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Risk of Osteoporosis and Fractures in Patients with Thyroid Cancer: A Case-Control Study in U.S. Veterans

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Thyroid cancer • Osteoporosis • Fractures • Veterans

Abstract

Background. Data on osteoporosis and fractures in patients with thyroid cancer, especially men, are conflicting. Our objective was to determine osteoporosis and fracture risk in U.S. veterans with thyroid cancer.

Materials and Methods. This is a case-control study using the Veterans Health Administration Corporate Data Warehouse (2004–2013). Patients with thyroid cancer (n = 10,370) and controls (n = 10,370) were matched by age, sex, weight, and steroid use. Generalized linear mixed-effects regression model was used to compare the two groups in terms of osteoporosis and fracture risk. Next, subgroup analysis of the patients with thyroid cancer using longitudinal thyroid-stimulating hormone (TSH) was performed to determine its effect on risk of osteoporosis and fractures. Other covariates included patient age, sex, median household income, comorbidities, and steroid and androgen use.

Results. Compared with controls, osteoporosis, but not fractures, was more frequent in patients with thyroid cancer (7.3% vs. 5.3%; odds ratio [OR], 1.33; 95% confidence interval [CI], 1.18–1.49) when controlling for median household income, Charlson/Deyo comorbidity score, and androgen use. Subgroup analysis of patients with thyroid cancer demonstrated that lower TSH (OR, 0.93; 95% CI, 0.90–0.97), female sex (OR, 4.24; 95% CI, 3.53–5.10), older age (e.g., ≥85 years: OR, 17.18; 95% CI, 11.12–26.54 compared with <50 years), and androgen use (OR, 1.63; 95% CI, 1.18–2.23) were associated with osteoporosis. Serum TSH was not associated with fractures (OR, 1.01; 95% CI, 0.96–1.07).

Conclusion. Osteoporosis, but not fractures, was more common in U.S. veterans with thyroid cancer than controls. Multiple factors may be contributory, with low TSH playing a small role. ***The Oncologist*** 2019;24:1166–1173

Implications for Practice: Data on osteoporosis and fragility fractures in patients with thyroid cancer, especially in men, are limited and conflicting. Because of excellent survival rates, the number of thyroid cancer survivors is growing and more individuals may experience long-term effects from the cancer itself and its treatments, such as osteoporosis and fractures. The present study offers unique insight on the risk for osteoporosis and fractures in a largely male thyroid cancer cohort. Physicians who participate in the long-term care of patients with thyroid cancer should take into consideration a variety of factors in addition to TSH level when considering risk for osteoporosis.

Introduction

More than 50,000 Americans are diagnosed with thyroid cancer every year [1]. Moreover, survival rates for the majority of patients with thyroid cancer remain excellent, with more than 700,000 patients with thyroid cancer currently living in the U.S. [1]. As the number of thyroid cancer survivors grows, more individuals may experience long-term health effects from the cancer itself, as well as from thyroid cancer treatments [1–4]. These health risks include osteoporosis and fractures.

Thyroid surgery with or without radioactive iodine ablation is the standard of care for patients with thyroid cancer [5]. In select patients, thyroid-stimulating hormone (TSH) suppression is also warranted to prevent cancer recurrence [5]. It has been postulated that TSH suppression therapy, which induces a state of subclinical hyperthyroidism, may contribute to bone loss in patients with thyroid cancer, particularly in postmenopausal women [1]. However, previous studies exploring the link between thyroid cancer treatment

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and osteoporosis and fractures in men have yielded conflicting results because of heterogeneity in study design, small sample sizes, cross-sectional nature, lack of biochemical data, and varying degrees of control for confounding variables [1, 6–10].

To address this knowledge gap, we used a largely male study cohort, the Veterans Health Administration Corporate Data Warehouse (VHA CDW), to compare osteoporosis and fracture risks in patients with thyroid cancer versus matched controls. We subsequently performed a subgroup analysis of the patients with thyroid cancer using longitudinal TSH to determine factors associated with osteoporosis and fractures.

