Papaleontiou Maria (Orcid ID: 0000-0003-2276-0046)

Risk of Osteoporosis and Fractures in Thyroid Cancer Patients: A case-control study in United States Veterans

Papaleontiou M, MD[1], Banerjee M, PhD[2], Reyes-Gastelum D, MS[1], Hawley ST, PhD, MPH[3], Haymart MR, MD[1].

[1]Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan
[2]School of Public Health, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan
[3]Division of General Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

Corresponding author and person to whom reprint requests should be addressed:
Maria Papaleontiou, MD
Division of Metabolism, Endocrinology and Diabetes
Department of Internal Medicine, University of Michigan
North Campus Research Complex
2800 Plymouth Road, Bldg 16, Rm 453S
Ann Arbor, MI 48109
Phone: (734) 764-9733
Fax: (734) 936-8944
Email: mpapaleo@med.umich.edu

Running Title: Osteoporosis and fractures in thyroid cancer

Keywords: thyroid cancer, osteoporosis, fractures, veterans

ABSTRACT

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

Methods: This is a case-control study using the Veterans Health Administration Corporate Data Warehouse (2004-2013). Thyroid cancer patients (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 thyroid cancer patients using longitudinal TSH was performed to determine its effect on risk of osteoporosis and fractures. Other covariates included patient age, sex, median household income, comorbidities, steroid and androgen use.

Results: Compared to controls, osteoporosis, but not fractures, was more frequent in thyroid cancer patients [7.3% versus 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 thyroid cancer patients demonstrated that lower TSH (OR 0.93, 95% CI 0.90-0.97), female sex (OR 4.24, 95%

2

CI 3.53-5.10), older age (e.g., ≥85 years: OR 17.18, 95% CI 11.12-26.54 compared to <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.

IMPLICATIONS FOR PRACTICE

Data on osteoporosis and fragility fractures in thyroid cancer patients, especially in men, are limited and conflicting. Due to 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. Our 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 thyroid cancer patients 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 thyroid cancer patients currently living in the United States [1].

3

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, 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 thyroid cancer patients, particularly in post-menopausal women [1]. However, previous studies exploring the link between thyroid cancer treatment and osteoporosis and fractures in men have yielded conflicting results due to 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 thyroid cancer patients versus matched controls. We subsequently performed a subgroup analysis of the thyroid cancer patients using longitudinal TSH to determine factors associated with osteoporosis and fractures.

METHODS

Study Design

4

This was a retrospective case-control study (1:1 match of thyroid cancer patients to controls) using deidentified national data from the VHA CDW between 2004 and 2013. A subsequent subgroup analysis of only the thyroid cancer patients 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 (VINCI) system. The Veterans Health Administration is the largest integrated healthcare 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 1200 facilities in the United States [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 United States [13].

Selection of Cases: We included male and female veterans aged 18 years or older, who had a thyroid cancer diagnosis between 1/1/2004 and 12/31/2013 [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

5

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 non-thyroidal 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 old), 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.

6

Comorbidities were determined by the Charlson/Deyo comorbidity score, which was

calculated using the Charlson/Deyo comorbidity score mapping table (see

Supplemental Material). This score was categorized as 0, 1 and ≥2. For thyroid cancer

patients, serum TSH measurements were gathered from the patients' laboratory records

and organized into a longitudinal dataset (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 Material. Additionally, information on

medications used to treat osteoporosis was obtained from outpatient pharmacy

prescriptions for bisphosphonates (alendronate, risedronate, ibandronate, zolendronic

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

7

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 de-identified data were obtained from the Corporate Data Warehouse. For the thyroid cancer patients, 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 Material . Data were censored at death or at last follow-up.

Statistical Analyses

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 thyroid cancer patients 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, steroid and androgen use. Serum TSH was analyzed as a continuous variable and was log-transformed prior to analysis due to non-linear effect of TSH.

8

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 thyroid cancer patients 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). A 95% CI was used to determine statistical significance. A p value <0.05 was considered statistically significant.

RESULTS

A total of 10,370 thyroid cancer patients 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. Thyroid cancer patients had more comorbidities (28.4% versus 15.7% with Charlson/Deyo comorbidity score ≥2) and more androgen use (7.0% versus 4.2%) than controls. Overall, 882 (8.5%) of thyroid cancer patients were on osteoporosis medications compared to 560 (5.4%) of controls. Of those with a diagnosis of osteoporosis, a total of 49.6% of thyroid cancer patients were on an osteoporosis

9

medication versus only 29.6% of controls. Additionally, 23.7% of thyroid cancer patients underwent bone density scans compared to 9.7% controls (p<0.001) during the study period.

As demonstrated in Table 2, osteoporosis was more frequent in thyroid cancer patients compared to matched controls (7.3% versus 5.3%; 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 thyroid cancer patients compared to controls (2.4% versus 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 to matched controls (OR 0.71, 95% CI 0.59-0.85).

