RESEARCH

Long-term cardiovascular and cerebrovascular morbidity in Israeli thyroid cancer survivors

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Abstract

Objective: Thyroid cancer (TC) survivors may be at risk of subsequent cardiovascular and cerebrovascular (CaV&CeV) morbidity. The 2009 American Thyroid Association (ATA) guidelines recommended less aggressive treatment for low-risk TC patients. The aim of this study was to assess the atherosclerotic CaV&CeV outcome of Israeli TC survivors compared to individuals with no thyroid disease, and the atherosclerotic CaV&CeV outcome before (2000–2008) and after (2009–2011) implementation of the 2009 ATA guidelines.

Methods: All members of the largest Israeli healthcare organization who were diagnosed with TC from 1/2000 to 12/2014 (study group) and age- and sex-matched members with no thyroid disease (controls) were included. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards models.

Results: The mean follow-up was 7.6 ± 4.2 and 7.8 ± 4.1 years for the study (n = 5,677, 79% women) and control (n = 23,962) groups, respectively. The former had an increased risk of new atherosclerotic CaV&CeV events (adjusted HR 1.26, 95% CI 1.15–1.39). The 5-year incidence of CaV&CeV was lower (adjusted HR 0.49, 95% CI 0.38–0.62) from 2009 to 2011 compared to 2000 to 2008, but remained higher in the study group than in the control group (adjusted HR 1.5, 95% CI 1.14–1.69).

Conclusions: This large Israeli population-based cohort study showed greater atherosclerotic CaV&CeV morbidity in TC survivors compared to individuals with no thyroid diseases. There was a trend toward a decreased 5-year incidence of atherosclerotic CaV&CeV events among TC survivors following the implementation of the 2009 ATA guidelines, but it remained higher compared to the general population.

Key Words
- thyroid carcinoma
- cardiovascular morbidity
- cerebrovascular morbidity
- hyperlipidemia
- hypertension

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Introduction

Thyroid cancer (TC) usually affects young adults, the majority of whom are women. Recent trends have shown a dramatic increase in the incidence of TC (1, 2) together with high survival rates (3). The treatment protocol of TC generally consists of thyroidectomy, radioiodine ablation and treatment with levothyroxine

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at dosages aimed to achieve suppression of the thyroid-stimulating hormone (TSH). However, lower TSH levels in TC survivors were found to be associated with a higher risk of cardiovascular (CaV) mortality (4). Data from the Surveillance, Epidemiology and End Results program, which estimated the probability of death resulting from TC, other cancers and non-cancer causes in a cohort of 29,225 TC survivors, showed that the most frequent causes of non-cancer mortality in TC survivors were heart diseases (39%) and cerebrovascular (CeV) diseases (10.4%) (5). A Dutch case–control study revealed a 3.3-fold increase in the risk of CV mortality among TC survivors (4). Several small-scale studies of TC survivors with suppressed TSH showed impairment in cardiac structure (6, 7) and function (8, 9, 10, 11, 12), as well as a prothrombotic profile (13). An increase in the prevalence of atrial fibrillation (AF) in subjects with low TSH levels is well established (14, 15), including TC survivors with suppressed TSH (16). An increased prevalence of cardiovascular risk factors was reported for TC survivors compared to individuals matched by age, sex and birth state (17). An increased incidence of cardiovascular risk factors at 1–5 years after the diagnosis of TC and an increased risk of CaV&CeV morbidity among TC survivors have also been reported (18, 19).

The 2009 Guidelines of the American Thyroid Association recommended against radioiodine ablation for microcarcinomas and low-risk carcinomas and more restrictive surgery for those patients (20). The first objective of this large population-based historical cohort study was to assess the incidence of atherosclerotic CaV and CeV morbidity in Israeli TC survivors compared to a sex- and age-matched control group with no thyroid disease, while controlling for cardiovascular risk factors and previous CaV&CeV morbidity. The second objective was to compare the 5-year incidence of CaV&CeV morbidity before and after the issuance of the revised guidelines in 2009.

