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Thyroid Disease and Hepatocellular Carcinoma Survival: A Danish Nationwide Cohort Study

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Keywords
Hepatocellular carcinoma · Thyrotoxicosis · Nontoxic goiter · Myxedema · Thyroid disease

Abstract
Introduction: Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer mortality worldwide. Recent animal studies suggest that thyroid hormone treatment improves HCC prognosis. The aim of this study was to describe the association between thyroid disease and HCC prognosis in humans. ***Methods:*** We performed a nationwide cohort study including all persons with an HCC diagnosis from 2000 to 2018. Patients' age, sex, HCC treatment, and diagnoses of thyrotoxicosis, nontoxic goiter, and myxedema were obtained from Danish national healthcare registries. We used regression models to examine the association between thyroid disease and mortality hazard and restricted mean survival time after HCC diagnosis, adjusting for confounding by sex and age. ***Results:*** We included 4,812 patients with HCC and 107 patients with thyroid disease. Median follow-up time was 5 months (total 5,985 person-years). The adjusted mortality hazard ratio was 0.68 (95% CI: 0.47–0.96) for thyrotoxicosis and 0.60 (95% CI: 0.41–0.88) for nontoxic goiter. The restricted mean survival time during the 5 years following HCC diagnosis was 6.8 months (95% CI: 1.1–12.6) longer for HCC patients with thyrotoxicosis than for patients without thyroid disease, and it was 6.9 months (95% CI: 0.9–12.9) longer for HCC patients with nontoxic goiter than for patients without thyroid disease. ***Conclusions:*** In this large nationwide cohort study, thyrotoxicosis and nontoxic goiter were associated with prolonged HCC survival.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer mortality worldwide [1]. The patients may be allocated to a number of treatment modalities according to tumor burden, liver function, and performance status. However, treatment options for advanced HCCs remain limited, and overall survival is short [2].

Within recent years, the thyroid hormones, tri-iodothyronine (T3) and thyroxine (T4), have been associated with the course of HCC [3]. A recently published animal study showed that treatment with T3 slowed HCC progression by

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affecting cell metabolism and cell differentiation in both preneoplastic lesions and established HCCs toward a more benign phenotype. Additionally, T3 treatment of HCC-bearing rats caused fewer nodules and decreased tumor size [4]. This and similar studies report that T3 changes the genetic expression of cells from both preneoplastic lesions and established HCCs toward normal hepatocytes [5–7]. Collectively, the altered genetic expressions were associated with re-differentiation, suppression of cell migration/invasion, and ultimately HCC regression.

These experimental studies were motivated by older clinical studies. A population-based cohort study in women from 1990 found similar mortality rates for HCC [3] in women with or without thyroid disease. A case-control study from 2007 found a higher prevalence of hypothyroidism in patients with HCC of unknown etiology compared with controls and patients with both HCC and hepatitis C virus and/or alcoholic liver disease [8]. In another case-control study from 2009, long-term hypothyroidism was associated with an increased HCC risk in women independent of presence of HCC risk factors [9]. A population-based cohort study from 2018 found a higher risk of all gastrointestinal cancers within the first year of diagnosis of hyperthyroidism or hypothyroidism, but after 5 years, there was only a nonsignificantly higher risk of cancers of the biliary tract in women with hypothyroidism or hyperthyroidism and of liver cancer in women with hyperthyroidism [10].

Thus, animal studies have provided experimental evidence of protective effects of thyroid hormones on HCC development. The available clinical studies are not fully in agreement, but overall point in the same direction as the animal studies. The effect of thyroid disease on HCC prognosis remains unclear but may be important from both a biological and therapeutic perspective. On this basis, the aim of this study was to describe the association between thyroid diseases and HCC prognosis in a population-based cohort study.

Methods

Settings

This study was conducted in the Danish population of 5,781,190 citizens (as of January 1, 2018). All Danish citizens are issued free, tax-supported healthcare which grants equal access to general practitioners and hospital care. Danish citizens are issued a personal identification number (CPR number) at birth or immigration, which allows for linkage of all Danish health registries. The National Patient Registry contains data on all hospital contacts since 1977 of all citizens with a CPR number, including diagnosis codes, procedure codes, and nonsurgical treatment codes [11]. The Danish Cancer Registry contains data on all incident cancer cases in Denmark since 1943 [12]. The CPR number also allows for complete follow-up of vital status from birth or immigration to death or emigration via the CPR registry.