Materials and Methods

Study Design

This was a retrospective case-control study (1:1 match of patients with thyroid cancer to controls) using deidentified national data from the VHA CDW between 2004 and 2013. A subsequent subgroup analysis of only the patients with thyroid cancer using longitudinal TSH data was also conducted. This study was exempt from the University of Michigan Institutional Review Board and approved by the Ann Arbor Veteran Affairs Institutional Review Board.

Data Source and Study Population

The study population was selected from the VHA CDW within the Veteran Affairs Informatics and Computing Infrastructure system. The Veterans Health Administration is the largest integrated health care system in the country, with the mission of providing patient-centered, comprehensive clinical services for veterans [11]. It serves over 9 million veterans via an extensive network of more than 1,200 facilities in the U.S. [12]. The VHA CDW is a dynamic repository of patient-level administrative and clinical data, aggregated from across the VHA's national health delivery system in the U.S. [13].

Selection of Cases

We included male and female veterans aged 18 years or older who had a thyroid cancer diagnosis between January 1, 2004, and December 31, 2013 (using International Classification of Diseases [ICD]-9 code 193), who were on thyroid hormone replacement therapy (identified as taking either T4 alone or a T4 plus T3 combination preparation), and who had at least two outpatient TSH measurements following the date of thyroid cancer diagnosis. We excluded thyroid function tests measured in the inpatient setting and in patients at long-term care units, as these patients often have abnormal thyroid function tests associated with nonthyroidal illness. Only cases with a complete set of data were included.

Selection of Controls

Veterans without a diagnosis of thyroid cancer and who were not on thyroid hormone replacement served as controls. For each case, we randomly selected one control from multiple possible matches, matching by sex, age, weight, and steroid use (1:1 match). Cases and controls were matched by age according to the date of birth, with dates being within a year of each other. Weight between cases and controls was matched within 5 pounds, based on the closest measurement to the date of thyroid cancer diagnosis or study entry. Only controls with a complete set of data were included.

Covariates

Data collected included information on patient sex, patient age (categorized as <50, 50–64, 65–74, 75–84, and ≥85 years), patient weight, median household income (determined by zip code of residence from the Area Resource File), duration of steroid use (categorized as none/<3 months versus ≥3 months), androgen use, and comorbidities. Median household income was included as a measure of socioeconomic status, which has been shown to be associated with osteoporosis and fracture risk [14–16]. Steroid and androgen use were determined using outpatient prescription data. Comorbidities were determined by the Charlson/Deyo comorbidity score, which was calculated using the Charlson/Deyo comorbidity score mapping table (see supplemental online Appendix 1). This score was categorized as 0, 1, and ≥2. For patients with-thyroid cancer, serum TSH measurements were gathered from the patients' laboratory records and organized into a longitudinal data set (median TSH, 1.19 mIU/L; range, 0.001–125 mIU/L). The number of serum TSH measurements per patient ranged between 2 and 111 (median, 14).

Bone Density Scans and Osteoporosis Medications

We captured bone density scans performed following diagnosis of thyroid cancer for patients and at time of study entry for controls. Bone mineral density scans were captured only if performed prior to diagnosis of osteoporosis and/or fractures. For claims codes used, please see supplemental online Appendix 1. Additionally, information on medications used to treat osteoporosis was obtained from outpatient pharmacy prescriptions for bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), denosumab, teriparatide, and raloxifene.

Outcome Measures

Patients were identified as having osteoporosis by using ICD-9 codes 733.0x. We used inpatient and outpatient ICD-9 and Current Procedural Terminology-4 (CPT-4) codes to identify patients who had at least one fragility fracture during the study period, including hip, pelvic, vertebral, and forearm/wrist fractures. Patients with traumatic or pathological fractures were excluded from the analyses. ICD-9 and CPT-4 codes were entered into the patients' medical records by their treating physicians. These deidentified data were obtained from the Corporate Data Warehouse. For the patients with thyroid cancer, events of osteoporosis diagnosis and fractures were only counted if they occurred after the diagnosis of thyroid cancer (median time to event, 20 months for osteoporosis, 36 months for fractures). For details on the ICD-9 and CPT-4 codes used, refer to the supplemental online Appendix 1. Data were censored at death or at last follow-up.