Table 4 demonstrates results from a subsequent subgroup longitudinal analysis of characteristics associated with osteoporosis in thyroid cancer patients 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%) thyroid cancer patients 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%

10

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 to age<50 years old) 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 1000 thyroid cancer patients with a serum TSH <0.1 mIU/L compared to 11.2/1000 cases when TSH 0.1-0.5, 8.0/1000 cases when TSH 0.5-5.5 and 7.7/1000 cases when TSH >5.5 mIU/L at any point in time. For example, in these model-predicted cases, if we take 1000 patients with their TSH values between 0.1-0.5, we expect to see 11.2 cases of osteoporosis.

Table 5 shows results from a subgroup analysis of characteristics associated with fractures in thyroid cancer patients 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 to age<50 years old), higher Charlson/Deyo comorbidity score (e.g., ≥ 2: OR 1.95, 95% CI 1.47-2.59, compared to 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 males only, it was similarly shown that thyroid cancer patients had a higher incidence of osteoporosis than matched controls (OR 1.46, 95%

11

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 the Supplemental Material, Tables S1 and S2.

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 to 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 thyroid

12

cancer patients on thyroid hormone therapy are scarce and none of the existing studies focused specifically on men. A more recent study by Blackburn BE et al evaluated aging-related diseases among thyroid cancer survivors (N=3,706, of which 821 were men) compared to a matched cancer-free cohort (N=15,587). They found that osteoporosis, but not fractures, were increased in thyroid cancer patients compared to controls (p<0.01). However, this study lacked TSH data [3].

Prior studies attempting to elucidate the relationship between TSH suppression and osteoporosis and fractures in thyroid cancer patients 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 post-menopausal women [1, 19, 20]. Wang et al showed that 5.4% of women with thyroid cancer treated at a single institution were diagnosed with post-operative osteoporosis after a median follow up of 6.5 years (N=537). Interestingly,

13

post-operative TSH suppression (TSH ≤0.4 mIU.L) significantly increased the risk of post-operative 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, due to 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 regards to risk for fractures in thyroid cancer patients, 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 thyroid cancer patients were more likely to be treated with osteoporosis medication (HR 1.22, 95% CI 1.18-1.26) compared to 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].

14

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 thyroid cancer patients is understudied and the rich VA dataset allowed for a subgroup analysis in males. Our findings are generalizable to veterans across the United States, and potentially to non-veteran, largely male cohorts.

The study also has limitations. First, as is inherent to large administrative databases, there may be coding errors for some diagnoses/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 have not 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

15

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 utilized outside healthcare 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 where 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 due to physician concern about the potential effects of iatrogenic thyrotoxicosis on bone. These findings have clinical implications. Thyroid cancer patients may be subject to increased screening with bone density scans irrespective of their overall risk for osteoporosis/fractures, leading to unnecessary increased healthcare utilization and increased costs. Also, physicians may be overestimating the effect of thyroid cancer treatments on bone health. On the other hand, osteoporosis may be underdiagnosed in the population at large without thyroid

16

cancer despite 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 thyroid cancer patients compared to 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 thyroid cancer patients appears to be multifactorial, with iatrogenic hyperthyroidism playing only a small role. Physicians who participate in the long-term care of thyroid cancer patients 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.

ACKNOWLEDGEMENTS

REFERENCES

1   Papaleontiou M, Hawley ST, Haymart MR. Effect of thyrotropin suppression therapy on bone in thyroid cancer patients. Oncologist 2016;21:165-171.

2   Haymart MR, Esfandiari NH, Stang MT, et al. Controversies in the management of low-risk differentiated thyroid cancer. Endocr Rev 2017;38:351-378.

3   Blackburn BE, Ganz PA, Rowe K, et al. Aging-related disease risks among young thyroid cancer survivors. Cancer Epidemiol Biomarkers Prev 2017;26:1695-1704.

4   Biondi B and Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. Thyroid : official journal of the American Thyroid Association 2010;20:135-146.

5   Haugen BR, Alexander EK, Bible KC, et al. 2015 american thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid : official journal of the American Thyroid Association 2016;26:1-133.

18

6   Stepan JJ and Limanova Z. Biochemical assessment of bone loss in patients on long-term thyroid hormone treatment. Bone Miner 1992;17:377-388.

7   Gorres G, Kaim A, Otte A, et al. Bone mineral density in patients receiving suppressive doses of thyroxine for differentiated thyroid carcinoma. Eur J Nucl Med 1996;23:690-692.

8   Heijckmann AC, Huijberts MS, Geusens P, et al. Hip bone mineral density, bone turnover and risk of fracture in patients on long-term suppressive l-thyroxine therapy for differentiated thyroid carcinoma. Eur J Endocrinol 2005;153:23-29.

