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Abnormal and Euthyroid Ranges of Thyroid Hormones in Serum and Liver Cancer Mortality: A Cohort Study

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ABSTRACT

Background: This study aimed to evaluate the relationship of serum thyrotropin (TSH) and thyroid hormone concentration with liver cancer mortality.

Methods: A cohort of 517,996 Korean adults, who did not have liver cancer at baseline and attended a health screening including free thyroxine (FT4) and TSH, were followed for up to 16 years. High and low TSH and FT4 were defined as those above the upper bound of reference interval and those below the lower bound of reference interval of their corresponding reference intervals, respectively. Mortality information was ascertained through National Death Records. The adjusted HR (aHR) with 95% confidence interval (CI) were estimated using a Cox proportional hazard model.

Results: During a median follow-up of 8.1 years, 376 deaths from liver cancer were identified. Subjects with low FT4 levels were associated with an elevated risk of liver cancer mortality with a corresponding multivariable aHR 2.25 (95% CI: 1.62–3.12) compared with those with normal FT4 levels. Within the euthyroid range, there was also a dose-dependent inverse relationship between FT4 level and liver cancer mortality ($P < 0.001$). Levels of TSH and free T3 had no significant association with liver cancer mortality.

Conclusions: The risk of liver cancer mortality increased as FT4 level decreased, both within the normal and abnormal ranges of thyroid function.

Impact: Thyroid function within the abnormal and normal ranges might affect liver cancer mortality. Further study is warranted to elucidate the role of thyroid hormone in development of liver cancer including the underlying biological mechanism.

Introduction

Liver cancer is one of the common cancers and accounts for 8.2% of all malignancy-related mortality globally (1, 2). Despite recent advances in the management of liver cancer, it is still difficult to treat compared with other solid malignancies because the outcome depends on liver function as well as tumor burden (3). Primary liver cancer, which includes hepatocellular carcinoma (HCC), is mainly attributed to chronic viral hepatitis [hepatitis B virus (HBV) or hepatitis C virus (HCV)], aflatoxin, and heavy alcohol consumption (4). Following the introduction of the HBV vaccination, HBV-related HCC has decreased in recent decades (5). However, in general, HCC incidence has increased because of a rise in other related causes such as HCV, alcohol, and nonalcoholic fatty liver disease (NAFLD; refs. 1, 5, 6). In addition, 5%–30% of HCCs have been observed in individuals without known cause for underlying liver disease or cryptogenic cirrhosis (7, 8). Identifying the risk factors of HCC is crucial in understanding its pathogenesis, and could possibly lead to novel therapeutic targets and preventive strategies for reducing HCC.

Thyroid hormone is a key regulator of cellular processes in the human body. It controls cell proliferation, differentiation, apoptosis, and metabolism (9), and has been reported to have both tumor-promoting and -suppressing effects (10). Hypothyroidism is related to obesity, insulin resistance, hyperlipidemia, and lipid peroxidation, which are all contributors of liver damage, and can also directly affect liver health (7, 11). Indeed, some researchers have also found a positive association between low thyroid function in NAFLD/nonalcoholic steatohepatitis and liver fibrosis, a crucial predictor of HCC (12, 13). Until now, there are scarce data about the relationship of thyroid hormone with liver cancer. Two case–control studies showed that the prevalence of hypothyroidism was significantly elevated in patients with HCC (7, 14); however, these studies were limited by temporal ambiguity between exposure and outcome and it remains unclear whether thyroid hormone influences the risk of liver cancer.

Therefore, this study examined whether serum thyrotropin (TSH) and thyroid hormone concentrations are associated with liver cancer mortality in a cohort of 517,996 Korean adults who attended a health checkup exam.

Materials and Methods

Study population

This study was a part of the Kangbuk Samsung Health Study, a cohort study of Korean adults who annually or biannually attended a

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comprehensive health examination at one of the Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea as described previously (15, 16). In Korea, annual or biennial health screening exams of employees are required by the Industrial Safety and Health Law. The study population comprised participants who attended a health checkup exam between 2002 and 2015 ($n = 538{,}021$).

We excluded 20,025 participants with one or more of the exclusion criteria at baseline as follows: undetermined death status ($n = 4$); missing information on thyroid hormone levels (FT4 or TSH), body mass index (BMI), or age ($n = 8{,}020$); a history of cancer ($n = 8{,}291$); and currently being treated with thyroid disease medication ($n = 5{,}299$; ref. 17). Finally, 517,996 participants were included in the analysis. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB 2019-10-008). The requirement for informed consent was waived because of the use of a preexisting deidentified dataset that combined data routinely collected during the health screening process and mortality data (see below for further details).

