteria were as follows: (1) diagnosis of other malignancies (C00–C97, except C73) before the diagnosis of thyroid cancer; (2) no thyroid surgery or thyroidectomy performed prior to 2006; (3) missing baseline key information; (4) <40 years as of 2006; (5) prescribed steroids for >90 days between 2002 and 2019; and (6) diagnosed with osteoporosis within 1 year of thyroid cancer diagnosis or 2 years before thyroidectomy (Fig. 1). The date of the first thyroidectomy was considered the index date for patients in the thyroid cancer group. Based on the age at thyroid cancer diagnosis, the group diagnosed before age 50 years was defined as the younger cancer group, and the group diagnosed after age 50 years was defined as the older cancer group.

Control group

The control group was identified from the cohort based on the following algorithm: first, individuals with any codes of malignancies (C00–C97) between 2002 and 2019 were excluded; second, we excluded individuals who had prescriptions for thyroid hormone or who had undergone thyroidectomy between 2002 and 2019; and third, we randomly assigned an index date to each individual from the collection of index dates of patients in the thyroid cancer group. Finally, we excluded individuals in the control group if any of the following criteria were met at the index date: (1) last follow-up on or before the index date; (2) death on or before the index date; (3) missing baseline information; (4) prescribed steroids for >90 days between 2002 and

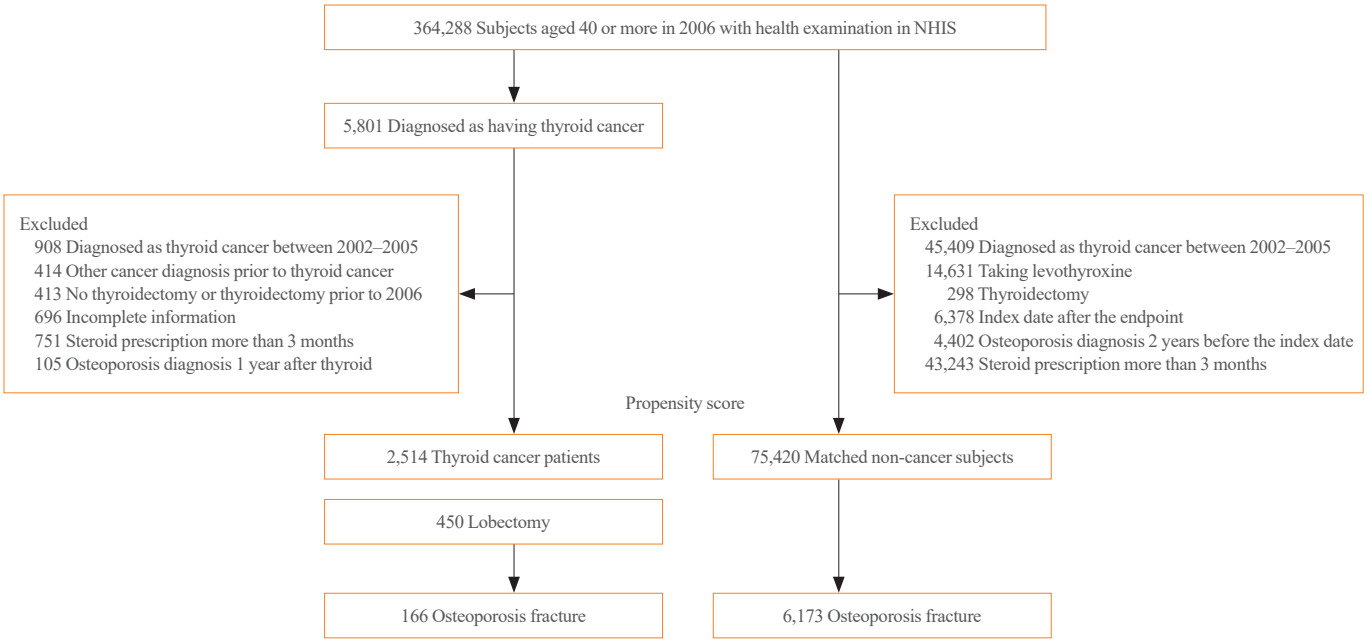

Fig. 1. Flowchart of the study population. NHIS, National Health Insurance Service.