9   Marcocci C, Golia F, Vignali E, et al. Skeletal integrity in men chronically treated with suppressive doses of l-thyroxine. J Bone Miner Res 1997;12:72-77.

10   Reverter JL, Colome E, Holgado S, et al. Bone mineral density and bone fracture in male patients receiving long-term suppressive levothyroxine treatment for differentiated thyroid carcinoma. Endocrine 2010;37:467-472.

11   Kizer KW, Demakis JG, Feussner JR. Reinventing va health care: Systematizing quality improvement and quality innovation. Med Care 2000;38:I7-16.

12   Kilbourne AM, Elwy AR, Sales AE, et al. Accelerating research impact in a learning health care system: Va's quality enhancement research initiative in the choice act era. Med Care 2017;55 Suppl 7 Suppl 1:S4-S12.

13   Fihn SD, Francis J, Clancy C, et al. Insights from advanced analytics at the veterans health administration. Health Aff (Millwood) 2014;33:1203-1211.

19

14   Du Y, Zhao LJ, Xu Q, et al. Socioeconomic status and bone mineral density in adults by race/ethnicity and gender: The louisiana osteoporosis study. Osteoporos Int 2017;28:1699-1709.

15   Crandall CJ, Miller-Martinez D, Greendale GA, et al. Socioeconomic status, race, and bone turnover in the midlife in the us study. Osteoporos Int 2012;23:1503-1512.

16   Cauley JA, Chalhoub D, Kassem AM, et al. Geographic and ethnic disparities in osteoporotic fractures. Nat Rev Endocrinol 2014;10:338-351.

17   Nih consensus development panel on osteoporosis prevention, diagnosis, and therapy, march 7-29, 2000: Highlights of the conference. South Med J 2001;94:569-573.

18   Drake MT, Murad MH, Mauck KF, et al. Clinical review. Risk factors for low bone mass-related fractures in men: A systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:1861-1870.

19   Fujiyama K, Kiriyama T, Ito M, et al. Suppressive doses of thyroxine do not accelerate age-related bone loss in late postmenopausal women. Thyroid : official journal of the American Thyroid Association 1995;5:13-17.

20   Wang LY, Smith AW, Palmer FL, et al. Thyrotropin suppression increases the risk of osteoporosis without decreasing recurrence in ata low- and intermediate-risk patients with differentiated thyroid carcinoma. Thyroid : official journal of the American Thyroid Association 2015;25:300-307.

21   Novack DV. TSH, the bone suppressing hormone. Cell 2003;115:129-130.

20

22   Abe E, Marians RC, Yu W, et al. Tsh is a negative regulator of skeletal remodeling. Cell 2003;115:151-162.

23   Bassett JH and Williams GR. Role of thyroid hormones in skeletal development and bone maintenance. Endocr Rev 2016;37:135-187.

24   Svare A, Nilsen TI, Bjoro T, et al. Hyperthyroid levels of tsh correlate with low bone mineral density: The hunt 2 study. Eur J Endocrinol 2009;161:779-786.

25   Gorka J, Taylor-Gjevre RM, Arnason T. Metabolic and clinical consequences of hyperthyroidism on bone density. Int J Endocrinol 2013;2013:638727.

26   Abrahamsen B, Jorgensen HL, Laulund AS, et al. The excess risk of major osteoporotic fractures in hypothyroidism is driven by cumulative hyperthyroid as opposed to hypothyroid time: An observational register-based time-resolved cohort analysis. J Bone Miner Res 2015;30:898-905.

27   Karner I, Hrgovic Z, Sijanovic S, et al. Bone mineral density changes and bone turnover in thyroid carcinoma patients treated with supraphysiologic doses of thyroxine. Eur J Med Res 2005;10:480-488.

28   Shin DW, Suh B, Lim H, et al. J-shaped association between postoperative levothyroxine dosage and fracture risk in thyroid cancer patients: A retrospective cohort study. J Bone Miner Res 2018;33:1037-1043.

29   Khan N, Abbas AM, Almukhtar RM, et al. Prevalence and predictors of low bone mineral density in males with ulcerative colitis. J Clin Endocrinol Metab 2013;98:2368-2375.

FIGURE LEGENDS

Figure 1. Subgroup analysis of U.S. veterans with thyroid cancer using longitudinal

TSH (analyzed as a categorical variable) and osteoporosis risk (2004-2013).