Subjects and methods

Study participants

This historic cohort study was carried out within the framework of the Clalit Health Services (CHS), the largest healthcare organization in Israel that covers around 55% of the total population. Computerized medical records were reviewed of all members from age 18 years and above who were insured by CHS from January 1, 2000, to June 30, 2016. Inclusion criteria for the TC group were a diagnosis of TC between January 1, 2001, and December 31, 2014, a history of partial or total thyroidectomy and treatment with levothyroxine. The non-TC control group included CHS members without any documented history of cancer or of any thyroid dysfunction who were matched by sex and age (±2 years) to each TC patient at a ratio of 5:1. Exclusion criteria for both groups were any primary cancer prior to study entry (other than TC for the study group), with the exception of squamous or basal cell carcinoma of the skin. Patients with significant renal impairment (creatinine above 1.5 mg/dL) from both groups were excluded from the statistical analysis because of the influence of renal failure on the clinical decision of radioactive iodine administration in the TC group. After exclusion of persons with renal failure, the ratio between the exposed and non-exposed groups became 1:4.2.

Study design and data sources

The following data were collected for both groups: demographic characteristics, body mass index, smoking habits, background morbidity, previous and newly diagnosed diabetes mellitus, hypertension, dyslipidemia, CaV and CeV diseases, medications during the follow-up of the study period and laboratory tests that included levels of glucose and creatinine, the lipid profile and thyroid function test results closest to study entry.

The atherosclerotic CaV&CeV disease was defined by ICD code as a diagnosis recorded before and during the study period of at least one of the following conditions: ischemic heart disease, myocardial infarction, transient ischemic attack, cerebrovascular accident (stroke), carotid artery stenosis or occlusion. It also included the members having undergone one of the following procedures: percutaneous transluminal coronary angioplasty, coronary artery bypass graft or carotid endarterectomy. New-onset AF was not included as a variable.

Diabetes mellitus prior to and during the follow-up period was defined as having at least one of the following: (1) a diabetes mellitus diagnosis recorded in the CHS database; (2) two fasting plasma glucose measurements higher than 125 mg/dL; (3) a random plasma glucose measurement higher than 199 mg/dL; (4) a record of hypoglycemic medications.

Hypertension prior to and during the follow-up period was defined as having at least one of the following: (1) a hypertension diagnosis recorded in the CHS database; (2) three or more measurements of systolic blood pressure

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higher than 140 mmHg or diastolic blood pressure higher than 90 mmHg; (3) a record of hypertension medication.

Dyslipidemia prior to and during the follow-up period was defined as having at least one of the following: (1) a hyperlipidemia diagnosis recorded in the CHS database; (2) at least two plasma low-density lipoprotein cholesterol measurements higher than 160 mg/dL, a triglyceride measurement higher than 150 mg/dL or a high-density lipoprotein cholesterol level lower than 40 mg/dL for males or lower than 50 mg/dL for females; (3) a record of hypolipidemic medications.

Ethics

The study was approved by the Medical Ethics Committee of CHS. Exemption from obtaining signed informed consent forms was granted since the study was based on existing databases and no direct contact was made with the participants.

Statistical analysis

Data were analyzed with SPSS software, version 23.0. (SPSS Inc.). Significance levels were set at 0.05. Data are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Chi-square tests and independent *t*-tests were performed to compare the two groups for categorical and continuous variables, respectively. Multivariate analysis using a Cox regression model for time to atherosclerotic CaV&CeV event was performed, adjusted for conventional risk factors. The covariates were age, sex, hypertension, diabetes mellitus, current smoking, dyslipidemia and previous CaV or CeV disease. Survival was calculated as time from study entry to the first CaV or CeV event or to death from all causes, or to the end of the follow-up period (June 30, 2016), whichever occurred earlier. The HR and 95% CIs for the first CaV or CeV events in total, by sex, and by age groups (<44, 45 to 54, 55 to 64, 65 to 74 and >75 years) were computed using the Cox proportional hazards regression model. A subanalysis using the same models but referring to the new CaV&CeV events only was performed following the exclusion of individuals with a history of CaV&CeV morbidity at study entry. We further demonstrated the cumulative survival curves adjusted to conventional risk factors. A subanalysis compared the 5-year incidence of CV&CeV morbidity following a diagnosis of TC from January 1, 2000, to December 31, 2008, and from January 1, 2009, to June 30, 2011.