Data collection

Information on demographic characteristics, lifestyle habits, and medical history were collected using a standardized, self-administered questionnaire (15, 16). Smoking status was categorized as never, former, or current smokers. Average alcohol consumption per day was calculated using the frequency and amount of beverage consumed per drinking day (15, 16). The weekly frequency of moderate or vigorous physical activity was also evaluated. A family history of cancer was defined as having one or more first-degree relatives with any type of cancer disclosed in a self-reported questionnaire. Sitting blood pressure (BP) and anthropometric parameters were measured by trained nurses. Obesity was defined as BMI ≥ 25 kg/m^2, the cutoff for a diagnosis of obesity in Asian populations (18). Hypertension was defined as BP $\geq$ 140/90 mmHg, or the use of BP-lowering medication.

Laboratory analyses

Fasting blood tests, including lipid profile, glucose, albumin, liver enzymes, insulin, platelets, hepatitis B surface antigen (HBsAg), HCV antibodies (HCV Ab), high-sensitivity C-reactive protein (hsCRP), and thyroid function, were described previously (15, 19). The homeostatic model assessment–insulin resistance (HOMA-IR) was calculated as follows: fasting blood insulin (μU/mL) × fasting blood glucose (mmol/L)/22.5. Diabetes mellitus was defined as a fasting serum glucose level ≥ 126 mg/dL or current use of antidiabetic medication. Metabolic syndrome was defined using the following harmonized criteria (20): (i) abdominal obesity, (ii) fasting blood glucose ≥ 100 mg/dL or current use of blood glucose–lowering agents, (iii) BP ≥ 130/85 mmHg or current use of antihypertensive medication, (iv) triglyceride levels ≥ 150 mg/dL or current use of lipid-lowering medication, and (v) HDL-C < 40 mg/dL in men or < 50 mg/dL in women. Because only a subset of participants had waist circumference measurements, we substituted overall adiposity [i.e., BMI ≥ 25 kg/m^2 (18)] for abdominal obesity.

TSH and FT4 were a routine part of health checkup programs and were measured for most participants (19). Between 2002 and 2009, serum TSH and FT4 levels were assessed with a Radioimmunoassay Kit (RIA-gnost FT4 and hTSH, Schering-Cis Bio International) which had lower limits of detection of 0.06 ng/dL and 0.025 μIU/mL, respectively. The normal range of TSH and FT4 was 0.25 to 5.0 μIU/mL and 0.9 to 1.8 ng/dL, respectively. During the same period, serum free triiodothyronine (FT3) was assessed via a Radioimmunoassay Kit (RIA-mat, Byk-Sangtec Diagnostica) with a lower limit of detection of 0.6 pg/mL and a normal range of 2.0 to 4.25 pg/mL. Thereafter, thyroid function measurement was performed using electrochemiluminescent immunoassay (Roche) with lower limits of detection of 0.005 μIU/mL for TSH, 0.023 ng/dL for FT4, and 0.26 pg/mL for FT3. The normal range was 0.25–5.0 μIU/mL for TSH, 0.93–1.7 ng/dL for FT4, and 2.0–4.4 pg/mL for FT3. The coefficients of variation for low- and high-level quality control specimens were 2.1%–3.2% and 2.2%–3.1% for TSH, 1.6%–2.6% and 1.9%–3.6% for FT4, and 1.2%–3.9% and 1.7%–4.1% for FT3, respectively. In the primary analysis, we used the reference interval as used in prior researches of this type of population because the ethnicity and age of individuals (Asian midlife individuals) were also considered to define the reference range (21–23). High and low TSH, FT4, and FT3 were defined as those above the upper bound of reference interval and those below the lower bound of reference interval of their corresponding reference intervals. Being euthyroid was defined as having levels of TSH and FT4 within their corresponding normal ranges, no history of thyroid disease, and not currently being treated with thyroid medications.

Overt thyroid dysfunction was determined according to clinically defined TSH and FT4 cutoffs and were defined as TSH > 5.0 μIU/mL and FT4 of the below normal range for hypothyroidism, and TSH < 0.25 μIU/mL and FT4 of the above normal range for hyperthyroidism. Subclinical thyroid dysfunction was defined as TSH > 5.0 μIU/mL and FT4 within the normal range for subclinical hypothyroidism, and TSH < 0.25 μIU/mL and FT4 within the normal range for subclinical hyperthyroidism.

The fatty liver was determined on abdominal ultrasound (US) operated by experienced radiologists who were unaware of the study aim and diagnosed on the basis of standard criteria, including the presence of a diffuse increase of fine echoes in the liver parenchyma compared with kidney or spleen parenchyma, deep beam attenuation, and bright vessel walls (24). Liver cirrhosis was diagnosed on the basis of changes in the liver volume distribution, surface nodularity, accentuation of the fissure, heterogeneity, bright and coarsening of the hepatic architecture, cirrhotic nodules, and signs of portal hypertension (25).

