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Cardiovascular Mortality in 6900 Patients with Differentiated Thyroid Cancer: A Swedish Population-based Study

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Abstract

Background: Patients with differentiated thyroid cancer (DTC) are usually administered life-long TSH suppression treatment to reduce the recurrence risk, but however concomitantly risk hyperthyroidism and consequently cardiovascular (CV) mortality as an adverse effect. This study's objective was to assess the risk of CV mortality in Swedish DTC patients relative to the general Swedish population.

Methods: In this nationwide cohort-study, each patient was followed from one year post DTC diagnosis to the date of death, migration or 31 of December 2014. CV mortality in DTC patients was compared with the general population through standardized mortality ratios (SMRs). All patients diagnosed with DTC in Sweden in 1987-2013 were at baseline included in the study, and the vast majority of patients were assumed to have received life-long TSH suppression treatment in compliance with the prevalent national guidelines.

Results: Out of 6900 DTC patients included, 550 (7.97%) died with an underlying CV diagnosis. On an aggregate level, the cohort did not experience a higher risk of CV mortality, although men ran an increased risk of CV mortality (SMR 1.16 CI 95% 1.02-1.31). The cohort overall also had an elevated risk of mortality in atrial fibrillation (SMR 1.36 CI 95% 1.12-1.64). We found that the age category of <45 years at diagnosis that lived 20 years after diagnosis experienced higher CV mortality (SMR 3.80 95% CI 1.71-8.46) than expected in the general population.

Conclusion: We found no increased rate of CV mortality on an aggregate level in patients diagnosed with DTC, compared with CV mortality in the general Swedish population. However, following a DTC diagnosis, the data suggests that young patients with long follow-up duration were observed to face an elevated risk of CV mortality. We also noted that patients encountered elevated risks of AF mortality, and that male DTC patients faced elevated risk of CV mortality in general.

Keywords: Thyroid stimulating hormone; Cardiovascular; Mortality; Differentiated thyroid cancer

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Abbreviations

AF: Atrial Fibrillation; CV: Cardiovascular; DTC: Differentiated Thyroid Cancer; HF: Heart Failure; SMR: Standardized Mortality Ratio; TSH: Thyrotropin Thyroid Stimulating Hormone

Introduction

Papillary and follicular cancers all fall into the category of differentiated thyroid cancer (DTC), which is by far the most common thyroid carcinoma, accounting for more than 95% of the cases [1]. Although a subject of recent debate [1], the general cornerstones of the initial curative treatment traditionally consist of total thyroidectomy and radioactive iodine treatment [2]. After these procedures, thyrotropin levels (TSH) are often suppressed with levothyroxine usually in a life-long manner, since clinical data demonstrate that TSH stimulates cancer cells [1-3], where the cancer stage determines the level of TSH suppression [1]. The prognosis of DTC is good, where the 10 year relative survival surpasses 90% [4]. As a consequence of the good prognosis, the majority of patients

Table 1: Descriptive characteristics of patients diagnosed with differentiated thyroid cancer in Sweden during 1987 to 2013 (follow up to 2014).

	Entire Cohort		Cardiovascular Deaths	
	N	%	N	%
All	6900	100	550	7.97
Sex				
Male	1812	26.26	203	11.20
Female	5088	73.74	347	6.82
Age at inclusion				
<45	2523	36.57	14	0.55
45-54	1338	19.39	28	2.09
55-64	1161	16.83	79	6.80
65-74	1062	15.39	207	19.49
>=75	816	11.83	222	27.21
Year of inclusion				
1987-1995	1941	28.12	334	17.21
1996-2004	1992	28.87	166	8.33
2005-2013	2967	43.00	50	1.69
TNM[1]				
T-stage				
Missing	668	22.51	7	1.05
0	28	0.94	0	0.00
I	1085	36.57	12	1.11
II	634	21.37	15	2.37
III	408	13.75	5	1.23
IV	144	4.85	11	7.64
N-stage				
Missing	1118	37.68	12	1.07
0	1262	42.53	28	2.22
I	587	19.78	10	1.70