Statistical Analysis

First, descriptive statistics were generated for both cases and controls. Next, generalized linear mixed-effects regression

model based on a logit link was used to identify factors associated with the risk of osteoporosis and fragility fractures in cases and controls. Variables included in the regression model were median household income, Charlson/Deyo comorbidity index, and androgen use. Matched samples were analyzed as pairs, and a random intercept was used for the pairs.

Subsequently, we conducted subgroup analyses of patients with thyroid cancer using separate generalized linear mixed-effects regression models for osteoporosis and fractures based on a logit link (n = 10,370). Covariates for these models included longitudinal TSH, patient age at diagnosis, sex, median household income, comorbidities, and steroid and androgen use. Serum TSH was analyzed as a continuous variable and was log transformed prior to analysis because of nonlinear effect of TSH. Additionally, TSH was used as a time-varying covariate. This allowed for serial TSH measurements for each of the observed timepoints during the study period to be accounted for, incorporating changes to thyroid status over time in the analyses.

Finally, a subgroup analysis of the patients with thyroid cancer using longitudinal TSH as a categorical variable was conducted (TSH categories: <0.1 mIU/L, 0.1–0.5 mIU/L, 0.51–5.5 mIU/L, >5.5 mIU/L), with osteoporosis risk as the outcome measure. Serum TSH was used as a time-varying covariate. Serum TSH values in this plot represent model-predicted cases based on information from the data.

All analyses were conducted using SAS Enterprise Guide Version 7.15 HF3 (7.100.5.6132; 64-bit; SAS, Cary, NC). A 95% confidence interval (CI) was used to determine statistical significance. A p value <.05 was considered statistically significant.

Results

A total of 10,370 patients with thyroid cancer were matched by age, sex, weight, and steroid use with 10,370 controls during the study period of 2004–2013. As shown in Table 1, the majority of patients were male (83.8%). The median age was 61 years. Patients with thyroid cancer had more comorbidities (28.4% vs. 15.7% with Charlson/Deyo comorbidity score ≥2) and more androgen use (7.0% vs. 4.2%) than controls. Overall, 882 (8.5%) of patients with thyroid cancer were on osteoporosis medications, compared with 560 (5.4%) of controls. Of those with a diagnosis of osteoporosis, a total of 49.6% of patients with thyroid cancer were on an osteoporosis medication versus only 29.6% of controls. Additionally, 23.7% of patients with thyroid cancer underwent bone density scans compared with 9.7% controls (p < .001) during the study period.

As demonstrated in Table 2, osteoporosis was more frequent in patients with thyroid cancer compared with matched controls (7.3% vs 5.3%; odds ratio [OR], 1.33; 95% CI, 1.18–1.49), after controlling for median household income, Charlson/Deyo comorbidity score, and androgen use.

Table 3 shows that fractures were less common in patients with thyroid cancer compared with controls (2.4% vs. 2.8%; OR, 0.72; 95% CI, 0.60–0.86), after controlling for median household income, Charlson/Deyo comorbidity score, and androgen use. Additionally, when adjusting for diagnosis of osteoporosis and being on osteoporosis medication(s) in the multivariable analysis model, it was similarly observed that there is a lower incidence of fractures in the thyroid cancer group compared with matched controls (OR, 0.71; 95% CI, 0.59–0.85).