Three liver fibrosis scores, the NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4), and aspartate transaminase to platelet ratio index (APRI), were used to categorize the probability of liver fibrosis. NFS was calculated according to the following published formula: NFS = $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ impaired fasting glucose or diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dL). Two cut-off points were selected to categorize subjects with NAFLD into three groups according to their probability of advanced fibrosis: high (NFS > 0.676), intermediate (NFS: 0.676 to −1.455), and low (NFS < −1.455; ref. 26). FIB-4 was calculated with the following formula: FIB-4 = [age (years) × AST (U/L)]/[platelet count ($\times 10^9$/L) × ALT (U/L)$^{1/2}$] and categorized into a low (FIB-4 < 1.30), intermediate (FIB-4, 1.30 to < 2.67), and high (FIB-4 ≥ 2.67) probability of advanced fibrosis (27). The APRI was calculated as follows: APRI = 100 × (AST/upper limit of normal)/platelet count ($\times 10^9$/L). Cutoffs of 0.5 and 1.5 were used to define low and high probabilities of advanced fibrosis, respectively (28). The upper limit of the reference interval used at Kangbuk Samsung Hospital was 40 U/L for men and 32 U/L for women for AST and was 35 U/L for ALT in both men and women.

Mortality follow-up

Vital status until the end of 2017 was ascertained on the basis of national death certificate data from the Korea National Statistical Office, which is expected to be complete because all deaths of Koreans are reported to the Korean National Statistical Office. The cause of

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death was ascertained on the basis of the underlying cause listed on each death certificate, as classified according to the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10). The cause of death on the death certificate and patient diagnosis in the medical utilization data was reported to be acceptably concordant; specifically, 72.2% for all-cause deaths and 94.9% for cancer deaths (29). Liver cancer mortality was defined as death with an underlying cause of ICD-10 C22, which is malignant neoplasm of the liver and intrahepatic bile ducts (30).

Statistical analysis

Because there are large differences in age and sex between liver cancer mortality cases and nonrelated cases, all baseline characteristics were presented as age- and sex-adjusted mean or proportion as well as 95% confidence intervals (CI) according to the presence of liver cancer mortality. The two groups were compared after performing linear regression model for continuous variables or logistic regression model for categorical variables, with age and sex as covariates in the regression models. The adjusted mean or proportion was estimated using the margins command in *STATA*.

Subjects were followed from the baseline visit until either the onset time of liver cancer mortality or December 31, 2017, whichever occurred first. Death cases due to other causes were censored at the date of death. Cox proportional hazards regression analyses were used to estimate HRs and 95% CIs for liver cancer mortality. For effective control for age, age was chosen as the timescale, which was documented by the age at which subjects received their initial examination (left truncation) and the age at which subjects exited the analysis at the date of death or upon the end of 2017. The graphs of the estimated log [−log (*SURVIVAL*)] were evaluated for testing the proportional hazards assumption and indicated no violations against the proportional hazards assumption.

The risk of liver cancer mortality was evaluated across levels of TSH, FT4, and FT3 separately and then by clinical diagnosis. First, models were adjusted for age (timescale) and sex and then further adjusted for additional potential confounders including study center (Seoul and Suwon), year of health exam, smoking (never, former, current, or unknown), alcohol consumption (none, < 20, or ≥ 20 g/day, unknown), frequency of exercise (< 3, ≥ 3 times/week, or unknown), education level (< community college graduate, ≥ community college graduate, or unknown), family history of malignancy, BMI, viral hepatitis, fatty liver, liver cirrhosis, and FIB-4 (Model 1). Previous studies have suggested that overt hypothyroidism and even low normal FT4 level are closely related to metabolic syndrome and its individual components such as obesity, dyslipidemia, hypertension, and insulin resistance, while metabolic factors might increase a risk of liver cancer or liver-related death (31–33). In this case, metabolic factors can play a role as mediator of the relationship of thyroid function with liver cancer mortality. Thus, we separately presented Model 2 with inclusion of further adjustment for metabolic factors (hypertension, diabetes, total cholesterol, HDL-C, and triglycerides) because metabolic factors can be both mediators and confounders. In addition, time-dependent analyses were performed where changes in thyroid hormone status (TSH, FT4, and FT3 separately in each model) and other covariates during follow-up were updated as a time-varying covariate. To test for linear trends, the median value of each thyroid hormone category was treated as a continuous variable in the Cox proportional hazard models.