[1]Restricted to patients diagnosed in 2005 or later

do not die from the thyroid cancer itself, but instead risks dying from the postoperative cancer treatment and or other illnesses [5]. A natural consequence of TSH suppression is subclinical hyperthyroidism, which several previous studies have examined in relation to cardiovascular (CV) diseases and mortality. In patients without DTC, subclinical hyperthyroidism has been shown to increase the heart rate and left ventricular size [6,7], and is comorbid with atrial fibrillation (AF) and heart failure (HF) [8,9]. A recent study also indicates that patients with DTC have a higher incidence of AF compared to healthy individuals [10]. The literature is however inconclusive whether subclinical hyperthyroidism primarily generates HF, which in turn gives rise to AF, or whether subclinical hyperthyroidism creates AF through a direct pathway mechanism [11]. In the case of DTC patients with TSH suppression, studies report increased incidence of AF, HF, decreased arterial elasticity and negative prothrombotic effects [12-16]. Furthermore, in patients without DTC, subclinical hyperthyroidism is also associated with increased CV mortality [17,18]. However, most studies conducted on patients with DTC do not indicate increased CV mortality [19-21], with the exception of one recent study [22] that suggests an increased risk of CV-mortality thus giving clinicians reason to question the main body of evidence. This study examines a nationwide population-based cohort during

Table 2: Number of cardiovascular deaths and corresponding standardized mortality ratios (SMRs) following a diagnosis of differentiated thyroid cancer in Sweden 1987-2013.

Cardiovascular Mortality					
Endpoint	N	%	Overall SMR	Male SMR	Female SMR
Cardiovascular Mortality	550	100	1.02	1.16	0.95
95% CI			0.94-1.10	1.02-1.31	0.86-1.05
Ischemic Heart Disease	261	47.25	0.95	1.07	0.88
95% CI			0.84-1.07	0.88-1.28	0.75-1.03
Ischemic Heart Attack	127	23.10	0.95	1.00	0.92
95% CI			0.80-1.14	0.76-1.32	0.73-1.16
Heart Failure	237	43.10	0.97	1.11	0.91
95% CI			0.86-1.11	0.89-1.37	0.78-1.07
Atrial Fibrillation	108	19.64	1.36	1.25	1.40
95% CI			1.12-1.64	0.97-1.80	1.12-1.75
Cerebrovascular Disease	169	30.73	0.93	0.98	0.90
95% CI			0.80-1.08	0.75-1.30	0.75-1.08
Cerebral Infarction	109	19.82	0.98	1.11	0.93
95% CI			0.82-1.19	0.80-1.56	0.75-1.17

Individual cardiovascular outcomes exceed the total amount of cardiovascular mortalities due to double accounting of the International Classification of Disease system as well as potential comorbidity.

an extensive duration of follow-up, and aims at assessing the risk of CV mortality in DTC patients relative to the general population. We hypothesized that DTC patients run a higher risk of CV mortality relative to the general population.

Materials and Methods

The publicly funded Swedish health-care system, in combination with a unique personal identity number assigned to all residents [23], enables high standard nationwide registers containing all hospital admissions and discharges, cancer diagnoses, causes of death and migration [24]. We identified individuals diagnosed with DTC International Classification of Disease (ICD) 7 194, pathology-anatomy diagnosis 096 (medullar and anaplastic thyroid cancer are excluded), during 1987-2013 from the Swedish Cancer Registry. Only the first diagnosis of thyroid cancer during the study period was considered for individuals with more than one diagnosis. Information on date and cause of death was collected from the Cause of death registry. Only individuals that stayed in the cohort at least one year post diagnosis were included in the final study cohort.