2019; or (5) diagnosed with osteoporosis 2 years before the index date (Fig. 1).

Study outcomes

The primary outcome was the risk of osteoporotic fractures, including those of the spine, hip, humerus, and wrist [16,17]. Osteoporotic fracture is defined as a fracture in these areas that occurs without significant trauma. In cases where the subject had multiple fractures, the earliest fracture was used for analysis. The definition of osteoporosis treatment was based on the ICD-10 codes for osteoporosis (M80–M82) and the use of oral osteoporosis treatment for ≥6 months or at least one prescription of injectable osteoporosis treatment. The osteoporosis medication and diagnostic codes for fractures are summarized (Supplemental Table S1). Patients were followed from the index date until the date of fracture, loss to follow-up, or December 31, 2019, whichever came first.

Covariates

Demographic characteristics, including age at the index date, sex, income (lower, 40%; middle, 30%; and upper, 30%), body mass index (BMI), smoking status (none, ex-, or current smoker), alcohol consumption (none; mild to moderate as 1–5 times a week and <7 drinks on any day per week; or heavy as >6 times a week or ≥7 drinks on any day per week), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), and total cholesterol at the index date, were assessed based on a health examination. The history of diabetes, hypertension, hyperlipidemia, cerebrovascular disease, and ischemic heart disease at the index date was assessed based on claims using ICD-10 codes prior to the index date.

For patients with thyroid cancer, the levothyroxine doses were assessed using electronic prescription records for levothyroxine sodium. The daily doses and prescription durations were obtained for each prescription. If subsequent prescriptions were issued before or at the end of a previous prescription, the previous prescription was replaced by the new prescription. To account for time-varying levothyroxine doses during follow-up, the average daily levothyroxine dose (μg/kg/day) was defined as the cumulative levothyroxine dose divided by the total number of days of levothyroxine use per year and body weight and was assessed each year during the follow-up period. Calcium and vitamin D supplements were calculated by dividing the cumulative doses by the total number of days of prescription. This evaluation was performed exclusively in the thyroid cancer group because the claims data for calcium and vitamin D supplements may have been less accurate in the control group.

Statistical analysis

The baseline demographics, clinical characteristics, and medical history are presented as medians (interquartile ranges) for continuous data and frequencies (percentages) for categorical data.

Propensity score matching with a matching ratio of 30:1 was performed to balance the distribution of covariates between the thyroid cancer and control groups. The propensity scores were estimated using a logistic regression model that included the index date (formatted as 'year-month'), age at the index date, sex, income, BMI, smoking status, alcohol consumption, SBP, DBP, FPG, total cholesterol, and history of diabetes, hypertension, hyperlipidemia, cerebrovascular disease, and ischemic heart disease at the index date. The covariate balance between the thyroid cancer and control groups was assessed using standard mean differences (SMDs), where an SMD of <10% indicates good balance.

Crude incidence rates per 1,000 person-years were calculated for the occurrence of osteoporotic fractures and treatment. The risk of osteoporotic fracture by location was evaluated using competing risk analysis, where death and spine, hip, humerus, and wrist fractures were considered competing events. Kaplan–Meier estimates were used to estimate the survival probability for patients with osteoporotic fractures. Cumulative incidence estimates for the occurrence of osteoporotic fractures by loca-

