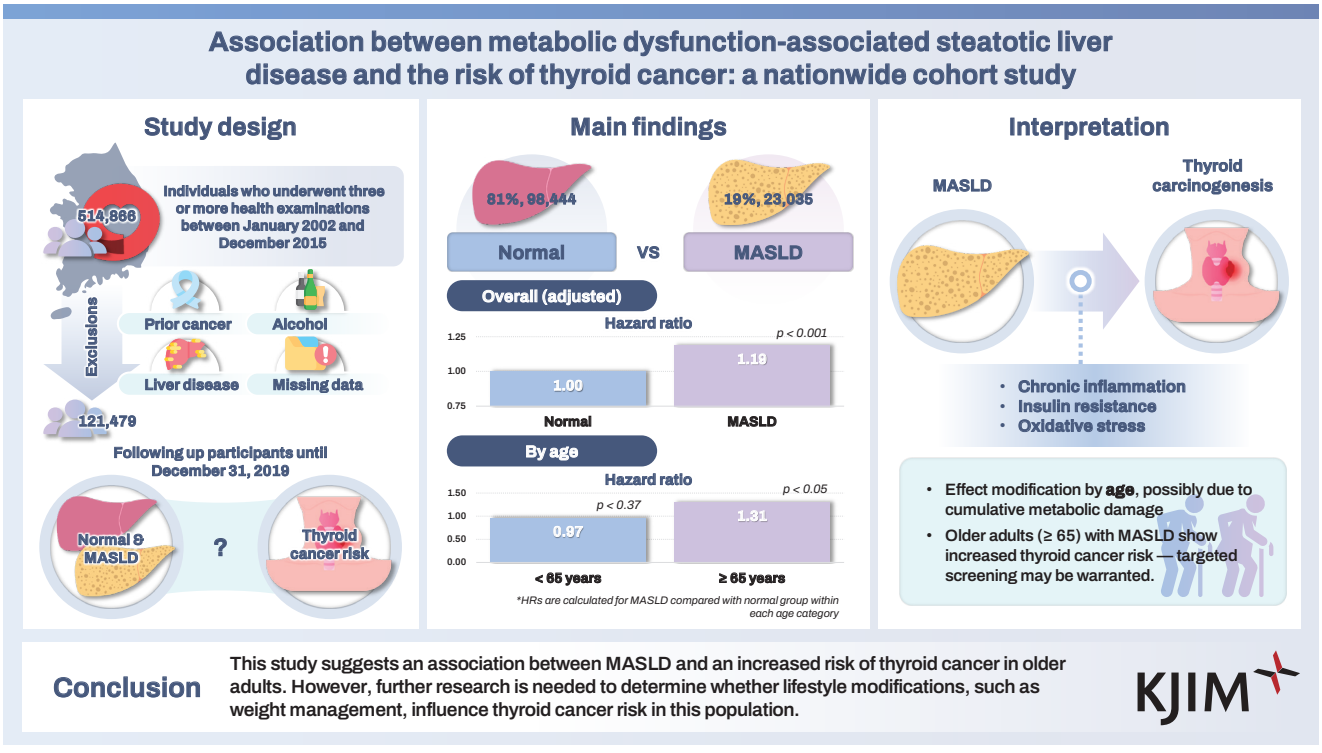
ORIGINAL ARTICLE

Korean J Intern Med 2025;40:813-822
https://doi.org/10.3904/kjim.2025.006

Association between metabolic dysfunction-associated steatotic liver disease and the risk of thyroid cancer: a nationwide cohort study

Jeongmin Lee[1], Jeongeun Kwak[1], Min-Hee Kim[1], Seung-Hwan Lee[2], Jae-Hyoung Cho[2], Dong-Jun Lim[2], Jung Min Lee[1], Sang-Ah Chang[1], and Hun-Sung Kim[2,3]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [3]Department of Medical Informatics, College of Medicine, The Catholic University of Korea, Seoul, Korea



Background/Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with various metabolic disorders; however, its relationship with thyroid cancer remains unclear. This study investigated the association between MASLD and the risk of thyroid cancer.