End-points

To strengthen a potential causal relationship between TSH suppression and CV mortality, each patient was followed from one year post DTC diagnosis to the date of death, migration or 31 of December 2014, whichever came first. The end-point of interest was CV death, while migration, other mortalities and end of follow-up were considered censoring events. We investigated 7 different end-points of CV death: Ischemic Heart Disease (ICD-9:410-414, ICD-10:I20-25), Ischemic Heart Attack (ICD-9:410. ICD-101:I21, I22), Heart Failure (ICD-9:428 ICD-10:I50), Cerebral Infarction (ICD-9:431,434,436. ICD-10:I61, I63, I64), Cerebrovascular Disease (ICD-9:430-434,436-438. ICD-10:I60-69) and Atrial Fibrillation (ICD-9:427D, 427A. ICD-10:I48), and CV death overall (any of the listed ICD-codes above). The seven different end-points were all categorized by considering both primary and contributing causes of death.

Table 3: The standard mortality ratios (SMRs) of 550 cardiovascular deaths in 6900 patients diagnosed with differentiated thyroid cancer in Sweden.

	Cardiovascular Mortality	
N=550	SMR	95% CI
Overall	1.02	0.94-1.10
Male	1.16	1.02-1.31
Female	0.95	0.86-1.05
Age <45	1.58	0.94-2.67
Age 45-54	1.21	0.85-1.76
Age 55-64	1.19	0.96-1.47
Age 65-74	1.16	1.02-1.32
Age 75+	0.87	0.77-0.98
Years 1987-1995	0.98	0.89-1.09
Years 1996-2004	1.06	0.92-1.22
Years 2005-2013	1.10	0.89-1.38
Follow Up (Years)		
0-10	0.79	0.68-0.91
10-20	0.91	0.75-1.11
20-27	1.14	0.82-1.57

Table 4: The standardized mortality ratios (SMRs) of atrial fibrillation mortality (n=108) in patients diagnosed with differentiated thyroid cancer in Sweden.

Atrial Fibrillation Mortality	SMR	
N=108	SMR	95% CI
Overall	1.36	1.12-1.64
Male	1.25	0.87-1.80
Female	1.40	1.12-1.75
Age 45-54	3.96	1.78-8.81
Age 55-64	2.40	1.57-3.69
Age 65-74	1.68	1.26-2.24
Age 75+	0.84	0.67-1.23
Years		
1987-1995	1.60	1.26-2.04
1996-2004	1.20	0.85-1.67
2005-2013	0.88	0.47-1.63
Follow Up (Years)		
0-10	1.11	0.74-1.67
10-20	1.35	0.90-2.01
20-27	1.43	0.77-2.66

Covariates

The cohort was categorized with respect to age at diagnosis (under 45, 45-54, 55-64, 65-75 and 75+ years), calendar year at diagnosis (1987-1995, 1996-2004, 2005-2013) and sex. TNM classification was reported for patients included 2005 or later.

Statistical analyses

The cohort's relative risk of CV death, as compared to the general population, was calculated through standardized mortality ratios (SMRs), by comparing the rate in the study cohort to rates in the general population taking sex, age (one year strata) and calendar year (one year strata) into consideration. SMRs were calculated for the aggregate cohort, as well as for subgroups of sex, age at diagnosis (in categories given above), year of diagnosis (in periods given above) and follow up time since diagnosis (measured in years). Complementary calculations for TNM classification were also performed for robustness validation. All aforementioned SMRs were computed for all CV mortalities combined as well as for CV subcategories (according to ICD-9 and ICD-10 as described in the "end-points" section). STATA 12, StataCorp LP Lakeway Drive, Texas USA, was used for statistical analyses. Ethical approval was acquired from the Regional Ethical Board at Karolinska Institute (Stockholm, Sweden), Dnr:2014/714-31.

