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Patients with Differentiated Carcinoma Are at increased Risk for Cardiovascular and All-Cause Mortality

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SUMMARY

Background

Because of the high survival rate of patients with differentiated thyroid cancer, potential long-term effects of cancer treatment are of concern. Although increased cardiovascular risk has been reported in patients with subclinical hyperthyroidism, to date TSH-suppressive thyroid hormone therapy has not been associated with increased mortality in thyroid cancer survivors (1-4).

Methods

This is a retrospective study using thyroid cancer cases from one cohort and general population controls from a second cohort. Cases were patients, 26 to 77 years of age, treated with thyroidectomy and radioactive iodine ablation for differentiated thyroid cancer at Groningen University Medical Center in the Netherlands between 1980 and 2010. Of 606 potentially eligible cases with differentiated thyroid cancer, 82 were excluded because of missing data and 110 were lost to follow-up. Three sex- and age-matched controls were randomly selected for each case from the general population subsample of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study cohort, a prospective study conducted in the same region of the Netherlands. A total of 1572 controls were selected, and 1277 completed follow-up. Until 2007, thyroid hormone doses for all cancer cases were targeted to a goal TSH less than the reference range. Starting in 2007, the TSH target in low-risk patients was <0.1 mIU/L for the first 2 years, followed by a goal level of 1.0 mIU/L. Starting in 2007, the goal TSH for high-risk cancer cases was <0.01 mIU/L.

Causes of death were classified as due to cardiovascular disease, progression/recurrence of thyroid cancer, or other/unknown. The primary outcome was cardiovascular mortality. Secondary outcomes were all-cause mortality and associations between TSH-suppressive thyroid hormone therapy and outcomes. Causes of mortality for the cancer cases were determined from medical records and contact with physicians, whereas mortality for the controls was ascertained using Statistics Netherlands. Baseline was defined as the date of thyroid cancer diagnosis for the cases and the date of PREVEND entry for the controls. Cardiovascular risk factors were ascertained at baseline, including age, sex, body-mass index, use of diabetes medications, smoking status, use of antihypertensive medications, use of antihyperlipidemic medications, and history of cardiovascular disease (defined as a previous stroke, myocardial infarction, peripheral-artery disease, or revascularization procedure). Patients with thyroid cancer were classified as low-risk (TNM staging Tx-T2Nx-N0Mx-M0), intermediate risk (T_3 or N1), or high risk (T_4 or M1). Cumulative radioactive iodine doses and use of adjuvant external neck radiotherapy were ascertained for all patients with thyroid cancer.

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Cox proportional-hazards regression, Kaplan–Meier survival analyses, and log-rank tests were used for analyses. Both crude and multivariate analyses were performed. For analyses of associations between TSH suppression and event-free survival, the geometric mean TSH values for each year of follow-up, excluding values resulting from periods of thyroid hormone withdrawal or use of recombinant human TSH, were used as predictors, and mean annual TSH was categorized as <0.02, 0.02 to 0.2, and >0.2 mIU/L.

Results

At baseline, treated diabetes (4.2% vs. 2.5%) and hypertension (17.7% vs. 11.5%) were more common among the cancer cases than among controls, and the patients with cancer were less likely to be current smokers (22.9% vs. 29.7%). The 414 patients were followed for a median of 8.5 years, during which time 22 died of cardiovascular disease, 39 of thyroid cancer, and 39 of other causes. The 1277 controls were followed for a median of 10.5 years, during which time 24 died of cardiovascular disease and 61 of other causes. Cardiovascular (P = 0.012) and all-cause (P<0.001) mortality were higher in the cases than in the controls. The hazard ratio for cardiovascular mortality in the cases compared with controls, adjusted for age, sex, and cardiovascular risk factors, was 3.35 (95% CI, 1.66 to 6.74) and the adjusted hazard ratio for all-cause mortality was 4.40 (95% CI, 3.15 to 6.14). For every 10-fold decrease in serum TSH, the hazard ratio for cardiovascular mortality, adjusted for age, sex, cardiovascular risk factors, thyroid cancer risk classification, cumulative radioactive iodine dose, tumor histology, and use of external-beam neck radiotherapy was 3.08 (95% CI. 1.32 to 7.21). After adjustment, mean TSH was not significantly associated with all-cause mortality.

Conclusions

Differentiated thyroid cancer was associated with an increased risk for cardiovascular and all-cause mortality, even after adjustment for age, sex, and cardiovascular risk factors. Lower serum TSH levels in the patients with thyroid cancer were associated with increased cardiovascular mortality risk.

ANALYSIS AND COMMENTARY

This is the first study to demonstrate increased cardiovascular mortality risk in patients with differentiated thyroid cancer. The cardiovascular risk was inversely associated with levels of serum TSH. Although not explored in this study, potential mechanisms for this association are increased incidence of atrial fibrillation, impaired diastolic function, and increased left ventricular mass in patients receiving TSH-suppressive thyroid hormone doses.

Strengths of the study include the relatively large sample size, long duration of follow-up, and adjustment for important risk factors. Limitations include the use of retrospective data (leading to limited information about some covariates, such as the use of antidiabetic medications as a proxy for the presence of diabetes), the use of two different cohorts with different mortality surveillance mechanisms, and substantial losses (19% to 21%) to follow-up. Future prospective cohort studies are needed to better understand predictors of cardiovascular risk among thyroid cancer survivors.

These data support the restriction of more stringent TSH suppression to patients with higher-risk thyroid cancers. The 2009 American Thyroid Association (ATA) thyroid cancer guidelines advocate initial TSH suppression to <0.1 mIU/L in high- and intermediate-risk patients, and to 0.1 to 0.5 mIU/L in low-risk patients (5). For long-term treatment, the guidelines recommend that TSH should be maintained at <0.1

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mIU/L indefinitely in patients with persistent disease. In those who presented with high-risk disease, but who become clinically and biochemically disease-free, TSH should be maintained at 0.1 to 0.5 mIU/L for 5 to 10 years. For low-risk patients who appear to be free of disease, the serum TSH may be allowed to rise to 0.3 to 2.0 mIU/L. Revised ATA thyroid cancer guidelines are currently in development and may provide additional guidance regarding risk stratification in the use of TSH suppression.

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