Study Population

We identified all incident cases of HCC in Denmark from 2000 to 2018 using the Danish Cancer Registry and the primary diagnosis codes for HCC (ICD-10: C220.x) in the National Patient Registry. We then identified all diagnoses of thyrotoxicosis (ICD-10: E05.x), myxedema (ICD-10: E02.x, E03.x, E00.1, and E07.1), and nontoxic goiter (ICD-10: E04.x) in the National Patient Registry. Last, we identified all treatments for HCC using the NOMESCO Classification of Surgical Procedures (NCSP) codes for liver transplantation (NCSP: JJC 00-40), liver resection (NCSP: JJB xx), and transarterial chemoembolization or selective internal radiation therapy (NCSP: PCT 20). Using nonsurgical treatment codes, we identified all Sorafenib® treatments (BWHA407), stereotactic radiation therapies of the liver (BWGC22), and palliative treatments (BXBAx). Referrals to oncology or palliative medicine departments were identified using the department classification codes (022 and 014). The patients' first HCC treatment was defined as the first of the aforementioned treatments after the first HCC diagnosis.

Patient and Public Involvement

Due to the retrospective design of this study, patients and public were not involved in planning the study.

Statistical Methods

To define each person's exposure to thyroid disease, we first defined the "baseline exposure" as the most recent thyroid disease diagnosis (thyrotoxicosis, myxedema, nontoxic goiter, or never thyroid disease) prior to the HCC diagnosis. In cases of thyroid disease diagnoses after the HCC diagnosis, we split the survival times at each diagnosis date creating a time-varying exposure status. This was done to minimize misclassification bias. Online supplementary Figure 1 (see www.karger.com/doi/10.1159/000520679 for all online suppl. material,) displays the study design.

We estimated crude survival since HCC diagnosis by thyroid disease exposure using the Kaplan-Meier method. To investigate the effects of thyroid diseases on HCC prognosis, we employed Cox regression to estimate adjusted mortality hazard ratios (HRs) for the 3 thyroid diseases. We adjusted the HRs for the effects of sex and age.

Additionally, to compute the differences in restricted mean survival times at 5 years after HCC, adjusted for sex and age, we generated pseudo-values to fit a generalized linear model [13]. The subjects were considered at risk from the day of their first HCC diagnosis, and the primary outcome was all-cause mortality. Follow-up ended at death or censoring on December 31, 2019.

Sensitivity Analyses

To test the robustness of the analyses, we repeated the Cox regression using only primary diagnosis codes for thyroid diseases to define exposure. Furthermore, to examine whether the effects of thyroid diseases on HCC prognosis were mediated by the initial HCC treatment, we conducted a stratified Cox regression stratified by the subjects' first HCC treatment and adjusted for sex and age. We repeated the stratified analysis using only primary diagnosis codes to define exposure (online suppl. Table 1).

Table 1. Baseline characteristics of HCC patients at the time of inclusion

	No thyroid disease	Thyrotoxicosis	Myxedema	Nontoxic goiter
N, prevalence, %	4,706	31 (0.6)	46 (1.0)	30 (0.6)
Male sex, %	77.5	48.4	32.6	46.7
Age, median (IQR)	69 (61–76)	74 (66–79)	74 (66–81)	71 (64–75)
Curative-intent HCC treatment, %	15.9	19.4	10.9	26.7
Years since latest thyroid disease diagnosis, median (IQR)	n/a	1.2 (0.2–2.4)	1.1 (0.1–2.8)	3.1 (1.2–4.2)

HCC, hepatocellular carcinoma; IQR, interquartile range.

Table 2. Restricted mean survival time up to 5 years after HCC diagnosis

	Restricted mean survival time, months
Reference patient (70-year-old male without thyroid disease)	13.4 (12.8–14.0)
Thyroid disease	
Never thyroid disease	Ref
Thyrotoxicosis	+6.8 (+1.1 to +12.6)
Myxedema	−2.0 (−6.6 to +2.6)
Nontoxic goiter	+6.9 (+0.9 to +12.9)
Sex	
Male	Ref
Female	+1.6 (+0.4 to +3.0)
Age	
70 years old	Ref
+10 years of age	−3.1 (−3.6 to −2.6)

HCC, hepatocellular carcinoma.