Results

The mean follow-up periods were 7.6±4.2 and 7.8±4.1 years for the study (n=5,677) and the control (n=23,962) groups, respectively. The characteristics of both groups were similar following age and sex matching, although the study group had a slightly higher proportion of men (21.4 vs 20.5%) and its mean age was slightly older (50±16 vs 47±15 years) than the control group due to the exclusion of members with renal failure (Table 1).

At baseline, the prevalence of both hypertension and dyslipidemia was higher in the study group compared to

Table 1 Baseline characteristics of the non-thyroid cancer and thyroid cancer survivors groups.

	Non-thyroid cancer group (n = 23,962)	Thyroid cancer survivors group (n = 5677)
Male sex, *n* (%)	4912 (20.5)	1216 (21.4)
Age (years)		
Mean (S.D.)	47 (15)	50 (16)
Median (range)	46 (18–100)	49 (18–108)
Smoking		
Past, *n* (%)	1249 (5.2)	371 (6.5)
Current, *n* (%)	6080 (25.4)	947 (16.7)
Never or no response, *n* (%)	16,633 (69.4)	4359 (76.8)
Weight, mean (S.D.) (kg)	76 (21)[d]	78 (21)[e]
Height, mean (S.D.) (cm)	163 (8.6)	164 (8.7)
BMI, mean (S.D.), kg/m^2	28.0 (6.8)[d]	28.5 (6.5)[e]
<18.5, *n* (%)	256 (2.0)	38 (1.4)
18.5–24.99, *n* (%)	4527 (34.7)	820 (30.9)
25–29.99, *n* (%)	4221 (32.4)	893 (33.7)
≥30, *n* (%)	4031 (30.9)	900 (33.9)
SBP, mean (S.D.), mmHg	122 (16)	123 (15)
DBP, mean (S.D.), mmHg	74.6 (10.6)	75.4 (9.0)
Pulse, mean (S.D.), beat/min	76 (10.4)	76 (10.2)
Cerebrovascular disease[a], *n* (%)	624 (2.6)	53 (0.9)
Cardiovascular disease[b], *n* (%)	1330 (5.6)	119 (2.1)
Composite variable[c], *n* (%)	1631 (6.8)	154 (2.7)
Hypertension, *n* (%)	4647 (19.3)	1405 (24.7)
Diabetes, *n* (%)	2694 (11.2)	707 (12.5)
Dyslipidemia, *n* (%)	6855 (28.5)	1865 (33.0)
Fatty liver, *n* (%)	285 (1.2)	101 (1.8)
Atrial fibrillation, *n* (%)	119 (0.5)	170 (0.3)
Rheumatic disease, *n* (%)	17 (0.1)	8 (0.1)

[a]Transient ischemic attack, cerebral vascular attack, carotid artery stenosis and occlusion, carotid endarterectomy; [b]ischemic heart disease, acute myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft; [c]composite variable of atherosclerotic cerebrovascular and cardiovascular disease; [d]number of the non-thyroid cancer participants with available data 13,077 (54%); [e]number of the thyroid cancer survivors with available data 2658 (46.8%). BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; S.D., standard deviation.