Subgroup analyses were performed by age (< 50 vs. ≥ 50 years), sex (men vs. women), smoking status (never smokers vs. ever smokers), alcohol consumption (< 20 vs. ≥ 20 g/day), regular exercise (< 3 vs. ≥ 3 times/week), BMI (< 25 vs. ≥ 25 kg/m^2), HOMA-IR (< 2.5 vs. ≥ 2.5), metabolic syndrome (no vs. yes), diabetes (no vs. yes), viral hepatitis defined as having either HBV or HCV infection (no vs. yes), fatty liver on US (no vs. yes), cirrhosis on US (no vs. yes), and noninvasive fibrosis score (low vs. intermediate or high probability). Likelihood ratio tests were used to evaluate interactions between hypothyroidism and subgroups while comparing models with or without multiplicative interaction terms. STATA version 15.0 (StataCorp LP) was used for statistical analyses. All two-tailed *P* values less than 0.05 were considered statistically significant.

Results

Population characteristics

The mean age of study participants at baseline was 39.1 years (SD, 10.4; median, 36; interquartile range, 31–44; range, 18–94) and 53.7% were male (**Table 1**). Liver cancer mortality was positively associated with age, male sex, current smokers, diabetes, and high levels of liver enzymes, BMI, hsCRP, and HOMA-IR. Liver cancer mortality was inversely associated with high education attainment, total cholesterol, LDL-C, and triglycerides. Liver cancer mortality cases were more likely to have HBsAg, HCV Ab, and liver cirrhosis but less likely to have fatty liver on US. Age- and sex-adjusted FT4 level at baseline was lower in the participants with liver cancer mortality but levels of TSH and FT3 did not significantly differ between liver cancer mortality cases and nonrelated cases. Baseline characteristics are also presented according to the thyroid hormone status (Supplementary Tables S1–S3).

Risk of liver cancer–related mortality in relation to thyroid dysfunction

During 4,457,095 person-years of follow-up, 376 death cases due to liver cancer were identified (liver cancer mortality rate, 8.4 per 100,000 person-years). The median follow-up was 8.1 years (maximum, 16 years; interquartile range, 4.9–12.4 years) and the average number of follow-up visits was 2.8 (SD, 2.6; median, 2; interquartile range, 1–4; range, 1–17). Liver cancer mortality by thyroid hormone level at baseline in the overall population is shown in **Table 2**. In a Cox proportional hazard regression analysis adjusting for age (timescale), sex, study center, year of examination, smoking status, alcohol consumption, frequency of exercise, education, BMI, family history of cancer, viral hepatitis, fatty liver, liver cirrhosis, and FIB-4 (Model 1), the HRs (95% CIs) for liver cancer mortality, comparing abnormally low and high TSH levels with normal TSH level, were 0.68 (0.17–2.71) and 1.10 (0.61–1.96), respectively (Model 1). After additional adjustment for diabetes, hypertension, total cholesterol, HDL-C, and triglycerides (Model 2), these associations remained. Multivariable-adjusted HRs (95% CIs) for liver cancer mortality comparing abnormally low and high FT4 levels with the normal FT4 level (the reference category) were 2.25 (1.62–3.12) and 0.31 (0.04–2.18), respectively. Multivariable-adjusted HR (95% CI) for liver cancer mortality comparing abnormally high with the normal level of FT3 was 0.82 (0.11–5.85; Model 1). Among individuals with the abnormally low FT3 level (n = 625), no liver cancer mortality cases were observed. When changes in thyroid hormones and confounding factors during follow-up were incorporated as time-varying covariates, the results qualitatively did not change with the corresponding HR (95% CI) of 1.29 (0.72–2.31) in the abnormally high TSH category and 1.51 (1.07–2.12) in the abnormally low FT4 category.

When the associations of overt and subclinical thyroid dysfunction with liver cancer mortality were assessed (Supplementary Table S4), liver cancer mortality was lowest in people with overt hyperthyroidism

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Table 1. Estimated[a] mean values (95% CI) and adjusted[a] proportion (95% CI) of baseline characteristics of study participants by liver cancer mortality.