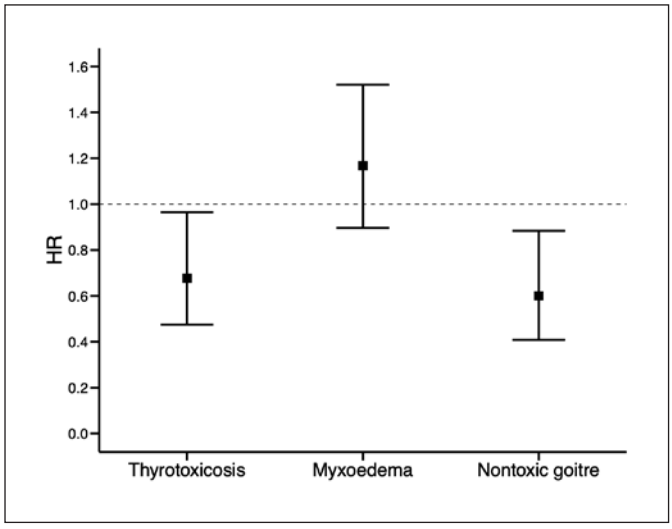

Fig. 1. The effects of thyroid diseases on the hazard of all-cause mortality adjusted for sex and age.

Results

Participants and Descriptive Data

A total of 4,812 persons with an HCC diagnosis were included. The median follow-up time was 5 months (IQR: 1–18) (total person-years 5,985; 233 person-years with thyroid disease and 5,752 person-years without thyroid disease), and 90% (4,331/4,812) of the cohort died. More patients with diagnoses of thyrotoxicosis or nontoxic goiter received curative treatment for HCC than patients with myxedema or no history of thyroid disease at baseline (Table 1).

At baseline, the prevalence of thyrotoxicosis, myxedema, and nontoxic goiter was 0.6% ($N = 31$), 1.0% ($N = 46$), and 0.6% ($N = 30$), respectively. As expected, compared with patients without thyroid disease, a larger proportion of patients with thyroid disease were female (Table 1). During follow-up, 33 additional cases of thyroid disease were diagnosed (11 thyrotoxicosis, 16 myxedema, and 6 nontoxic goiter), and 5 persons changed from 1 thyroid disease to another.

Effect of Thyroid Diseases

Thyrotoxicosis and nontoxic goiter were associated with lower mortality after HCC diagnosis, with HRs of 0.68 (95% CI: 0.47–0.96) and 0.60 (95% CI: 0.41–0.88), respectively, adjusting for age and sex (Fig. 1). At 5 years after HCC diagnosis, patients with thyrotoxicosis or nontoxic goiter had a significantly longer restricted mean survival time of 20.3 and 20.2 months, respectively, compared with 13.4 months of the reference patient (a 70-year-old male without thyroid disease), corresponding to an estimated lifetime improvement of nearly 7 months (Table 2). Myxedema was not associated with HCC survival or restricted mean survival (Table 2).

Sensitivity Analyses

We performed sensitivity analyses to assess the robustness of our results (online suppl. Table 1). The effect of thyroid disease on all-cause mortality after HCC diagnosis remained similar when excluding secondary diagnosis codes for thyroid diseases, stratifying for HCC treatment, or both. Using exclusively primary diagnosis codes and adjusting for hepatitis B and C virus resulted in similar HRs (data not shown).

Discussion

In this large nationwide cohort study, thyrotoxicosis or nontoxic goiter was associated with improved survival after HCC diagnosis. The associations held true after adjusting for age and sex, excluding secondary diagnosis codes, and stratifying by HCC treatment. This is the first study to show a positive association between the thyroid diseases and HCC survival.

Our study has several strengths. It is nationwide, securing inclusion of all patients with an HCC diagnosis. Healthcare data were available both before and after HCC diagnosis. The validity of cancer diagnoses (including HCC) in Denmark is very high [14, 15]. The diagnosis codes for thyroid disease have not been validated, but other comparable codes for endocrine diseases, such as diabetes, have a high validity [16]. To assess the validity of the thyroid diagnosis in this study, we investigated the proportion of relevant specialties who registered the diagnoses. Relevant specialties included endocrinology, internal medicine (other than endocrinology), otorhinolaryngology, and general surgery. For the primary diagnoses, the proportion of relevant specialties was 100% for thyrotoxicosis, 90% for nontoxic goiter, and ≥76% for myxedema. When including secondary diagnoses, the proportion of relevant specialties was lower, yet still at least 70–85%. Thus, we consider the validity of the thyroid diagnosis in this study to be high. Additionally, the sensitivity analyses underscore the robustness of the results.

Nevertheless, our study has limitations. First, despite the nationwide design, the number of thyroid disease cases in our HCC cohort is limited although still allowing for analyses for effects of age, sex, and HCC treatment modality. However, we had no access to information on other potential confounders, such as lifestyle (smoking, alcohol, and diet), genetics, and performance status. Second, a diagnosis of thyrotoxicosis and myxedema most often leads to treatment, effectively changing these patients' exposure and blurring or counterweighing a potential association between thyroid hormonal status and HCC survival. Third, a patient with thyroid disease has regular follow-ups, which may lead to earlier HCC detection and treatment than patients with no regular healthcare contacts. However, we did not find more HCC cases in patients with myxedema, which would be the case if surveillance bias was suspected. Fourth, we had no access to data on prescriptions for thyroid medication or blood levels of thyrotropin (TSH) and thyroid hormones.