Table 1. Characteristics of Patients with Thyroid Cancer and Matched Controls

Baseline variable	Total thyroid cancer (*n*=2,514)	1:30 Matched control (*n*=75,420)	Standardized difference after matching, %
Age, yr	54 (50–60)	54 (50–61)	2.3
Sex			1.5
Women	2,065 (82.1)	62,394 (82.7)	
Men	449 (17.9)	13,026 (17.3)	
BMI, kg/m^2	24 (22.2–26.1)	23.9 (22–26.1)	4.5
Body weight, kg	60 (54–67)	59 (54–66)	6.3
Income			4.2
Low	724 (28.8)	22,739 (30.1)	
Middle	610 (24.3)	18,824 (25)	
High	1,180 (46.9)	33,857 (44.9)	
Smoking			0.8
None	2,173 (86.4)	65,352 (86.7)	
Ex-smoker	180 (7.2)	5,246 (7)	
Current	161 (6.4)	4,822 (6.4)	
Alcohol consumption			0.7
None	1,856 (73.8)	55,589 (73.7)	
Mild to moderate	487 (19.4)	14,783 (19.6)	
Heavy	171 (6.8)	5,048 (6.7)	
Clinical data			
SBP, mm Hg	123 (112.25–132)	121 (111–132)	2.1
DBP, mm Hg	78 (70–82)	78 (70–82)	2.8
FPG, mg/dL	95 (87–105)	94 (87–104)	0.8
TC, mg/dL	199 (175–224)	199 (175–225)	0.1
Comorbidities			
Diabetes	619 (24.6)	17,577 (23.3)	3.1
Hypertension	1,083 (43.1)	30,949 (41)	4.1
Hyperlipidemia	1,181 (47)	32,858 (43.6)	6.9
Cerebrovascular disease	249 (9.9)	7,490 (9.9)	0.1
Cardiovascular disease	299 (11.9)	8,914 (11.8)	0.2

Values are expressed as median (interquartile range) or number (%). Household income information was grouped into categories based on the following percentages: lower, 40%; middle, 30%; and upper, 30%. The alcohol consumption categories were as follows: none, mild to moderate (1–5 times a week and <7 drinks on any day per week), and heavy (>6 times a week or ≥7 drinks on any day per week).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol.

tion were obtained using Aalen–Johansen estimates.

Using propensity score-matched data, Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and its robust standard error for each osteoporosis outcome, considering the correlation between observations within matching pairs. For the thyroid cancer group, subgroup analyses were performed to evaluate the effect of levothyroxine dose, vitamin D intake, and calcium intake on each osteoporosis outcome using a multivariate Cox regression model with time-varying exposures.

Dose-response analyses were conducted to examine the overall or non-linear relationship between levothyroxine dose and osteoporotic fractures in levothyroxine users. To characterize the relationship between the dose of levothyroxine and the incidence of osteoporotic fractures, the levothyroxine dose was treated as a continuous variable and analyzed using restricted cubic spline analysis, with five knots located at the 5th, 25th, 50th, 75th, and 95th percentiles of the levothyroxine dose. The reference dose of levothyroxine was 1.60 μg/kg/day. All the statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA), with *P* values <0.05 indicating statistical significance.

RESULTS

Characteristics of the thyroid cancer patients and controls

After propensity score matching at a ratio of 1:30, a total of 2,514 patients with thyroid cancer and 75,420 matched controls were selected from the cohort (Fig. 1). We found no significant differences in clinical characteristics, including age, sex, income level, smoking and alcohol history, anthropometric measures, laboratory values, or underlying diseases, between the thyroid cancer patients and control participants (Table 1). The median age of the subjects was in the mid-50s, women accounted for more than 80% of the population, and the median BMI was 24 kg/m^2. Among all patients with thyroid cancer, 2,064 (82.1%) underwent total thyroidectomy, and 450 (17.9%) underwent lobectomy. The proportion of men was slightly greater in the lobectomy group (21.1% vs. 17.2%, *P*=0.055), and the ratio of smokers and drinkers was greater in the lobectomy group (*P*=0.024 and *P*=0.031, respectively) (Supplemental Table S2).

Risk of osteoporotic fracture in patients with thyroid cancer

During the study period, 166 (6.6%) and 6,173 (8.2%) patients with osteoporotic fractures were identified in each group (Table 2). The incidence of osteoporotic fractures was 9.0 and 11.2 per 1,000 person-years in the thyroid cancer and control groups, respectively (Table 2). The HR of thyroid cancer for osteoporotic fractures was 0.81 (95% confidence interval [CI], 0.69 to 0.94; *P*=0.006). Additionally, there was no significant difference in fractures between the thyroid cancer group and the control group in men, whereas in women, the incidence of fractures was significantly lower in the thyroid cancer group (HR, 0.81; 95% CI, 0.7 to 0.95; *P*=0.01).