23

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

Characteristics	Thyroid Cancer Patients N (%)	Controls N (%)
Sex[a]		
Male	8689 (83.8)	8689 (83.8)
Female	1681 (16.2)	1681 (16.2)
Age (years)[a]		
<50	2017 (19.4)	2018 (19.5)
50-64	4539 (43.8)	4538 (43.8)
65-74	2267(21.9)	2265 (21.8)
75-84	1356 (13.1)	1357 (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	1314 (12.7)	1412 (13.6)
$35,000 - $59,999	6125 (59.0)	6387 (61.6)
≥ $60,000	2931 (28.3)	2571 (24.8)
Charlson/Deyo Comorbidity Score		
0	6137 (59.2)	7802 (75.2)
1	1284 (12.4)	944 (9.1)
≥ 2	2949 (28.4)	1624 (15.7)
Androgen Use		
No	9642 (93.0)	9935 (95.8)
Yes	728 (7.0)	435 (4.2)
Steroid Use[a]		
No or < 3 months	9144 (88.2)	9144 (88.2)
≥ 3 months	1226 (11.8)	1226 (11.8)
Use of Osteoporosis Medication		
No	9488 (91.5)	9810 (94.6)
Yes	882 (8.5)	560 (5.4)
Bone Density Scans		
No	7911 (76.3)	9369 (90.3)
Yes	2459 (23.7)	1001 (9.7)

24

Osteoporosis[d]
No	9616 (92.7)	9826 (94.7)
Yes	754 (7.3)	544 (5.3)

Fractures
No	10117 (97.6)	10083 (97.2)
Yes	253 (2.4)	287 (2.8)

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

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

	Osteoporosis in Thyroid Cancer Patients	**Osteoporosis in Controls**[a]	**OR (95% CI)**
	N (%)	**N (%)**	
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 one year), weight (matched within 5 pounds; reported in kg as mean (standard deviation)), and steroid use.
[b] Reference group is controls.

25

Abbreviations: OR, odds ratio; CI, confidence interval; ref, reference

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

	Fractures in Thyroid Cancer Patients	Fractures in Controls[a]	OR (95% CI)
	N (%)	N (%)	
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 one year), weight (matched within 5 pounds; reported in kg as mean (standard deviation)), and steroid use.
[b] Reference group is controls.
[c] Median household income by geographic region.
Abbreviations: OR, odds ratio; CI, confidence interval; ref, reference

Table 4. Subgroup analysis of longitudinal TSH and other characteristics associated with osteoporosis in thyroid cancer patients (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 (years)		
Below 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)
Thyroid Stimulating Hormone		

27

(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 months	744 (7.7)	1.0 (ref)
≥ 3 months	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: OR, odds ratio; CI, confidence interval; ref, reference

Table 5. Subgroup analysis of longitudinal TSH and other characteristics associated with fractures in thyroid cancer patients (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 (years)		
Below 50	26 (1.3)	1.0 (ref)

28

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)
Thyroid Stimulating Hormone (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 months	241 (2.5)	1.0 (ref)
≥ 3 months	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.
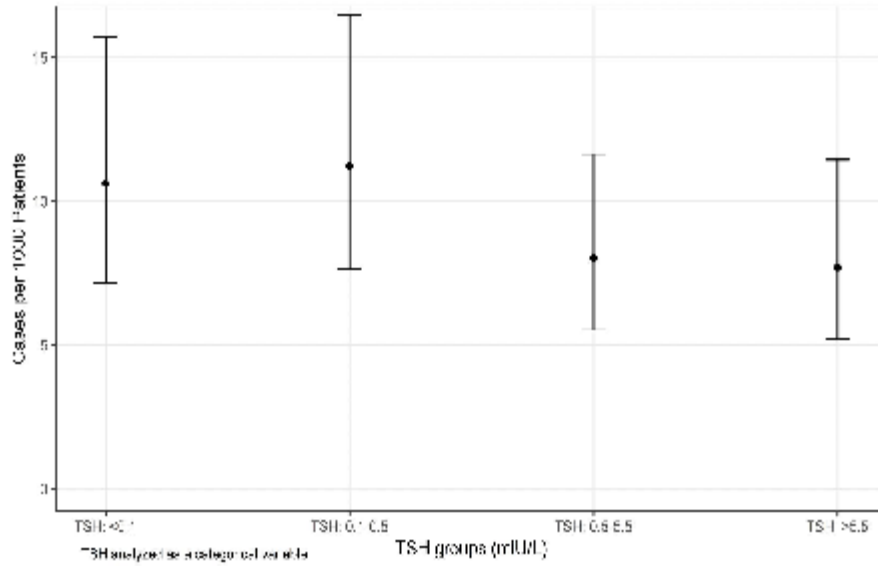Abbreviations: OR, odds ratio; CI, confidence interval; ref, reference

29

Figure 1. Subgroup analysis of longitudinal TSH and osteoporosis risk in U.S. veterans with thyroid cancer (2004-2013)

Figure 1. Subgroup analysis of longitudinal TSH and osteoporosis risk in U.S. veterans with thyroid cancer (2004-2013)