Table 1. Characteristics of patients with thyroid cancer and controls (2004–2013)

Characteristics	Patients with thyroid cancer, *n* (%)	Controls, *n* (%)
Sex[a]		
Male	8,689 (83.8)	8,689 (83.8)
Female	1,681 (16.2)	1,681 (16.2)
Age, yr[a]		
<50	2017 (19.4)	2018 (19.5)
50–64	4,539 (43.8)	4,538 (43.8)
65–74	2,267(21.9)	2,265 (21.8)
75–84	1,356 (13.1)	1,357 (13.1)
≥85	191 (1.8)	192 (1.8)
Weight[a,b]	93.8 (20.1)	93.7 (20.0)
Median household income[c]		
<$35,000	1,314 (12.7)	1,412 (13.6)
$35,000–$59,999	6,125 (59.0)	6,387 (61.6)
≥$60,000	2,931 (28.3)	2,571 (24.8)
Charlson/Deyo comorbidity score		
0	6,137 (59.2)	7,802 (75.2)
1	1,284 (12.4)	944 (9.1)
≥2	2,949 (28.4)	1,624 (15.7)
Androgen use		
No	9,642 (93.0)	9,935 (95.8)
Yes	728 (7.0)	435 (4.2)
Steroid use[a]		
No or <3 mo	9,144 (88.2)	9,144 (88.2)
≥3 mo	1,226 (11.8)	1,226 (11.8)
Use of osteoporosis medication		
No	9,488 (91.5)	9,810 (94.6)
Yes	882 (8.5)	560 (5.4)
Bone density scans		
No	7,911 (76.3)	9,369 (90.3)
Yes	2,459 (23.7)	1,001 (9.7)
Osteoporosis[d]		
No	9,616 (92.7)	9,826 (94.7)
Yes	754 (7.3)	544 (5.3)
Fractures		
No	10,117 (97.6)	10,083 (97.2)
Yes	253 (2.4)	287 (2.8)

[a]Cohorts were matched for sex, age according to the date of birth (matched within 1 year), weight [matched within 5 pounds; reported in kg as mean (SD)], and steroid use.
[b]Weight reported in kg as mean (SD).
[c]Median household income by geographic region.
[d]Osteoporosis diagnosed by ICD-9 codes.

Table 2. Osteoporosis in patients with thyroid cancer compared with matched controls

	Osteoporosis in patients with thyroid cancer, *n* (%)	Osteoporosis in controls,[a] *n* (%)	OR (95% CI)
Cohort[b]	754 (7.3)	544 (5.3)	1.33 (1.18–1.49)
Median household income[c]			
<$35,000	89 (6.8)	69 (4.9)	1.0 (ref)
$35,000–$59,999	440 (7.2)	327 (5.1)	1.07 (0.89–1.29)
≥$60,000	225 (7.7)	148 (5.8)	1.20 (0.97–1.47)
Charlson/Deyo comorbidity score			
0	385 (6.3)	332 (4.3)	1.0 (ref)
1	108 (8.4)	62 (6.6)	1.47 (1.22–1.77)
≥2	261 (8.9)	150 (9.2)	1.70 (1.48–1.95)
Androgen use			
No	709 (7.3)	526 (5.3)	1.0 (ref)
Yes	45 (6.4)	18 (4.3)	0.84 (0.64–1.11)

[a]Cohorts were matched for sex, age according to the date of birth (matched within 1 year), weight [matched within 5 pounds; reported in kg as mean (SD)], and steroid use.
[b]Reference group is controls.
[c]Median household income by geographic region.
Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference.

Table 3. Fractures in patients with thyroid cancer compared with matched controls

	Fractures in patients with thyroid cancer, *n* (%)	Fractures in controls,[a] *n* (%)	OR (95% CI)
Cohort[b]	253 (2.4)	287 (2.8)	0.72 (0.60–0.86)
Median household income[c]			
<$35,000	31 (2.4)	44 (3.1)	1.0 (ref)
$35,000–$59,999	158 (2.6)	172 (2.7)	1.01 (0.77–1.31)
≥$60,000	64 (2.2)	71 (2.8)	0.98 (0.73–1.32)
Charlson/Deyo comorbidity score			
0	88 (1.4)	136 (1.7)	1.0 (ref)
1	41 (3.2)	40 (4.2)	2.40 (1.84–3.14)
≥2	124 (4.2)	111 (6.8)	3.44 (2.83–4.19)
Androgen use			
No	238 (2.5)	280 (2.8)	1.0 (ref)
Yes	15 (2.1)	7 (1.6)	0.69 (0.44–1.07)