Results and Discussion

Results

Table 1 displays basic characteristics of the cohort. Between 1987 and 2013, 6900 patients were diagnosed with DTC, survived and did not emigrate, at least one year post diagnosis. The mean follow-up time for the whole cohort was 9.66 years and the median was 8.01years (max 26.99 years, min 0.00 years). In the cohort, there were 550 (7.97%) cases of CV deaths, which constituted 26.47% of total mortalities (n=2078). The cohort predominantly consisted out of women (73.74%), however the number of events was relatively higher among men (11.20% in men vs. 6.82% in women). The proportion experiencing an event increased with the age at inclusion, as well as for more advanced TNM stages.

Table 2 describes SMRs for all CV mortalities as well as for CV mortalities categorized by ICD sub-diagnoses and sex. Among CV mortalities, ischemic heart disease, HF and Cerebrovascular disease were the most common death causes, accounting for 47.45%, 43.10% and 30.73% of the cases respectively. Ischemic heart attack (23.10%), cerebral infarction (19.82%), and AF (19.64%) were also common death causes, but were represented to a lesser extent. It is important to note that since ICD codes for the individual end-points overlap (e.g. ischemic heart disease and myocardial infarction), and there are cases of co-mortalities (e.g. AF and cerebral infarction), the individual end-points will sum up to more than 100% of the total CV mortalities. When accounting for all CV mortalities, only men ran a significantly elevated morality rate than expected (SMR 1.16 CI 95% 1.02-1.31). The cohort did in general not run an increased hazard of death in any particular CV death cause except for AF (SMR 1.36 CI 95% 1.12-1.64).

Table 3 displays detailed SMRs for CV mortality overall. The age group 65-74 was prone to a somewhat higher rate of CV death than expected (SMR 1.16 CI 95% 1.02-1.32), which also turned out to be the case for men (SMR 1.16 CI 95% 1.02-1.31) in general. Further analysis displayed that men's elevated rate was primarily attributable to the age group 45-54 years' olds (SMR 1.84 95% CI1.16-2.93). Moreover, the SMR for overall CV mortality was not statistically significant for any of the calendar periods of diagnosis. In complementary analyses restricted to patients diagnosed in 2005 or later, stage T4 exhibit edan increased mortality rate (SMR 1.87 CI 95% 1.19-2.94), whereas variations with the N or M stage were uninformative on CV mortality.

Atrial fibrillation

Table 4 exhibits mortality in AF. Unlike the general case of CV mortalities, the cohort experienced an increased rate of death due to AF (SMR 1.36 1.12-1.64). This increased rate primarily pertained to women (SMR 1.40 CI 95% 1.12-1.75) where as the SMR in men was in general not statistically significant. Furthermore, young age at diagnosis did increase the rate of death in AF compared to the

Table 5: The standardized mortality ratios (SMRs) of cardiovascular deaths in patients diagnosed with differentiated thyroid cancer in Sweden, stratified by age-clusters and follow-up time.

Age at diagnosis	Follow-up (years)	SMR	95% CI
<45	0-10	0.99	0.32-3.07
<45	10-20	1.18	0.49-2.83
<45	20-27	3.80	1.71-8.46
45-54	0-10	1.29	0.75-2.22
45-54	10-20	0.94	0.51-1.74
45-54	20-27	1.65	0.69-3.97
55-64	0-10	1.12	0.80-1.58
55-64	10-20	1.07	0.76-1.50
55-64	20-27	1.08	0.63-1.87
65-74	0-10	1.12	0.93-1.34
65-74	10-20	1.03	0.83-1.28
65-74	20-27	0.80	0.45-1.40
>=75	0-10	0.68	0.59-0.79
>=75	10-20	0.77	0.57-1.04

general population, where the highest SMR was to be found in the group 45-54 year olds (SMR 3.96 CI 95% 1.78-8.81). The SMR of AF mortality was higher for those diagnosed in earlier calendar years, where patients included 1987-1995 displayed an SMR of 1.60 (CI 95% 1.26-2.04). Complementary calculations regarding AF mortality did not prove variations within the TNM classification to be significant. The aforementioned results of AF mortality did not change notably when including patients at diagnosis date, instead of one year post diagnosis as conducted in this study.