Characteristics	Liver cancer mortality (−)	Liver cancer mortality (+)	*P*
Number	517,620	376	
Age (years)	39.0 (39.0–39.1)	54.9 (53.8–55.9)	<0.001
Male (%)	53.6 (53.5–53.8)	82.9 (79.1–86.7)	<0.001
BMI (kg/m^2)	23.3 (23.3–23.4)	23.9 (23.6–24.2)	0.001
Obesity (%)[b]	28.8 (28.7–28.9)	26.2 (22.5–30.0)	0.190
Current smoker (%)	24.4 (24.3–24.5)	30.2 (26.7–33.7)	0.001
Alcohol intake (%)[c]	18.3 (18.2–18.4)	16.7 (13.6–19.8)	0.322
Regular exercise (%)[d]	15.0 (14.9–15.1)	14.0 (11.0–17.1)	0.551
High education level (%)[e]	72.5 (72.3–72.6)	58.7 (53.2–64.2)	<0.001
Diabetes (%)	3.9 (3.8–3.9)	5.4 (4.1–6.6)	0.008
Hypertension (%)	15.0 (14.9–15.1)	13.8 (11.5–16.1)	0.319
Family history of cancer (%)	22.8 (22.7–22.9)	20.2 (16.6–23.8)	0.174
HBV (%)	3.6 (3.6–3.7)	53.4 (48.3–58.5)	<0.001
HCV (%)	0.18 (0.17–0.19)	2.6 (1.6–3.6)	<0.001
Cirrhosis (%)	0.0 (0.0–0.0)	2.4 (1.5–3.4)	<0.001
Fatty liver (%)	26.6 (26.5–26.8)	9.9 (7.7–12.1)	<0.001
Systolic BP (mmHg)	112.4 (112.4–112.4)	114.0 (112.7–115.3)	0.018
Diastolic BP (mmHg)	72.2 (72.2–72.3)	72.0 (71.1–72.9)	0.625
Glucose (mg/dL)	94.7 (94.7–94.8)	96.2 (94.6–97.8)	0.066
Total cholesterol (mg/dL)	194.0 (193.9–194.1)	176.2 (172.8–179.7)	<0.001
LDL-C (mg/dL)	115.4 (115.3–115.5)	97.1 (94.1–100.1)	<0.001
HDL-C (mg/dL)	57.1 (57.0–57.1)	59.5 (58.1–60.8)	<0.001
Triglycerides (mg/dL)	118.7 (118.5–118.9)	86.8 (78.9–94.6)	<0.001
AST (U/L)	23.8 (23.7–23.8)	49.2 (47.3–51.1)	<0.001
ALT (U/L)	25.1 (25.1–25.2)	47.6 (45.1–50.1)	<0.001
GGT (U/L)	30.4 (30.3–30.5)	99.7 (95.7–103.7)	<0.001
hsCRP (mg/dL)[f]	0.11 (0.11–0.11)	0.22 (0.19–0.26)	<0.001
HOMA-IR	1.74 (1.74–1.74)	2.37 (2.25–2.50)	<0.001
FT3 (pg/mL)[g]	3.24 (3.23–3.24)	3.13 (2.97–3.28)	0.167
FT4 (ng/dL)	1.28 (1.28–1.28)	1.21 (1.16–1.25)	0.002
TSH (μIU/mL)	2.29 (2.28–2.30)	2.27 (1.62–2.92)	0.958
NFS	−2.98 (−2.98 to −2.98)	−1.76 (−1.85 to −1.66)	<0.001
FIB4	0.81 (0.81–0.81)	2.55 (2.51–2.59)	<0.001
APRI	0.28 (0.27–0.27)	1.01 (0.98–1.04)	<0.001

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate transaminase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; FIB-4, fibrosis-4; FT3, free triiodothyronine; FT4, free thyroxin; GGT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; NFS, NAFLD fibrosis score; TSH, thyrotropin.

[a]Adjusted for age and sex.

[b]BMI ≥25 kg/m^2.

[c]≥20 g/day.

[d]≥3 times/week.

[e]≥College graduate.

[f]509,008 subjects with available hsCRP.

[g]451,444 subjects with available free T3 data.

(no case experienced liver cancer mortality) and highest in people with subclinical hypothyroidism, but there was no evidence of significant association of clinical thyroid disease with liver cancer mortality. When we reanalyzed using the reference intervals as in other studies, specifically, TSH 0.4–4.0 μIU/mL and FT4 0.85–1.94 ng/dL (34, 35), low FT4 tended to associate with elevated risk of liver cancer mortality but did not reach statistical significance (Supplementary Table S5).

Risk of liver cancer–related mortality in relation to thyroid hormones within the euthyroid range

Within the euthyroid range (**Table 3**; n = 495,202), a 0.1-unit increase in both FT4 and FT3 level was significantly and inversely related to liver cancer mortality with HR (95% CI) of 0.85 (0.79–0.92) per unit increase in FT4 and of 0.93 (0.89–0.98) per unit increase in FT3 adjusting for age (timescale), and confounders (Model 1). In the categorical analyses, the FT4 tertile was associated with a decreased risk of liver cancer mortality in a dose-response manner (Model 1). After further adjustment for metabolic factors (diabetes, hypertension, total cholesterol, HDL-C, and triglycerides), the relationship between FT4 level and liver cancer mortality remained significant. For TSH level within the euthyroid range, no significant association with liver cancer mortality was observed. When we reanalyzed using the reference intervals with TSH 0.4–4.0 μIU/mL and FT4 0.85–1.94 ng/dL (34, 35), the association between FT4, within the euthyroid range, and liver cancer mortality was similar to the original finding (Supplementary Table S6).

Subgroup analysis

The associations between low free T4 level and liver cancer mortality did not differ by the presence of viral hepatitis, fatty liver on US, liver

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Table 2. HRs (95% CIs) for liver cancer mortality by baseline thyroid hormone level in the overall population (n = 517,996).