[a]Cohorts were matched for sex, age according to the date of birth (matched within 1 year), weight [matched within 5 pounds; reported in kg as mean (SD)], and steroid use.
[b]Reference group is controls.
[c]Median household income by geographic region.
Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference.

Table 4 demonstrates results from a subsequent subgroup longitudinal analysis of characteristics associated with osteoporosis in patients with thyroid cancer only (*n* = 10,370), with serum log transformed TSH analyzed as a continuous variable. Median follow-up was 52 months. During the study period, 8,493 of 10,370 (82%) patients with thyroid cancer had at least one serum TSH ≤0.5 mIU/L, which would indicate TSH suppression. Lower TSH (OR, 0.93; 95% CI, 0.90–0.97), female sex (OR, 4.24; 95% CI, 3.53–5.10), and androgen use (OR, 1.63; 95% CI, 1.18–2.23) were associated with osteoporosis. Additionally, older age (e.g., ≥85 years: OR, 17.18; 95% CI, 11.12–26.54, compared with <50 years) was also associated with osteoporosis in these patients.

Figure 1 illustrates that when analyzing serum TSH as a categorical variable longitudinally, there were 10.6 osteoporosis cases per 1,000 patients with thyroid cancer with a serum TSH <0.1 mIU/L compared with 11.2 cases per 1,000 when TSH was 0.1–0.5, 8.0 cases per 1,000 when TSH 0.5–5.5 mIU/L, and 7.7 cases per 1,000 when TSH >5.5 mIU/L at any point in time. For example, in these model-predicted cases, if we take 1,000 patients with their TSH values between 0.1–0.5 mIU/L, we expect to see 11.2 cases of osteoporosis.

Table 5 shows results from a subgroup analysis of characteristics associated with fractures in patients with thyroid cancer only (*n* = 10,370), with longitudinal serum log transformed TSH analyzed as a continuous variable. There was no significant association between TSH level and risk for fractures (OR, 1.01; 95% CI, 0.96–1.07). However, female sex (OR, 1.54; 95% CI, 1.07–2.22), older age (e.g., ≥85 years: OR, 9.78; 95% CI, 5.15–18.57; compared with age <50), higher

Table 4. Subgroup analysis of longitudinal TSH and other characteristics associated with osteoporosis in patients with thyroid cancer (2004–2013)

Characteristics	Osteoporosis, *n* (%)	OR (95% CI)
Sex		
Male	539 (6.2)	1.0 (ref)
Female	215 (12.8)	4.24 (3.53–5.10)
Age, yr		
<50	70 (3.5)	1.0 (ref)
50–64	300 (6.6)	3.09 (2.34–4.07)
65–74	192 (8.5)	5.66 (4.17–7.67)
75–84	157 (11.6)	9.61 (6.99–13.21)
≥85	35 (18.3)	17.18 (11.12–26.54)
TSH[a]	1.08 (0.001–125)[b]	0.93 (0.90–0.97)
Median household income[c]		
<$35,000	89 (6.8)	1.0 (ref)
$35,000–$59,999	440 (7.2)	1.09 (0.86–1.38)
≥$60,000	225 (7.7)	1.18 (0.92–1.52)
Charlson/Deyo comorbidity score		
0	385 (6.3)	1.0 (ref)
1	108 (8.4)	1.07 (0.86–1.34)
≥2	261 (8.9)	1.03 (0.87–1.21)
Androgen use		
No	710 (7.3)	1.0 (ref)
Yes	44 (6.6)	1.63 (1.18–2.23)
Steroid use		
<3 mo	744 (7.7)	1.0 (ref)
≥3 mo	10 (1.6)	0.65 (0.34–1.24)

[a]TSH was log transformed and analyzed as a continuous, time-varying covariate for the analysis.
[b]TSH median and range reported in mIU/L.
[c]Median household income by geographic region.
Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference; TSH, thyroid-stimulating hormone.