Because fractures were mainly identified in women, we performed an analysis by dividing women according to whether they were younger or older than 50 years at the time of thyroid cancer diagnosis. There was no significant difference in the occurrence of fractures between women who were diagnosed with thyroid cancer when they were younger than 50 years (younger cancer group) and women who were not (Table 2). However, women who were diagnosed with thyroid cancer when they were older than 50 years (older cancer group) had a significantly reduced risk of fracture (HR, 0.72; 95% CI, 0.6 to 0.85; *P*<0.001).

Timing and effect of osteoporosis treatment in patients with thyroid cancer

During the study period, 281 (11.2%) patients with thyroid can-

Table 2. Risk of Osteoporotic Fractures in Patients with Thyroid Cancer

Outcome	Total thyroid cancer		Control		HR (95% CI)	*P* value
	No. of events (%)[a]	Incidence rate, /1,000 PY	No. of events (%)[a]	Incidence rate, /1,000 PY		
Overall	166 (6.6)	9.03 (7.76–10.51)	6,173 (8.2)	11.17 (10.90–11.45)	0.81 (0.69–0.94)	0.006
Men	9 (2.0)	2.81 (1.46–5.40)	384 (2.9)	3.97 (3.59–4.39)	0.71 (0.37–1.37)	0.306
Women	157 (7.6)	10.34 (8.84–12.09)	5,789 (9.3)	12.7 (12.38–13.03)	0.81 (0.70–0.95)	0.010
Age <50 years[b]	27 (5.3)	6.98 (4.84–5.60)	723 (3.9)	5.21 (4.84–5.60)	1.33 (0.91–1.96)	0.143
Age ≥50 years[b]	130 (6.5)	11.49 (9.68–13.65)	5,066 (8.9)	15.98 (15.55–16.43)	0.72 (0.60–0.85)	<0.001

PY, person-year; HR, hazard ratio; CI, confidence interval.
[a]Percentage of events of all participants; [b]Age at diagnosis of thyroid cancer or inclusion in the study.

Table 3. Status and Timing of Osteoporosis Treatment in Patients with Thyroid Cancer

Osteoporosis treatment	Total thyroid cancer		Control		HR (95% CI)	*P* value
	No. (%)[a]	Treatment rate, /1,000 PY	No. (%)[a]	Treatment rate, /1,000 PY		
Overall	281 (11.2)	15.64 (13.91–17.58)	7,411 (9.8)	13.39 (13.09–13.70)	1.17 (1.04–1.31)	0.010
Men	3 (0.1)	0.93 (0.30–2.88)	47 (0.06)	0.48 (0.36–0.64)	1.95 (0.60–6.31)	0.267
Women	278 (11.1)	18.86 (16.77–21.22)	7,364 (9.8)	16.16 (15.80–16.54)	1.16 (1.03–1.31)	0.012
Age <50 years[b]	31 (1.2)	7.95 (5.59–11.30)	622 (0.8)	4.43 (4.09–4.79)	1.78 (1.24–2.56)	0.002
Age ≥50 years[b]	247 (9.8)	22.79 (20.12–25.85)	6,742 (8.9)	21.40 (20.89–21.91)	1.06 (0.93–1.20)	0.387
Age at starting osteoporosis treatment, yr						
Age <50 years[b]	54.6±3.0		54.6±2.8			0.896
Age ≥50 years[b]	65.5±7.5		67.3±7.6			<0.001
Time from index date to osteoporotic fracture, mo						
Age <50 years[b]	73.0±42.1		71.5±37.6			0.833
Age ≥50 years[b]	63.4±32.5		50.8±33.9			<0.001

Values are expressed as mean±standard deviation unless otherwise indicated.
PY, person-year; HR, hazard ratio; CI, confidence interval.
[a]Percentage of events of all participants; [b]Age at diagnosis of thyroid cancer or inclusion in the study.