The role of thyroid diseases in HCC has been touched upon sporadically in the last decades, both in clinical and experimental studies. A few human studies found that myxedema was associated with a higher risk of HCC [8, 9], while animal studies found that treatment of HCC-bearing rats with T3 improved the prognosis of both premalignant lesions and advanced HCCs [4–7]. In our study, thyrotoxicosis and nontoxic goiter were positive prognostic factors in survival after HCC, which is in line with the animal studies.

Regarding thyrotoxicosis, the effect seems to depend on a bout of high circulating thyroid hormones because virtually all such patients are subsequently treated to euthyroidism as soon as the condition is diagnosed. This would be consistent with the animal experiments, where the rats were exposed to short bouts of thyrotoxicosis by T3 treatments.

Regarding nontoxic goiter, subclinical or mild hyperthyroidism is frequent in this group of patients. Many of these patients do not receive treatment for hyperthyroidism since their blood levels of T3 and T4 are within the normal range, while serum TSH is suppressed. The hyperthyroidism is therefore often undiagnosed, and it is still a matter of international debate whether subclinical thyrotoxicosis should be treated or not [17]. It is thus a possibility that these HCC patients were in fact long-time exposed to low-grade biological hyperthyroidism that gave rise to the prognostic improvement indicated by our data. Since this study was performed from the year 2000, it is even possible that patients with multinodular goiter, most of them harboring 1 or more "hot" nodules as demonstrated by thyroid scintigraphy, have had a further bout of hyperthyroidism by the compulsory iodide fortification program introduced in Denmark in 2000, by increasing thyroid hormone production in these autonomous nodules [18].

Myxedema is hormone replaced toward attempted euthyroidism. That may explain why there was no negative prognosis association with myxedema. Also, the initial

low circulating thyroid hormone concentrations seem not to have a negative effect on prognosis. This is different from the animal experiments where local states of hypothyroidism were detected in the tissue surrounding HCC nodules.

A diagnosis of either thyrotoxicosis or nontoxic goiter improved the HCC prognosis, and the association was strong for both conditions. The effect was not trivial, the survival time being prolonged by more than half a year, which is more than obtained by, e.g., sorafenib [19, 20]. The anytime aspect implies that any thyroid hormone effect was effective whether present before or after diagnosis of HCC. The before-HCC diagnosis effect may reflect an effect on HCC incidence, possibly via an effect on the course of early and yet undiagnosed HCCs. The post-HCC diagnosis positive effect is supported by the fact that more patients with thyrotoxicosis or nontoxic goiter were found to be eligible for intended curative HCC treatment.

Our registry-based results are concordant with the recently published animal experiments. Our data do not allow for further speculation about mechanism and do not define a potential preventive or therapeutic role of thyroid hormones in HCC. However, it is remarkable that both experimental and clinical data are compatible with a positive prognostic effect of thyroid hormones on HCC, design, and provenience notwithstanding. Based on our data, the effect of thyroid hormone treatment might be persistent. This may motivate therapeutic trials with thyroid hormone supplements as adjuvant HCC intervention. However, in conducting such a study, it is nevertheless important to avoid chronic overt thyrotoxicosis, which is known to result in osteoporosis, cardiovascular death, and poor cognition [21, 22].

Conclusions

In this large cohort study, we found that thyrotoxicosis and nontoxic goiter were associated with lower mortality after HCC diagnosis than patients without thyroid disease.

Statement of Ethics

The study was approved by the National Board of Health and by the Danish Data Protection Agency (Journal No. 1-16-02-321-19). According to the Danish law, approval from the Danish Committee on Health Research Ethics was not necessary. Since this is a register-based study, written consent was not required.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

No funding was received for this study.

Author Contributions

Vilstrup, Jepsen, Kraglund, and Kornerup contributed to study design; Kraglund and Jepsen contributed to data collection and analysis; Kornerup, Kraglund, Vilstrup, Jepsen, and Feldt-Rasmussen contributed to writing the manuscript.

Data Availability Statement

According to the Danish law, we cannot share the data. Interested researchers may apply for data from the Danish healthcare registries via https://sundhedsdatastyrelsen.dk/da/forskerservice.

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