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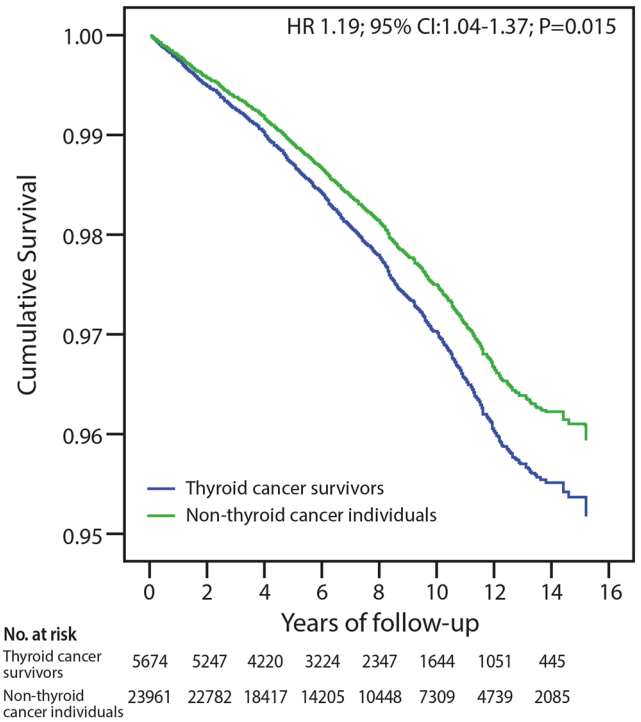

Figure 1
Kaplan–Meier survival curve showing the risk of new cerebrovascular events among the thyroid cancer survivors (n = 5677) and non-thyroid cancer (n = 23,962) groups, including individuals with previous cardiovascular and cerebrovascular morbidity. HR indicates the hazard ratio for new cerebrovascular events during follow-up adjusted for cardiovascular risk factors (age, sex, hypertension, diabetes mellitus, dyslipidemia and current smoking) and for previous atherosclerotic cerebrovascular and cardiovascular morbidity.

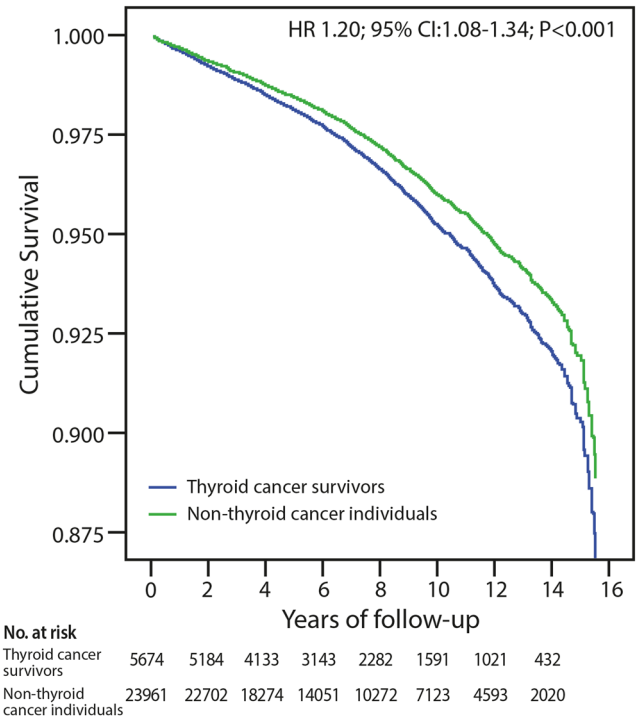

Figure 2
Kaplan–Meier survival curve showing the risk of new cardiovascular events among the thyroid cancer survivors (n = 5677) and non-thyroid cancer (n = 23,962) groups, including individuals with previous cardiovascular and cerebrovascular morbidity. HR indicates the hazard ratio for new cardiovascular events during follow-up, adjusted for cardiovascular risk factors (age, sex, hypertension, diabetes mellitus, dyslipidemia and current smoking) and for previous atherosclerotic cerebrovascular and cardiovascular morbidity.

the controls (24.7 vs 19.3% and 33.0 vs 28.5%, respectively, $P<0.05$ for both), while the prevalence of atherosclerotic CaV&CeV morbidity in the study group was lower (2.7% (154/5677) vs 6.8% (1631/23,962), respectively, $P<0.001$). The mean baseline levels of the laboratory tests, including glucose, lipid profile and kidney function, were similar for the two groups.