Table 4. Risk of Osteoporotic Fracture by Site

	Total thyroid cancer			Control			HR (95% CI)	*P* value
	No. of events (%)[a]	Incidence rate, 1,000 PY	Cumulative incidence at 10 years, % (95% CI)	No. of events (%)[a]	Incidence rate, 1,000 PY	Cumulative incidence at 10 years, % (95% CI)		
Total								
Spine	58 (35.0)	3.16 (2.44–4.08)	3.70 (2.70–4.90)	2,659 (43.1)	4.84 (4.63–4.99)	4.50 (4.40–4.70)	0.66 (0.51–0.85)	0.001
Hip	15 (9.0)	0.82 (0.49–1.35)	0.88 (0.50–1.40)	495 (8.0)	0.90 (0.82–0.98)	0.86 (0.78–0.95)	0.91 (0.55–1.52)	0.722
Humerus	18 (10.8)	0.98 (0.62–1.55)	1.00 (0.59–1.70)	511 (8.3)	0.92 (0.85–1.01)	0.88 (0.8–0.97)	1.06 (0.66–1.69)	0.814
Wrist	75 (45.2)	4.08 (3.25–5.12)	3.80 (2.90–4.80)	2,508 (40.6)	4.54 (4.36–4.72)	4.30 (4.10–4.40)	0.90 (0.72–1.13)	0.365
Age <50 years[b]								
Spine	12 (41.4)	2.54 (1.44–4.47)	2.60 (1.30-4.80)	306 (38.0)	1.76 (1.57–1.97)	1.70 (1.50–1.90)	1.44 (0.81–2.57)	0.213
Hip	1 (3.4)	0.21 (0.03–1.50)	0.20 (0.02-1.10)	43 (5.3)	0.25 (0.18–0.33)	0.27 (0.19–0.37)	0.86 (0.12–6.22)	0.878
Humerus	4 (13.8)	0.85 (0.32–2.26)	0.95 (0.30-2.40)	84 (10.4)	0.48 (0.39–0.60)	0.47 (0.37–0.59)	1.75 (0.64–4.78)	0.275
Wrist	12 (41.4)	2.54 (1.44–4.47)	2.30 (1.10-4.00)	374 (46.3)	2.15 (1.94–2.38)	2.10 (1.90–2.40)	1.18 (0.66–2.10)	0.575
Age ≥50 years[b]								
Spine	46 (33.6)	3.37 (2.52–4.50)	4.20 (2.90–5.70)	2,353 (43.8)	6.22 (5.97–6.47)	5.90 (5.60–6.20)	0.54 (0.40–0.72)	<0.001
Hip	14 (10.2)	1.02 (0.61–1.73)	1.10 (0.64–1.90)	452 (8.4)	1.19 (1.09–1.31)	1.10 (1.00–1.30)	0.86 (0.50–1.45)	0.562
Humerus	14 (10.2)	1.02 (0.61–1.73)	1.10 (0.56–2.00)	427 (8.0)	1.13 (1.03–1.24)	1.10 (0.96–1.20)	0.90 (0.53–1.54)	0.713
Wrist	63 (46.0)	4.61 (3.60–5.90)	4.30 (3.20–5.50)	2,134 (39.8)	5.64 (5.40–5.88)	5.20 (4.90–5.40)	0.82 (0.64–1.05)	0.119

PY, person-year; CI, confidence interval; HR, hazard ratio.
[a]Percentage of all fractures; [b]Age at diagnosis of thyroid cancer or inclusion in the study.

cer and 7,411 (9.8%) controls were treated for osteoporosis. Patients with thyroid cancer received more osteoporosis treatment than controls did (HR, 1.17; 95% CI, 1.04 to 1.31; $P<0.001$) (Table 3). The older patients in the cancer group were significantly younger at the start of osteoporosis treatment than were those in the control group (65.5±7.5 years vs. 67.3±7.6 years, $P<0.001$). Additionally, the time from enrollment to fracture onset was significantly longer in the older cancer group than in the control group (63.4±32.5 months vs. 50.8±33.9 months, $P<0.001$). However, there was no significant difference in the age at which osteoporosis treatment was initiated between the younger cancer group and the control group (54.6±3.0 vs. 54.6±2.8, $P=0.896$), nor was there a significant difference in the time from enrollment to fracture occurrence (73.0±42.1 months vs. 71.5±37.6 months, $P=0.833$).