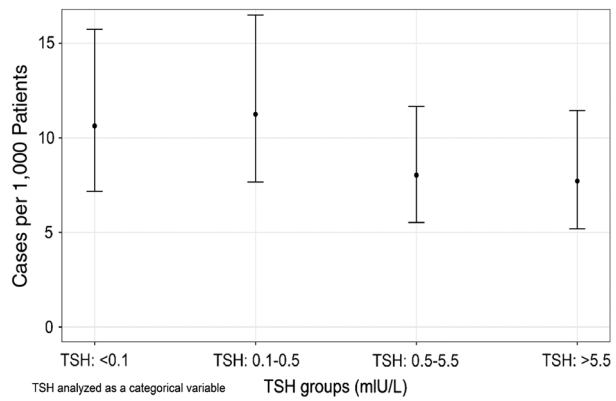

Figure 1. Subgroup analysis of U.S. veterans with thyroid cancer using longitudinal TSH (analyzed as a categorical variable) and osteoporosis risk (2004–2013).
Abbreviation: TSH, thyroid-stimulating hormone.

Table 5. Subgroup analysis of longitudinal TSH and other characteristics associated with fractures in patients with thyroid cancer (2004–2013)

Characteristics	Fractures, *n*(%)	OR (95% CI)
Sex		
Male	212 (2.4)	1.0 (ref)
Female	41 (2.4)	1.54 (1.07–2.22)
Age, yr		
<50	26 (1.3)	1.0 (ref)
50–64	112 (2.5)	1.77 (1.13–2.78)
65–74	50 (2.2)	1.78 (1.07–2.96)
75–84	48 (3.5)	3.28 (1.95–5.50)
≥85	17 (8.9)	9.78 (5.15–18.57)
TSH[a]	1.08 (0.001–125)[b]	1.01 (0.96–1.07)
Median household income[c]		
<$35,000	31 (2.4)	1.0 (ref)
$35,000–$59,999	158 (2.6)	1.16 (0.79–1.71)
≥$60,000	64 (2.2)	1.01 (0.65–1.55)
Charlson/Deyo comorbidity score		
0	88 (1.4)	1.0 (ref)
1	41 (3.2)	1.66 (1.14–2.41)
≥2	124 (4.2)	1.95 (1.47–2.59)
Androgen use		
No	238 (2.5)	1.0 (ref)
Yes	15 (2.2)	1.27 (0.75–2.16)
Steroid use		
<3 mo	241 (2.5)	1.0 (ref)
≥3 mo	12 (1.6)	1.92 (1.07–3.45)

[a]TSH was log transformed and analyzed as a continuous, time-varying covariate for the analysis.
[b]TSH median and range reported in mIU/L.
[c]Median household income by geographic region.
Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference; TSH, thyroid-stimulating hormone.

Charlson/Deyo comorbidity score (e.g., ≥2: OR, 1.95; 95% CI, 1.47–2.59, compared with 0), and steroid use ≥3 months (OR, 1.92; 95% CI, 1.07–3.45) were associated with fractures in these patients.

In subgroup analyses of men only, it was similarly shown that patients with thyroid cancer had a higher incidence of osteoporosis than matched controls (OR, 1.46; 95% CI, 1.26–1.68) and lower incidence of fractures (OR, 0.70; 95% CI, 0.58–0.85). Detailed results of these subgroup analyses are outlined in supplemental online Tables 6 and 7.