During the study period, 555 (9.8%) participants with TC and 1856 (7.7%) participants without TC had new or recurrent CaV&CeV events. In parallel, hypertension and dyslipidemia were higher in the former compared to the latter group (11.7 vs 9.6% and 22 vs 19.7%, respectively, $P<0.001$ for both) during the follow-up period.

The following factors were associated with a higher risk of new atherosclerotic CaV&CeV events in both groups in the univariate Cox regression analysis: a diagnosis of TC (HR 1.27, 95% CI: 1.14–1.42), older age (per each 1-year increment, HR 1.06, 95% CI: 1.06–1.07), male sex (HR 1.59, 95% CI: 1.45–1.74), previous CaV&CeV morbidity (HR 1.24, 95% CI: 1.07–1.45), hypertension (HR 1.81, 95% CI: 1.63–2.00), diabetes mellitus (HR 1.63, 95% CI: 1.49–1.78) and current smoking (HR 1.55, 95% CI: 1.41–1.71). Previous dyslipidemia was a risk factor for new CaV&CeV events in the control group but not in the study group (HR 1.36, 95% CI: 1.21–1.53 vs 1.14, 95% CI: 0.92–1.42, respectively).

TC was found to be a risk factor for new cerebrovascular events (HR 1.19, 95% CI: 1.04–1.37) in a multivariate Cox regression analysis adjusted for previous atherosclerotic CaV&CeV morbidity and cardiovascular risk factors (age, sex, hypertension, diabetes mellitus, dyslipidemia and current smoking) (Fig. 1) for new cardiovascular events (HR 1.20, 95% CI: 1.08–1.34) (Fig. 2) and for new atherosclerotic CaV&CeV events (HR 1.26, 95% CI: 1.15–1.39) (Fig. 3). After exclusion of the patients in both groups with a history of CaV&CeV morbidity, the HRs in the study group remained higher for new cerebrovascular events (HR 1.16, 95% CI: 1.01–1.36), for new cardiovascular events (HR 1.18, 95% CI: 1.05–1.33)

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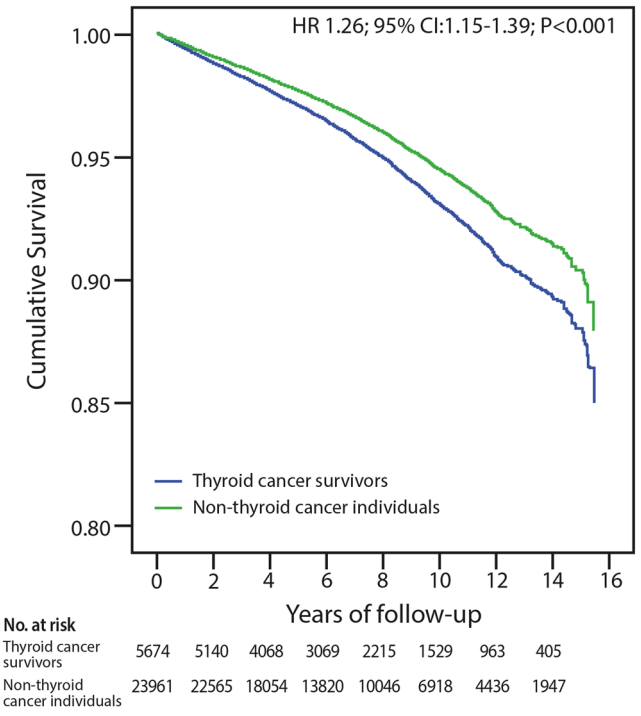

Figure 3
Kaplan–Meier survival curve showing the risk of all incident atherosclerotic events (cardiovascular and cerebrovascular) among the thyroid cancer survivors (n = 5677) and non-thyroid cancer (n = 23,962) groups, including individuals with previous cardiovascular and cerebrovascular morbidity. HR indicates the hazard ratio for all new atherosclerotic (cardiovascular and cerebrovascular) events during follow-up, adjusted for cardiovascular risk factors (age, sex, hypertension, diabetes mellitus, dyslipidemia and current smoking) and for previous atherosclerotic cerebrovascular and cardiovascular morbidity.