Age at diagnosis and follow-up duration

Table 5 portraits the relationship between age at diagnosis, follow-up duration and the SMR of CV mortality. Patients diagnosed at ages below 45 years had an SMR of 3.80 (CI 95% 1.71-8.46) 20 years after diagnosis. Shorter follow-up duration than 20 years in the age category <45 did not incur an increased rate of CV mortality. Further, there was no elevated rate of CV mortality for the group diagnosed at ages 45-54 during any follow-up duration, where all SMRs were not statistically significant. The oldest age category, 75 years or older at diagnosis, displayed SMRs less than 1.00 for all follow-up durations, where the data suggests a decreased rate of CV mortality the first years post inclusion (SMR 0.68 95% CI 0.59-0.79).

Discussion

The aim of this nationwide study was to evaluate CV mortality in patients with DTC in comparison to the general population, where we hypothesized that DTC patients run an elevated risk of CV mortality. On an aggregate level, we did not find this patient group to run a higher risk of CV mortality relative to the general Swedish population, and thus cannot fully support our hypothesis. However, we did identify certain clinically significant risk factors associated with an elevated rate of CV mortality in this patient group. The first finding was that young longtime survivors run a nearly 4-fold increased rate of CV mortality compared the general population's, which could potentially be explained by long-term TSH suppression therapy. Secondly, we found that DTC patients run an elevated rate of dying in AF. Thirdly, DTC patients' CV mortality rate was more elevated in men compared with women. In general, the results of this study are in line with the main body of previous literature demonstrating that TSH suppression treatment on an aggregate population level does not significantly increase CV mortality [19-21], where only one study provides conflicting results [22].

Alternative study designs and patient materials potentially explain why Hesselink et al. [22] found CV mortality to be substantially increased in DTC patients, whereas this study did not. Strengths with Hesselink's study include available clinical data, where they found a relationship between low TSH levels and the risk of CV mortality [22]. A limitation with this study is the lack of information on TSH levels. The National Swedish Clinical Guidelines under the study period stipulate TSH suppression therapy to all DTC patients, which makes it highly probable that suppression treatment was administered to the vast majority of patients in this study. This assumption is strengthened by the fact that the CV mortality rate was elevated in young patients with longer duration of disease, as well as in patients with advanced disease which were according to the national guidelines suppressed to a greater extent. Furthermore, complementary research suggests that the national guidelines have been static over the study period. Although new national guidelines were introduced in 2012, recommending suppression therapy for only one year in patients with low risk DTC (Sköldkörtelcancer, Nationellt Vårdprogram 2012), a change of praxis was not evident in a review of 50 case-records from patients diagnosed in 2006-2008, and 50 diagnosed in 2011-2013, respectively (M Johansson, unpublished data). Moreover, while Hesselink et al. [22] employed a case-control study design, comparing 524 DTC patients with a selected cohort of healthy individuals, we conducted a nationwide cohort study by relating 6900 DTC patients to the general population.

Although this paper is not first to provide evidence that DTC patients do not in general run a substantially elevated rate of CV mortality, it still offers significant contribution to the literature by being first to present a nationwide approach. Previous studies that share this insight have not investigated CV mortality in particular, but instead focused on overall mortality causes in patients with DTC as well as thyroid cancer in general. Eustatia-Rutten et al. [19] included 366 cases of DTC, out of which 5 were CV mortalities. Likewise, Links et al. [20] investigated survival in 504 DTC patients, and identified 9 cases of CV mortalities. Akslen et al. [21] studied 2479 cases of thyroid cancer, out of which 94 patients died due to a CV disease. Hesselink et al. [22] studied 524 DTC patients and identified 100 CV mortalities. Since the aforementioned studies and Hesselink had altering objectives, more weight was naturally assigned to the latter study since it was the first study whose sole purpose was to investigate CV mortality in DTC patients. To the best of our knowledge, this study alongside Hesselink et al. [22] are the only publications examining CV mortality in DTC patients, where our paper offers advantages regarding its nationwide approach.