Discussion

The findings of this study provide information regarding the risk of osteoporosis and fragility fractures in U.S. veterans with thyroid cancer and the factors associated with these adverse skeletal events. In this predominantly male population, osteoporosis, but not fractures, was more common in the thyroid cancer cohort compared with age-, sex-, weight-,

and steroid use-matched controls, even when controlling for comorbidities, median household income, and androgen use. Lower TSH, female sex, older age, and androgen use were associated with risk of osteoporosis in the thyroid cancer cohort in longitudinal analysis. However, primary correlates with osteoporosis were female sex and older age, both known risk factors [17, 18], whereas the effect of low TSH in this cohort was small.

Prior studies on the risk of osteoporosis in patients with thyroid cancer have included only small numbers of men [1, 6–10]. In the few studies with larger cohorts of men with thyroid cancer, findings have shown no change in bone mineral density [1, 8–10]. However, these prior studies were heterogeneous, were limited by varying degrees of control for confounding variables, and investigated diverse endpoints in mainly cross-sectional studies with small sample sizes (n = 4–33) [1]. Data on fracture risk in patients with thyroid cancer on thyroid hormone therapy are scarce, and none of the existing studies focused specifically on men. A more recent study by Blackburn et al. evaluated aging-related diseases among thyroid cancer survivors (n = 3,706, of which 821 were men) compared with a matched cancer-free cohort (n = 15,587). They found that osteoporosis, but not fractures, were increased in patients with thyroid cancer compared with controls ($p < .01$). However, this study lacked TSH data [3].

Prior studies attempting to elucidate the relationship between TSH suppression and osteoporosis and fractures in patients with thyroid cancer yielded controversial results [1, 19, 20]. Although theories for how TSH suppression may lead to bone loss include a possible direct effect on bone formation and bone resorption mediated by the TSH receptor on osteoblast and osteoclast precursors [21–23], it has previously not been clear if risks of TSH suppression pertained equally to men as to women. Additionally, data on how the severity and duration of low TSH affects bone health are conflicting [20, 24–26]. It is unknown whether findings from studies on endogenous hyperthyroidism should be extrapolated to exogenous hyperthyroidism, and the duration of persistently low TSH necessary to affect the skeleton remains unclear. TSH suppression has been shown to be associated with an increased risk of osteoporosis in the majority, but not all, of the studies including postmenopausal women [1, 19, 20]. Wang et al. showed that 5.4% of women with thyroid cancer treated at a single institution were diagnosed with postoperative osteoporosis after a median follow-up of 6.5 years (n = 537). Interestingly, postoperative TSH suppression (TSH ≤0.4 mIU/L) significantly increased the risk of postoperative osteoporosis among women with low and intermediate-risk differentiated thyroid cancer by 3.5-fold without changing risk for recurrence [20]. However, there has not been strong evidence that TSH suppression leads to increased risk of osteoporosis in men, because of existing studies being limited by lack of power [1]. Karner et al. conducted the only longitudinal study to date in men and showed no change in bone mineral density in men with thyroid cancer with suppressed TSH, except for loss of bone mass in the distal radius (n = 9) [27]. In addition to the small sample size, this study also lacked a control group. As our study focused on a large sample of U.S. veterans with thyroid cancer, the majority of which were male, we provide a unique insight on the role of TSH suppression therapy on osteoporosis in these patients, the effect of which appears to be small.

In regard to risk for fractures in patients with thyroid cancer, a large population-based Korean study (n = 185,956) that included men with thyroid cancer (n = 31,922) looked exclusively at fractures and found that patients with thyroid cancer were more likely to be treated with osteoporosis medication (hazard ratio [HR], 1.22; 95% CI, 1.18–1.26) compared with a matched comparison group. In this other study, patients were matched to controls by age, sex, residence, income, and disability. The authors also demonstrated a J-shaped dose-dependent relationship between TSH suppression and fracture risk, a finding we did not elucidate in our study [28].