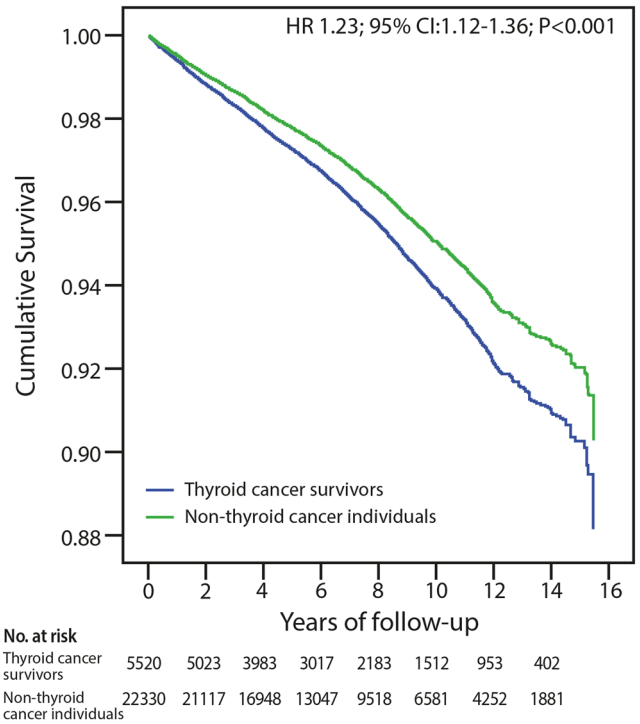

Figure 4
Kaplan–Meier survival curve showing the risk of all atherosclerotic events (cardiovascular and cerebrovascular) among the thyroid cancer survivors (n = 5,432) and non-thyroid cancer (n = 22,281) groups, after excluding individuals with previous cardiovascular and cerebrovascular morbidity. HR indicates the hazard ratio for all new atherosclerotic (cardiovascular and cerebrovascular) events during follow-up, adjusted for cardiovascular risk factors (age, sex, hypertension, diabetes mellitus, dyslipidemia and current smoking), after excluding individuals with previous cardiovascular and cerebrovascular morbidity.

and for new atherosclerotic CaV&CeV events (HR 1.23, 95% CI: 1.12–1.36) (Fig. 4).

Stratification by sex revealed an increased HR for new CaV&CeV events among the women in the study group with and without previous CaV&CeV morbidity (HR 1.25, 95% CI: 1.11–1.40 and HR 1.29, 95% CI: 1.14–1.46, respectively). The increased HR among men in the study group was statistically significant in the analysis that included survivors with previous CaV&CeV morbidity (HR 1.20, 95% CI: 1.01–1.42); however, the estimate lost its statistical significance in the analysis after the exclusion of survivors with previous CaV&CeV morbidity (HR 1.18, 95% CI: 0.97–1.44).

Stratification by age showed an increased risk of new atherosclerotic CaV&CeV events in the study group for the subgroups aged 55–64 years (HR 1.29, 95% CI: 1.08–1.53) and 65–74 years (HR 1.36, 95% CI: 1.14–1.61). The risk in those age groups remained elevated after the exclusion of individuals with previous CaV&CeV morbidity, (HR 1.32, 95% CI: 1.09–1.60 and HR 1.41, 95% CI: 1.16–1.72, respectively).

The time that had elapsed from TC diagnosis to the occurrence of new atherosclerotic CaV&CeV events was within 2 years for 9.5%, from 2 to 5 years for 27.2%, from 5 to 10 years for 35.8% and over 10 years for 27.5% of the TC survivors. We analyzed the data after exclusion of new CaV&CeV events that occurred during the first 2 years of follow-up in order to allow a minimal latency period and to assess long-term CaV&CeV morbidity. The HRs adjusted for cardiovascular risk factors (age, sex, hypertension, diabetes mellitus, dyslipidemia and current smoking) and for previous atherosclerotic CaV&CeV morbidity (if applicable) remained increased in the study group for new cerebrovascular events (HR 1.26, 95% CI: 1.06–1.50), for new cardiovascular events (HR 1.17, 95% CI: 1.02–1.34) and for new atherosclerotic CaV&CeV events (HR 1.27, 95% CI: 1.13–1.43).