Methods: This retrospective cohort study used data from the Korean National Health Insurance Service database on individuals who underwent three or more health examinations between January 2002 and December 2015. MASLD was diagnosed using the Hepatic Steatosis Index. Participants were followed up until December 31, 2019, to assess the incidence of newly diagnosed thyroid cancer.

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

Results: A total of 121,479 individuals were included in this study. In the age- and sex-adjusted analysis, the risk of thyroid cancer was significantly higher in the MASLD group than in the normal group (HR 1.19, 95% CI 1.11–1.29, $p < 0.001$). Age was a significant effect modifier of the relationship between MASLD and thyroid cancer (p for interaction < 0.05). Among individuals aged 65 years or older, the risk of thyroid cancer was higher in the MASLD group than in the normal group (HR 1.31, 95% CI 1.00–1.72, $p = 0.05$), whereas in individuals younger than 65 years, MASLD was not associated with thyroid cancer (HR 0.97, 95% CI 0.89–1.04, $p = 0.37$).
Conclusions: This study suggests an association between MASLD and an increased risk of thyroid cancer in older adults. However, further research is needed to determine whether lifestyle modifications, such as weight management, influence thyroid cancer risk in this population.

Keywords: Metabolic syndrome; Non-alcoholic fatty liver disease; Thyroid neoplasms

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has recently been proposed as a more precise term to describe liver disease linked to metabolic dysregulation, replacing the traditional concept of non-alcoholic fatty liver disease (NAFLD) [1]. NAFLD is characterized by the accumulation of fat in the liver that occurs in the absence of other identifiable causes of hepatic steatosis, such as a high alcohol intake, viral hepatitis, or other specific liver diseases [2]. In contrast, MASLD is defined by the presence of hepatic steatosis with either overweight/obesity or type 2 diabetes mellitus (T2DM). However, in individuals who are lean based on population-specific body mass index (BMI) criteria, are not overweight/obese, and do not have T2DM, its diagnosis requires at least two additional metabolic risk factors [3]. This new terminology more accurately reflects the underlying pathophysiology of liver disease in the context of metabolic syndrome and aligns with the increasing global prevalence of obesity.

Thyroid cancer is the most common endocrine malignancy. The incidence of thyroid cancer has increased over the past several decades [4,5]. The recognized risk factors for thyroid cancer include radiation exposure, familial predisposition, and specific genetic mutations. Emerging evidence suggests that metabolic disorders may also contribute to the risk of developing thyroid cancer [6,7]. The hypothesized association between MASLD and thyroid cancer could be mediated through mechanisms such as chronic inflammation, insulin resistance, and altered adipokine levels, which are key features of metabolic dysfunction [8]. Additionally, the oxidative stress and immune dysregulation associated with MASLD may further contribute to a pro-carcinogenic environment within the thyroid gland [9].

Despite the hypothesized association between MASLD and thyroid cancer, the relationship remains insufficiently explored, and it is unclear whether MASLD is an independent risk factor for thyroid cancer. Understanding this relationship is critical, particularly given the growing prevalence of various types of metabolic dysfunction worldwide and their broader implications for public health. This study aimed to investigate the association between MASLD and the risk of thyroid cancer and to clarify whether MASLD is an independent risk factor for thyroid cancer.

METHODS

Data collection

This retrospective cohort study used data from the Korean National Health Insurance Service (NHIS) database. South Korea operates a single, universal insurance system that covers almost the entire population. All NHIS enrollees are advised to undergo medical checkups at least once every 2 years. The NHIS database includes a qualification database (containing data on sex, age, income, and area of residence), a claims database (containing data on consultations, diagnosis according to the International Classification of Diseases 10th revision [ICD-10] codes, and prescriptions), a health checkup database (containing data on general health examination results and responses to questions on lifestyle and behavior), and death information [10].

https://doi.org/10.3904/kjim.2025.006

Participants

The participants in this study were individuals who underwent health examinations as part of the National Health Screening Program between January 1, 2002, and December 31, 2015. Individuals who underwent at least three health examinations during the study period were considered for inclusion. Individuals with thyroid cancer diagnosed before the index date; with a previous diagnosis of hepatitis, liver cirrhosis, or liver cancer; with heavy alcohol consumption; or with missing data were excluded (Fig. 1). The baseline characteristics for each participant were determined based on data collected during the most recent health examination within the study period. This approach was chosen to ensure that the most up-to-date metabolic and clinical information was used as the baseline in the analysis. The participants were followed up from their baseline health examination until December 31, 2019. In this study, the index date was defined as the date of the health examination. Participants were classified into the MASLD group and the Normal group at the time of the health examination, and follow-up was conducted accordingly. The follow-up period lasted five years from the index date, during which the incidence rate (IR) of thyroid cancer was compared between the two groups.