Risk of osteoporotic fractures by site

The wrist was the most common fracture site in the thyroid cancer group, followed by the spine, humerus, and hip, whereas the spine was the most common site in the control group, followed by the wrist, humerus, and hip. The thyroid cancer group had a significantly lower HR than the control group for spine fractures only (HR, 0.66; 95% CI, 0.51 to 0.85; $P=0.001$) (Table 4, Fig. 2), while no significant differences were found for other sites, which was mainly observed in the older cancer group (HR, 0.54; 95% CI, 0.4 to 0.72; $P<0.001$).

Effect of levothyroxine, vitamin D, and calcium dose on osteoporotic fractures in patients with thyroid cancer

The HR for osteoporotic fractures according to daily levothyroxine dose was plotted as a cubic curve using a restrictive cubic spline curve. The relationship between levothyroxine dose and fracture risk does not exhibit a significant non-linear association (Fig. 3). In patients with thyroid cancer, the dosages of vitamin D and calcium were not significantly associated with the risk of fracture (Supplemental Table S3).

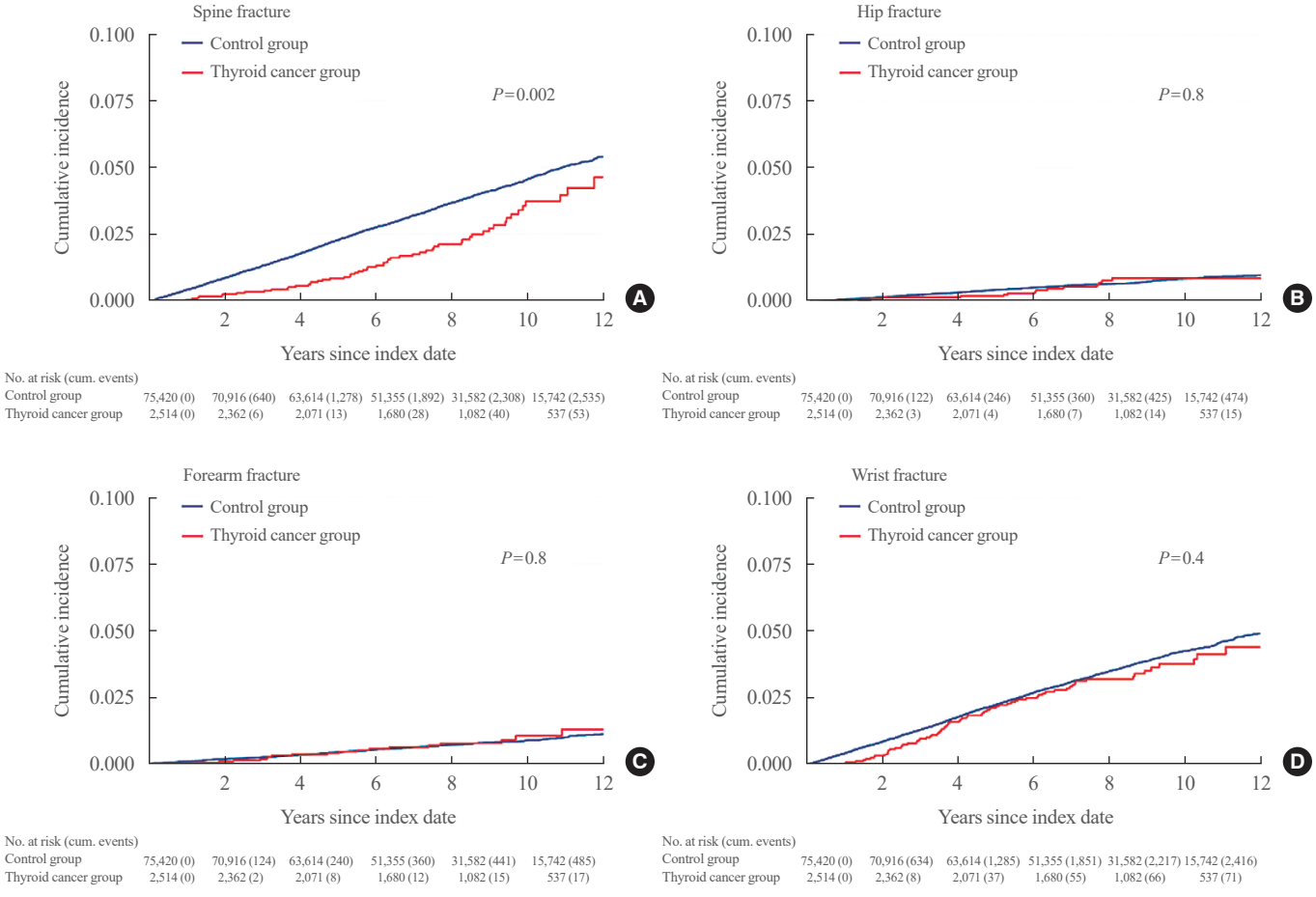

Fig. 2. Survival curve for fracture by site. (A) Spine fracture, (B) hip fracture, (C) forearm fracture, and (D) wrist fracture.

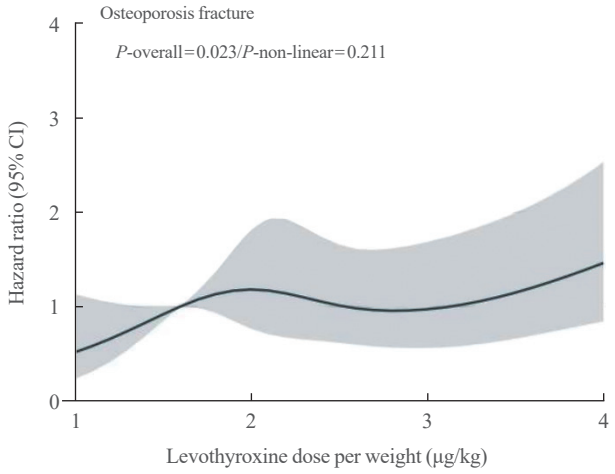

Fig. 3. Hazard ratios of osteoporotic fracture according to the daily dose of levothyroxine in patients with thyroid cancer by restricted cubic spline Cox regression analysis. Estimates were adjusted for index date, age at index date, sex, income, body mass index, drinking status, smoking status, blood pressure, fasting glucose level, cholesterol, diabetes, hypertension, hyperlipidemia, cerebrovascular disease, and cardiovascular disease. CI, confidence interval.

DISCUSSION