The 5-year incidence of CaV&CeV was lower following a TC diagnosis from 2009 to 2011 than from 2000 to 2008 (5.8% (63/1085) vs 8.2% (241/2939), respectively,

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HR 0.52 (95% CI: 0.41–0.66)). The HR was 0.49 (95% CI: 0.38–0.62) after adjusting for age, sex and previous CaV&CeV morbidity. Between the same two study periods, the incidence of dyslipidemia declined among the TC survivors from 10.4% (305/2939) to 4.9% (53/1085), $P<0.001$, and the incidence of hypertension declined from 13.2% (387/2939) to 6.1% (66/1085), $P<0.001$. However, the HR for new CaV&CeV morbidity remained increased among the TC survivors (HR 1.29, 95% CI: 1.11–1.50 and HR 1.5, 95% CI: 1.14–1.98, respectively) in a multivariate Cox regression analysis of both study groups before and after the issuance of the revised guidelines in 2009 compared to the non-TC individuals.

Discussion

The results of this large population study demonstrated that TC was independently associated with an increased risk of atherosclerotic CaV&CeV morbidity. Our findings concur with the increased incidence of cardiovascular risk factors at 1–5 years after diagnosis of TC and with the increased risk of CaV&CeV morbidity among TC survivors reported by the Utah Cancer Survivors Study and recently observed in Korean population (17, 18, 19). Importantly, our definitions of CaV&CeV disease were more stringent than those of the Utah Cancer Survivors study, as well as being related to the events themselves rather than to the conditions associated with atherosclerotic disease (e.g., hypertension, AF). In contrast, we found a reduction in the incidence of CaV&CeV morbidity, as well as a parallel decreased incidence of dyslipidemia and hypertension among TC survivors diagnosed during 2009 to 2011 when the ATA guidelines for less aggressive treatment were followed compared to 2000 to 2008 before they had been introduced. However, the incidence of CaV&CeV morbidity remained higher for the TC survivors compared to the non-TC individuals during those two time periods.

In the current cohort, the increased HRs for new CaV&CeV events were more prominent among TC survivors in the age groups of 55–64 years and 65–74 years and remained increased after exclusion of the individuals with previous CaV&CeV morbidity. The HR for new CaV&CeV events among the women with TC was higher before and after excluding those with previous CV&CeV morbidity at study entry. The HR for new CaV&CeV events among the men with TC was higher before but not after excluding those with previous CaV&CeV morbidity at study entry. Since men comprised only 21% of the cohort, the smaller numbers may be a reason for the lack of statistical significance.

There are several explanations for the new trends in the incidence of CaV&CeV morbidity in TC survivors. Treatment of TC generally consists of a thyroidectomy, radioiodine ablation and treatment with levothyroxine at dosages to achieve TSH suppression. La Coeur *et al*. observed that although the effect of radioiodine therapy on morbidity was not conclusive; however, their retrospective cohort study did reveal increased cerebrovascular events in both hyperthyroid and euthyroid patients treated with radioiodine for benign thyroid disorders (21). This supports the possible contribution of radioiodine treatment to cerebrovascular morbidity by accelerating or initiating atherosclerosis. However, the same investigators were not able to detect signs of atherosclerosis in that setting and that applied to both early signs of atherosclerosis, as assessed by changes in carotid intima media thickness during the first year following radioiodine therapy, as well as late signs of atherosclerosis, as assessed by comparing the presence of plaque in patients to controls at a median of 10 years after radioiodine treatment (22). Park *et al*. recently reported a marginal association between radiation therapy after surgery and an elevated risk of cerebrovascular disease compared with surgery only in TC survivors (18). Sanal *et al*. observed carotid artery intimal thickening after RAI for benign disease (23).