	Person-years (PY)	Number of events	Mortality rate (10^5 PY)	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)		HR (95% CI)[b] in model using time-dependent variables
					Model 1	Model 2	
TSH (μIU/mL)							
Low (n = 5,696)	50,844.1	2	3.9	0.54 (0.13–2.16)	0.68 (0.17–2.71)	0.65 (0.16–2.60)	0.72 (0.18–2.89)
Normal (n = 495,202)	4,281,492.6	362	8.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
High (n = 17,098)	124,758.3	12	9.6	1.04 (0.58–1.86)	1.10 (0.61–1.96)	1.14 (0.64–2.05)	1.29 (0.72–2.31)
P_{trend}				0.565	0.590	0.485	0.321
FT4 (ng/dL)							
Low (n = 9,812)	95,325.1	44	46.2	4.43 (3.22–6.10)	2.25 (1.62–3.12)	2.19 (1.58–3.05)	1.51 (1.07–2.12)
Normal (n = 499,493)	4,285,720.7	331	7.7	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
High (n = 8,691)	76,049.1	1	1.3	0.19 (0.03–1.38)	0.31 (0.04–2.18)	0.28 (0.04–2.02)	0.31 (0.04–2.22)
P_{trend}				<0.001	<0.001	<0.001	0.008
FT3 (pg/mL)[c]							
Low (n = 625)	4,113.8	0	0	—	—	—	—
Normal (n = 447,296)	3,888,255	305	7.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
High (n = 3,523)	27,958.2	1	3.6	0.61 (0.09–4.33)	0.82 (0.11–5.85)	0.81 (0.11–5.80)	0.87 (0.12–6.23)
P_{trend}				0.781	0.952	0.936	0.929

Note: Cox proportional hazard models using age as a timescale were used to estimate HRs and 95% confidence intervals.

Abbreviations: BMI, body mass index; CI, confidence interval; FIB4, fibrosis-4; FT3, free triiodothyronine; FT4, free thyroxin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; TSH, thyrotropin.

[a]Multivariable Model 1 was adjusted for age (timescale), sex (male or female), center (Seoul or Suwon), year of screening exam (1-year category), smoking status (never, past, current, or unknown), alcohol intake (none, < 20, or ≥ 20 g/day, unknown), regular exercise (< 3, ≥ 3 times a week, or unknown), BMI (continuous), education level (< community college graduate, ≥ community college graduate, or unknown), and family history of cancer (no, yes, or unknown), viral hepatitis (no or yes), fatty liver (no or yes), liver cirrhosis (no or yes), and FIB-4 (continuous). Model 2 was adjusted for the variables in Model 1 plus diabetes (no or yes), hypertension (no or yes), total cholesterol (continuous), triglycerides (continuous), and HDL-C (continuous).

[b]Estimated from Cox proportional hazard models with age as a timescale after adjusting for thyroid hormone categories (TSH, FT4, and FT3 separately in each model), alcohol intake (none, < 20, or ≥ 20 g/day, unknown), smoking status (never, past, current, or unknown), regular exercise (< 3, ≥ 3 times a week, or unknown), BMI (continuous), viral hepatitis (no or yes), fatty liver (no or yes), liver cirrhosis (no or yes), and FIB-4 (continuous) as time-dependent categorical variables and baseline sex (male, female), center (Seoul, Suwon), year of screening exam (1-year category), education level (< community college graduate, ≥ community college graduate, or unknown), and family history of cancer (no or yes) as time-fixed variables.

[c]451,444 subjects with available free T3 data.

Between 2002 and 2009, thyroid hormones were measured using a radioimmunoassay and the normal range was 0.9–1.8 ng/dL for FT4, 2.0–4.25 pg/mL for FT3, and 0.25–5.0 μIU/mL for TSH; thereafter, thyroid hormones were measured via electrochemiluminescent immunoassay and the normal range was 0.93–1.7 ng/dL for FT4, 2.0–4.4 pg/mL for FT3, and 0.25–5.0 μIU/mL for TSH. High and low TSH, FT4, and FT3 were defined as those above the upper bound of reference interval and those below the lower bound of reference intervals of their corresponding reference intervals, respectively.

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Table 3. HRs (95% CIs) for liver cancer mortality baseline thyroid hormone level within the euthyroid range (n = 495,202).