In this retrospective cohort study, we found that the risk of fracture, particularly spinal fracture, in women diagnosed with thyroid cancer after the age of 50 years was significantly lower than that in the control group. Moreover, in the older cancer group, osteoporosis treatment started earlier, and fractures occurred later in the cancer group than in the control group. These findings provide new insights into the association between thyroid cancer and osteoporosis-related complications, which may influence clinical decision making for patients with thyroid cancer.

Traditionally, osteoporosis occurs more frequently among postmenopausal women and older men (>70 years) who receive TSH suppression treatment because of thyroid cancer [18]. Patients undergoing treatment for thyroid cancer, particularly with TSH suppression therapy, may experience a reduction in BMD, which could predispose them to earlier initiation of osteoporosis treatment and a longer duration to fracture onset. In our study, it can be assumed that osteoporosis was diagnosed more often in the thyroid cancer group because patients with thyroid cancer were prescribed more osteoporosis treatments. Therefore, treatment for thyroid cancer can be a risk factor for developing osteoporosis. However, although fractures are a well-known complication of osteoporosis, the incidence of fractures decreased in the older thyroid cancer group in our study. This finding is probably explained by a greater probability of treating patients with thyroid cancer at an older age, as recommended by the current guidelines. The American Thyroid Association and the Korean Thyroid Association recommended the surveillance of bone mass during TSH suppression in patients with thyroid cancer, as well as a tailored approach to TSH suppression based on the risk and benefit [18,19]. Additionally, patients with thyroid cancer demonstrate a greater likelihood of hospital visits and more frequent health check-ups than does the general population. Moreover, within the framework of Korea's health insurance system, patients with thyroid cancer are predisposed to receive more cost-effective osteoporosis treatment.