TSH suppression therapy caused a state of subclinical hyperthyroidism and is a part of TC treatment. The current study does not have any data on the exact dosages of levothyroxine or the TSH-suppressive levels that were achieved. However, others have reported the contributions of the therapeutic components. A poorer cardiovascular profile has been reported among individuals with subclinical hyperthyroidism not associated with TC (24, 25, 26, 27, 28, 29, 30, 31). However, a pooled analysis of four prospective cohort studies failed to demonstrate any association between subclinical hyperthyroidism and stroke (32). Another study showed that adverse events related to arterial stiffness or central hemodynamics were not increased among TC survivors who were not treated with TSH suppression therapy when compared with a sex- and age-matched control group that did not undergo thyroidectomy (33). Similarly, no impairment in cardiac function or structure was observed among TC survivors who were treated for up to 9 years with levothyroxine therapy and whose TSH levels were higher than those recommended for TSH suppression (34). These studies suggest that levothyroxine therapy

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alone (without TSH suppression) does not contribute to a poorer metabolic profile. Due to the increased risk of side effects and the limited benefits of TSH suppression in low- and intermediate-risk differentiated TC (6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 35, 36), the updated ATA 2015 guidelines advocate it solely for patients with a high risk of differentiated TC recurrence (37).

A randomized placebo-controlled trial of individuals with 10 or more years of TSH suppressive therapy for TC found that glucose and lipid metabolism remained constant and similar between those who continued TSH-suppressive therapy during a 6-month period and those whose TSH treatment was reduced to a level compatible with euthyroidism (38). During the follow-up of the current study, the incidences of both hypertension and dyslipidemia were higher in the TC group compared to the non-TC group. These findings may explain, at least in part, the increased incidence of atherosclerotic CV&CeV morbidity observed among TC survivors. An especially interesting finding in the current study was a decreased incidence of hyperlipidemia, hypertension and new CaV&CeV events in TC survivors diagnosed between 2009 and 2011 compared to those diagnosed between 2000 and 2008. We suggest that the issuance and following of ATA 2009 guidelines (and 2015 ATA guidelines) for more restrictive surgery and conservative use of RAI treatment and the resulting reduction in metabolic changes may well have contributed to this trend. It is important to note that despite the decrease in the incidence of CaV&CeV morbidity among the TC survivors in the later follow-up period, it was still higher among the TC survivors compared to the non-TC individuals in both time periods. This would appear to indicate that TC survivors compose a high-risk group for cardiovascular events.

Several limitations of this study bear mention. While the large population size and the cohort design are strengths of this study, we had no data on tumor stage or responsiveness to radioiodine therapy. A major limitation of this study is that the TSH values after surgery and those during and at the end of follow-up were not recorded. Moreover, no distinction was made between the different types of TC. Differentiated TC comprises over 90% of the cases of TC, with a considerably better prognosis than the less common TC types (medullary and anaplastic).

In conclusion, the findings of this Israeli population-based cohort study demonstrated an increased risk of new atherosclerotic CaV&CeV events among TC survivors diagnosed between 2000 and 2014 and followed up until June 30, 2016, as well as a higher incidence of hyperlipidemia and hypertension among those who developed CaV&CeV disease in comparison to individuals with no thyroid diseases during the same follow-up period. In addition, we showed a trend toward decreased new atherosclerotic CaV&CeV events, as well as a parallel decreased incidence of hyperlipidemia and hypertension in TC survivors diagnosed between 2009 and 2011 when the treatment of low-risk TC became less aggressive than that recommended in the pre-2009 ATA guidelines. However, incidence of CaV&CeV morbidity remained increased in TC survivors compared to non-TC individuals during both time periods. The clinical implications of these findings is that while less aggressive treatment of low-risk TC patients causes fewer metabolic changes in TC survivors, it still leaves them at high risk for cardiovascular events and that cardiovascular risk factors should be closely followed and perhaps more aggressively treated in this setting. Future research should define the actual risk of atherosclerotic CaV&CeV morbidity in TC survivors, the majority of whom are women, and identify early signs and effective means of prevention.

Declaration of interest

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

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