	Person-years (PY)	Number of events	Mortality rate (10^5 PY)	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)	
					Model 1	Model 2
TSH (μIU/mL; n = 495,202)						
Tertile 1	1,368,095.3	114	8.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1,427,218	102	7.1	0.90 (0.69–1.17)	0.84 (0.65–1.10)	0.85 (0.65–1.11)
Tertile 3	1,486,179.2	146	9.8	1.20 (0.93–1.53)	1.14 (0.88–1.46)	1.18 (0.92–1.51)
P_{trend}				0.135	0.273	0.174
Per 0.1 unit increase				1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
FT4 (ng/dL; n = 499,493)						
Tertile 1	1,508,791.8	195	12.9	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1,372,388.7	76	5.5	0.48 (0.37–0.62)	0.63 (0.48–0.83)	0.62 (0.47–0.81)
Tertile 3	1,404,540.2	60	4.3	0.39 (0.29–0.52)	0.64 (0.48–0.87)	0.62 (0.46–0.84)
P_{trend}				<0.001	0.001	<0.001
Per 0.1 unit increase				0.74 (0.68–0.79)	0.85 (0.79–0.92)	0.85 (0.79–0.92)
FT3 (pg/mL; n = 447,296)						
Tertile 1	1,263,410	129	10.2	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1,488,876.9	114	7.7	0.68 (0.53–0.88)	0.79 (0.61–1.02)	0.81 (0.63–1.04)
Tertile 3	1,135,968.1	62	5.5	0.88 (0.43–0.80)	0.85 (0.62–1.16)	0.87 (0.63–1.19)
P_{trend}				<0.001	0.179	0.240
Per 0.1 unit increase				0.90 (0.85–0.94)	0.93 (0.89–0.98)	0.94 (0.89–0.99)

Note: Cox proportional hazard models using age as a timescale were used to estimate HRs and 95% CIs.
Abbreviations: BMI, body mass index; CI, confidence interval; FT4, free thyroxin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; TSH, thyrotropin.
[a]Multivariable Model 1 was adjusted for age (timescale), sex (male or female), center (Seoul or Suwon), year of screening exam (1-year category), smoking status (never, past, current, or unknown), alcohol intake (none, < 20, or ≥ 20 g/day, unknown), regular exercise (< 3, ≥ 3 times a week, or unknown), BMI (continuous), education level (< community college graduate, ≥ community college graduate, or unknown), and family history of cancer (no, yes, or unknown), viral hepatitis (no or yes), fatty liver (no or yes), liver cirrhosis (no or yes), and FIB-4 (continuous). Model 2 was adjusted for the variables in Model 1 plus diabetes (no or yes), hypertension (no or yes), total cholesterol (continuous), triglycerides (continuous), and HDL-C (continuous).
TSH tertile levels: tertile 1, 0.25–1.49; tertile 2, 1.50–2.36; and tertile 3, 2.37–5.00.
Free T4 tertile levels: tertile 1, 0.93–1.21; tertile 2, 1.22–1.34; and tertile 3, 1.35–1.80.
Free T3 tertile levels: tertile 1, 2.00–3.06; tertile 2, 3.08–3.28; and tertile 3, 3.29–4.40.

cirrhosis on US, intermediate or high probability of advanced fibrosis based on NFS, FIB-4, and APRI, or high alcohol intake (Supplementary Table S1). The association between FT4 level and liver cancer mortality was similar across subgroups, without significant interactions.

Discussion

This cohort study evaluated the relationship between thyroid hormone level (TSH, FT4, and FT3) and liver cancer mortality in a Korean cohort consisting of middle-aged subjects who attended a routine health checkup program. Abnormally, low FT4 level was independently associated with an elevated risk of liver cancer mortality. These findings remained significant even after potential confounding factors were taken into account and when changes in FT4 level and confounding factors during follow-up were incorporated as time-varying covariates. Within the euthyroid range, FT3 and FT4 levels were inversely associated with liver cancer mortality. This study suggests that thyroid function within both the abnormal and normal ranges could affect liver cancer mortality.

Previous observational studies and meta-analysis reported an association between thyroid function and chronic liver disease (36). In cross-sectional studies, hypothyroidism defined either by self-report or by the diagnosis based on thyroid function tests was positively associated with the presence and severe degree of NAFLD (36). A cross-sectional study showed that subclinical hypothyroidism and low normal thyroid function were independent predictors of nonalcoholic steatohepatitis and liver fibrosis in 425 patients with biopsy-proven NAFLD (13). A population-based cohort study of 9,419 participants (average age, 64.7 years) in Rotterdam, the Netherlands demonstrated that hypothyroidism and lower thyroid function, even within the euthyroid range, was related to an elevated risk of developing NAFLD based on a fatty liver index ≥ 60 and liver fibrosis assessed by transient elastography (37). However, limited data are available regarding the relationship of thyroid hormone with the risk of liver cancer in clinical studies. In a case–control study by Reddy and colleagues, the prevalence of hypothyroidism defined as TSH level > 5.0 or history of hypothyroidism was higher in patients with HCC of unknown origin versus patients with HCC with HCV or alcoholic liver disease (7). Another case–control study by Hassan and colleagues demonstrated that a history of hypothyroidism was independently associated with HCC regardless of HBV, HCV, and diabetes (14). However, these two case–control studies did not include thyroxine measurements and patients with HCC might be more likely to recall prior health status than healthy individuals (7, 14). The present large-scale cohort study of maximum 16 years of follow-up investigated the effect of thyroid hormones on the liver cancer mortality and found that low FT4 level in both abnormal and normal range was consistently and independently related to an elevated risk of liver cancer mortality.