Major strengths of our study include the large, national sample of predominantly male U.S. veterans, the case-control study design complemented by a longitudinal analysis containing biochemical data (serum TSH values measured at multiple points in time), the availability of pharmacy prescription data, and the long-term follow-up to detect adverse skeletal outcomes, such as osteoporosis and fragility fractures. In addition, osteoporosis in male patients with thyroid cancer is understudied, and the rich U.S. Department of Veteran's Affairs (VA) data set allowed for a subgroup analysis in males. Our findings are generalizable to veterans across the U.S., and potentially to nonveteran, largely male cohorts.

The study also has limitations. First, as is inherent to large administrative databases, there may be coding errors for some diagnoses and procedures. However, a previous study showed that manual chart review of randomly selected patients yielded a positive predictive value of 82% and 84% for using ICD-9 codes in the VA system to diagnose low bone mineral density and fragility fractures, respectively [29]. Second, confounding variables may be missing or poorly measured (e.g. alcohol, smoking). Third, reflective of the fact that this is a real-world setting, it is possible that veterans may have also received patient care in non-VA systems, and outcomes may not have been captured. In the real-world setting, physicians are expected to update medical records appropriately with true diagnoses, so we assume that if a diagnosis of osteoporosis exists in the records, then a bone density scan must have been performed previously to substantiate this. Furthermore, as we expect that patients diagnosed with osteoporosis would have had at least one bone mineral density scan, these two variables are highly correlated, and adding the number of bone mineral density scans as a covariate to our model is unlikely to yield further meaningful information. Additionally, even though the VHA provides an incentive for eligible veterans to obtain all of their prescriptions within the VA system at a low cost, it is possible that some veterans used outside health care systems for pharmacologic care. Next, serum TSH may have been checked more frequently in certain patients versus others. To accommodate for this difference, we used generalized linear mixed-effects regression models in which TSH was considered a time-varying covariate in our longitudinal analyses. Although we matched for age, sex, weight, and steroid use, additional covariates were not balanced between the two cohorts and may have contributed to the disparate rate of osteoporosis.

The higher number of bone density scans performed in the thyroid cancer cohort likely indicates screening bias,

perhaps owing to physician concern about the potential effects of iatrogenic thyrotoxicosis on bone. These findings have clinical implications. Patients with thyroid cancer may be subject to increased screening with bone density scans irrespective of their overall risk for osteoporosis and fractures, leading to unnecessary increased health care use and increased costs. Also, physicians may be overestimating the effect of thyroid cancer treatments on bone health. In contrast, osteoporosis may be underdiagnosed in the population at large without thyroid cancer despite the presence of other risk factors, which in turn may lead to undertreatment and subsequent fractures. Further research is needed to adequately explain the lower incidence of fractures in patients with thyroid cancer compared with the general population.

Conclusion

Our study offers unique insight on the risk for osteoporosis and fractures in a largely male thyroid cancer cohort. The higher incidence of osteoporosis seen in patients with thyroid cancer appears to be multifactorial, with iatrogenic hyperthyroidism playing only a small role. Physicians who participate in the long-term care of patients with thyroid cancer should take into consideration a variety of factors in addition to TSH level when considering risk for osteoporosis. These risk factors should include medications and other conditions adversely affecting bone health and, importantly, the patient's age and sex.

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Disclosures

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For Further Reading:
Maria Papaleontiou, Sarah T. Hawley, Megan R. Haymart. Effect of Thyrotropin Suppression Therapy on Bone in Thyroid Cancer Patients. ***The Oncologist*** 2016;21:165–171.

Implications for Practice:
The standard treatment for thyroid cancer includes total thyroidectomy with or without radioactive iodine ablation, often followed by thyrotropin suppression therapy. Despite current guidelines, controversy exists regarding the degree and duration of thyrotropin suppression therapy, and discordant results have been reported on its adverse effects on bone. The present review provides physicians with existing data on the skeletal effects of thyrotropin suppression therapy, highlighting the need for further research to identify the groups at risk of adverse skeletal effects. This knowledge will aid in developing tailored thyroid cancer treatment.