This study complied with the ethical standards of the Declaration of Helsinki, and the study protocol was approved by the Eunpyeong St. Mary's Hospital Institutional Review Board of Catholic Medical Center, The Catholic University of Korea (IRB approval No. PC23ZISI0117). The requirement for written informed consent was waived because the study was based on a retrospective analysis of previously collected, anonymized data.

Demographic variables and measurement

Demographic and lifestyle data were collected using a standardized self-administered questionnaire that included questions on smoking status (current smoker having consumed at least five packs [or 100 cigarettes] and currently smoking) and alcohol consumption (≥30 g per day for male and ≥20 g per day for female). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with participants seated after a rest period of at least 5 minutes. Body weight, height, and waist circumference were measured directly during each visit. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Laboratory tests included serum fasting glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride, which were measured after an overnight fast of at least 8 hours. T2DM was defined as a fasting glucose level ≥126 mg/dL on at least one claim per year recorded under ICD-10 codes E10–E14 (non-insulin-dependent diabetes mellitus) and the prescription of antidiabetic medication. Hypertension was defined as SBP/DBP ≥140/90 mmHg or at least one claim per year under ICD-10 codes I10–I13 (essential hypertension) or I15 (secondary hypertension) and the prescription of

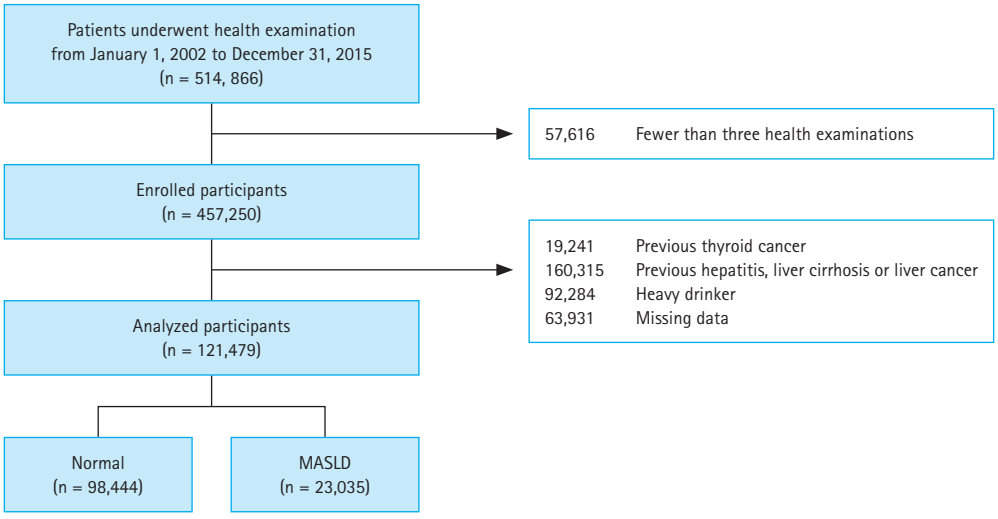


Figure 1. Flowchart of participant selection. MASLD, metabolic dysfunction-associated steatotic liver disease.

antihypertensive agents. Dyslipidemia was defined as a total cholesterol level ≥240 mg/dL or at least one claim per year under ICD-10 code E78 (disorders of lipoprotein metabolism and other lipidemias) and the prescription of lipid-lowering drugs.