The mechanism by which hypothyroidism could affect liver cancer mortality is not fully understood. Thyroid hormones act on almost all cells in humans (38) and regulate the basal metabolic rate of all cells,

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including hepatocytes, and modulate liver function (39). Indeed, decreased thyroid function is related to metabolic abnormalities including obesity, dyslipidemia, lipid peroxidation, and insulin resistance, which all contribute to liver damage (7, 11). However, in our study, the relationship of low FT4 level with increased risk of liver cancer mortality remained significant even after the adjustment of metabolic parameters; thus, the findings could not be explained by hypothyroidism-related metabolic abnormalities. There seem to be several other possible explanations regarding the inverse relationship of thyroid hormones with liver cancer risk. First, the downregulation of thyroid hormone receptors (TR) might be associated with HCC. Frau and colleagues reported that the downregulation of TRα1 and TRβ1 was seen in preneoplastic lesions and HCC in rats (40). Second, a functioning TSH receptor is overexpressed in human HCC tissues and it is related to unfavorable prognosis (41). TSH stimulation in the hypothyroid state might result in cell proliferation in HCC (41). The liver also metabolizes thyroid hormones and controls their systemic functions (39). Indeed, previous studies have reported that the prevalence of clinical and subclinical hypothyroidism is increased in patients with chronic liver disease such as NAFLD or nonalcoholic steatohepatitis, a risk factor for liver cancer (42–44). Thus, it may be possible that thyroid dysfunction indicates a manifestation of chronic liver disease. The inverse relationship of FT4 level with liver cancer mortality was, however, consistently observed even in the absence of chronic liver disease including fatty liver, alcohol intake, viral hepatitis, liver cirrhosis, or liver fibrosis based on noninvasive fibrosis indices. Further research is required to elucidate the mechanism underlying the association between thyroid function and liver cancer while considering the differential role of thyroid function in carcinogenesis, progression, and the prognosis of liver cancer.

We acknowledge several limitations that should be addressed. First, liver cancer incidence data were unavailable. Given the close parallel between the incidence of liver cancer and liver cancer mortality because the majority of patients with liver cancer die of liver cancer, findings might be expected similar for the incidence of liver cancer. In addition, this study did not differentiate HCC from other liver cancer in terms of mortality because we checked the death from liver cancer using ICD-10 code of C22. Therefore, further researches are required to evaluate the relationship of thyroid function with the incidence of liver cancer while differentiating HCC from other liver cancer. Second, the history of medication use for thyroid disease was collected via self-administered questionnaires without information on specific drug names, thereby limiting our ability to differentiate hyperthyroidism from hypothyroidism based on medication history. Thus, we excluded the participants taking medications for thyroid disease, resulting in an insufficient sample size of overt hypothyroidism and hyperthyroidism. Because of the same limitation, we were not able to evaluate the impact of thyroid hormone supplementation on liver cancer mortality. Future studies to investigate whether the liver cancer mortality is increased in people whose thyroid function becomes euthyroid under treatment for hypothyroidism would be useful. Even though comprehensive factors at baseline and follow-up were considered in our study, the possibility of some unmeasured or residual confounders cannot be excluded. Finally, our study findings from relatively young Korean adults who participated in a regular health checkup program could not be generalized to other age groups, populations with different demographic factors, or other race/ethnic groups. Despite these limitations, this study demonstrated the relationship of thyroid function, both within the normal and abnormal ranges, with liver cancer mortality risk based on a large-scale cohort with measurements of thyroid hormones.

In conclusion, the risk of liver cancer mortality increased as FT4 level decreased, both within the normal and abnormal ranges of thyroid function. The inverse relationship of free thyroxine with liver cancer mortality was consistently found after adjusting for potential confounders. Further studies are warranted to confirm the relationship between thyroid function and liver cancer in other populations and to clarify the biological mechanisms that might help better understand the development of liver cancer and prognosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

W. Sohn: Visualization, writing–original draft, writing–review and editing. **Y. Chang:** Conceptualization, data curation, methodology, writing–original draft, writing–review and editing. **Y.K. Cho:** Supervision, writing–review and editing. **Y. Kim:** Data curation, writing–review and editing. **H. Shin:** Supervision, writing–review and editing. **S. Ryu:** Conceptualization, resources, formal analysis, visualization, methodology, writing–original draft, writing–review and editing.

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