The fact that only spinal fractures were significantly reduced in the thyroid cancer group is thought to be because the effectiveness of anti-osteoporotic medication varies by bone site. Because excess thyroid hormone suppresses TSH and causes high bone turnover osteoporosis, antiresorptive agents are recommended for the treatment of osteoporosis in patients with thyroid cancer [20,21]. Patients with thyroid cancer are mainly prescribed bisphosphonate or denosumab, which are known to prevent approximately 42% and 68% of spinal fractures and 28% and 43% of hip fractures, respectively [22,23]. Although postmenopausal patients with thyroid cancer have a high risk of osteoporosis of the spine and hip [12,24], it is likely that the risk of spine fractures in the patients with thyroid cancer included in our study was reduced by active osteoporosis treatment.

Our results suggest that lower daily doses of levothyroxine are associated with a decreased risk of osteoporotic fractures. We conducted an analysis of the effect of levothyroxine dose adjusted for body weight to account for volume distribution. Our findings demonstrated that patients receiving lower doses of levothyroxine had a lower risk of fracture than those receiving higher doses. When the levothyroxine dosage exceeded 1.6 μg/kg/day, the risk of fracture tended to increase with increasing dosage per body weight. According to a recently published study, the dose of levothyroxine required to achieve mild suppression of TSH (0.1 to 0.5 mIU/L) in thyroid cancer patients after total thyroidectomy is approximately 1.71 or 1.86 μg/kg, depending on BMI [25]. Therefore, it is assumed that daily doses of levothyroxine exceeding 1.6 μg/kg are likely to have caused TSH suppression.

This study has several strengths, including a large sample size and robust statistical analysis, but it also has limitations. One such limitation is that the database did not provide information on supplementary health-related data or medical costs related to routine check-ups, particularly those not covered by the national

insurance system [26]. Given that the current national health screening for BMD in Korea is conducted only twice at 12-year intervals (at ages 54 and 66 years for women), it is necessary to consider cases where women receive bone densitometry tests that are not covered by health insurance [27]. Additionally, certain potential confounding factors, such as dietary habits (e.g., intake of calcium and vitamin D supplements), compliance with levothyroxine, and physical activity levels, were not considered. Specifically, simply multiplying the drug dosage does not account for the patient's drug compliance, and therefore may not accurately represent the actual level of TSH suppression. Moreover, the potential effect of postsurgical hypoparathyroidism was not accounted for in this study. Previous studies have reported inconsistent results regarding postsurgical hypoparathyroidism and its potential association with osteoporosis and osteoporotic fractures after thyroidectomy. Bollerslev et al. [28] reported no significant difference in BMD between patients with permanent postsurgical hypoparathyroidism and a control group. In contrast, Kim et al. [29] reported that patients with postsurgical hypoparathyroidism had a greater risk of osteoporosis. Recently, Ahn et al. [30] reported that thyroid cancer patients with postoperative hypoparathyroidism had a significantly lower risk of spinal fracture compared to thyroid cancer patients without postoperative hypoparathyroidism. Therefore, further research is needed to elucidate the relationships among postsurgical hypoparathyroidism, calcium supplementation, and bone health outcomes.

In conclusion, this study underscores the importance of bone health in patients with thyroid cancer, particularly women and younger patients. Our results suggest that while patients with thyroid cancer may be more prone to osteoporosis, paradoxically, they may be at a reduced risk of osteoporotic fractures, especially spinal fractures. Our findings underscore the need for personalized, comprehensive strategies to manage bone health in patients with thyroid cancer, as well as the need to investigate the complex interplay between thyroid cancer, its treatments, and bone health.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: E.J.K., W.S.Y., E.K.L., H.Y.A. Acquisition, analysis, or interpretation of data: Y.B.H., S.J., J.L., S.M. Drafting the work or revising: E.J.K., W.S.Y., J.L., E.K.L., H.Y.A. Final approval of the manuscript: E.J.K., W.S.Y., E.K.L., H.Y.A.

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