The major strength of this study is the vast patient material collected from a high quality population register, which included all cases of DTC incidence in Sweden over 26 years, thus allowing us to follow patients on average 9.66 years, making it the largest DTC cohort study that has investigated CV mortality so far. The registers cover the entire population, and given the national approach, the risk of selection bias should be negligible. Further, actions of precautions have been exercised in order not to overestimate results and to highlight potential risks of CV mortality in DTC patients. These include exclusion of mortalities up to one year post DTC

diagnosis, only inclusion of first thyroid cancer diagnosis, and also complementary calculations that verified significant results. As already discussed, the major limitation in this study was the lack of information on TSH levels. Other shortcomings include the inability to control for smoking and previous CV disease history, which are two major risk factors for CV mortality. Regarding history of CV disease, no previous study has found elevated prevalence of CV disease at DTC diagnosis. Smoking on the other hand has somewhat surprisingly been negatively associated with DTC incidence [25]. One could thus argue that the SMR of CV mortality in DTC patients, if anything, would be increased, were smoking to be considered. However, to stress the objective of this study, we did not aim at establishing an exact causal relationship between TSH levels and CV mortality in DTC patients. Our aim was to use the vast population registers, and study whether CV mortality in DTC patients differed from the remainder of the Swedish population. We are fully aware of the shortcomings of the register approach with respect to inference on causality, but simultaneously acknowledge the vast possibilities of studying a large cohort over time.

The pathophysiology mechanisms for elevated mortality in CV diseases remain not fully established. The literature is congruent in that subclinical hyperthyroidism increases left ventricular size [6,7] and is comorbid with AF [8,9]; a relationship that has also been proven in patients with DTC [12-16]. A recent study has however not succeeded in establishing a dose-response relationship between AF incidence in DTC patients and the level of TSH suppression, thus raising questions whether plasma TSH levels are adequate measures for tissue hyperthyroidism [10]. Furthermore, subclinical hyperthyroidism is associated with CV mortality in patients without DTC [17,18], where only one study [22] has been able to show increased mortality in DTC patients. Our study suggests a chronic process between TSH suppression and CV mortality in DTC patients, by providing evidence of increased CV mortality risk in patients diagnosed below 45 years of age, who probably have received TSH suppression treatment for 20 years or more. We have made complementary calculations, ensuring that these patients are not at a higher risk of CV mortality due to more advanced TNM stages, and thus more aggressive TSH suppression which consequently could explain the higher CV mortality risk.

We believe there is evidence to suggest that the risk of CV mortality increases with lower TSH levels among DTC patients. This was displayed in Hesselink's study [22], as well as suggested in this study by the increased risk ratios of young patients with long duration of disease, as well as in patients with advanced cancer stages. We further suggest an increased risk of CV mortality in certain groups of DTC patients, but however find the risk on an aggregate level not to differ from that of the Swedish population, thus being negligible. We identified the age at diagnosis together with the duration of disease and, -sex of the patient to potentially be predictors of increased rates of CV mortality, in particular increased rates of death due to AF, and hence suggest these factors to be of further discussion and concern in relation to TSH suppression in DTC patients. Nevertheless, due to the lack of TSH levels, this study does not provide ultimate causal evidence that low TSH levels solely explain the adversely elevated CV mortality risk rates discussed above. To include exact TSH levels over decades for 6900 patients is however obviously out of scope. We have therefore chosen to focus on the CV outcome of this patient group given the national guidelines' TSH suppression program, rather than attempting to provide definitive causal relationships, when not being able to perform a randomized controlled trial.

To summarize, this nationwide study showed no generally increased rate of CV mortality in patients diagnosed with DTC compared with CV mortality in the general Swedish population. However, following a DTC diagnosis, the data suggests that young patients with long follow-up duration were observed to face an elevated risk of CV mortality. We also noted that patients encountered elevated risks of AF mortality, and that male DTC patients faced higher relative risks of CV mortality in general.

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