Definition of MASLD

Histological staging and grading via liver biopsy remain the gold standard for diagnosing fatty liver disease. However, due to the invasive nature of this procedure and its potential complications, imaging modalities such as liver ultrasonography and computed tomography are more commonly used in clinical settings. In this study, MASLD was diagnosed based on laboratory tests and anthropometric measurements using the Hepatic Steatosis Index (HSI). HSI has been validated as a diagnostic tool for fatty liver disease in a study of the Korean population and was calculated using the following formula [11,12]:

$$HSI = 8 \times (ALT : AST\ ratio) + BMI\ (+2\ for\ female;\ +2\ for\ diabetes\ mellitus)$$

In this study, MASLD was defined as an HSI value ≥ 36.

Definition of the study outcome and follow-up duration

The primary endpoint was newly diagnosed thyroid cancer during the follow-up period. The NHIS database does not provide information on histology. Participants with thyroid cancer were defined as those who had two or more ICD 10 codes of C73 (malignant neoplasm of thyroid gland) recorded during the study period (from 2002 to 2015) and who underwent thyroid surgery within 2 years of receiving the first C73 diagnosis.

Statistical analysis

Continuous variables were reported as the mean ± standard deviation, and categorical variables were reported as the count and percentage. The significance of differences in continuous variables between groups was assessed using the independent samples t-test, and the significance of differences in categorical variables between groups was assessed using the chi-square test. The age- and sex-stratified annual trend in the incidence of thyroid cancer was analyzed using the chi-square test for trend. The IR of thyroid cancer was calculated as the number of events divided by the total follow-up duration (per 1,000 person-years). The risk of thyroid cancer in participants with MASLD compared with those without MASLD was assessed using Cox regression to estimate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs), taking fatty liver severity into consideration. The statistical significance of differences in incidence between groups was assessed using the log-rank test. Model 1 provided unadjusted estimates of the HR for thyroid cancer. Model 2 was adjusted for age and sex. Statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). p values < 0.05 were considered statistically significant.

RESULTS

A total of 514,866 individuals who underwent health examinations in the National Health Screening Program from January 1, 2002, to December 31, 2015, were considered for inclusion in the analysis, of whom 57,616 were excluded because they received fewer than three health checkups during the study period; 19,241 were excluded because they had a previous diagnosis of thyroid cancer; 160,315 were excluded because they had a previous diagnosis of hepatitis, cirrhosis, or liver cancer; 92,284 were excluded because of heavy alcohol consumption; and 63,931 were excluded because of missing data. After these exclusions, a total of 121,479 participants were included in the analysis (Fig. 1).

Baseline characteristics

Of the 121,479 participants, 23,035 (19.0%) were categorized as having MASLD based on the HSI (Table 1). The mean HSI was 31.1 ± 2.8 in the normal group and 39.1 ± 3.4 in the MASLD group (p < 0.001). The mean age of all participants was 56.9 ± 7.8 years. The proportion of male was significantly higher in the MASLD group than in the normal group (25.6% vs. 10.9%, p < 0.001). Compared with the normal group, the MASLD group had significantly higher mean waist circumference (86.0 ± 7.3 cm vs. 76.3 ± 7.0 cm, p < 0.001), mean fasting glucose level (110 ± 35 mg/dL vs. 98 ± 25 mg/dL, p < 0.001), mean total cholesterol level (211 ± 40 mg/dL vs. 205 ± 37 mg/dL, p < 0.001), mean triglyceride level (156 ± 98 mg/dL vs. 117 ± 75 mg/dL, p < 0.001), and mean LDL-C level (128 ± 39 mg/dL vs. 124 ± 36 mg/dL, p < 0.001), and significantly lower mean HDL-C level

https://doi.org/10.3904/kjim.2025.006

KJIM

Table 1. Baseline characteristics of participants

Characteristic	Total	Normal	MASLD	*p* value
Number (%)	121,479 (100.0)	98,444 (81.0)	23,035 (19.0)	
HSI	32.6 ± 4.3	31.1 ± 2.8	39.1 ± 3.4	< 0.001
Age (yr)	56.9 ± 7.8	57.0 ± 7.8	56.4 ± 6.9	< 0.001
Sex, male	16,656 (13.7)	10,759 (10.9)	5,987 (26.0)	< 0.001
BMI (kg/m^2)	23.5 ± 2.8	22.7 ± 2.2	26.9 ± 2.6	< 0.001
Waist circumference (cm)	78.1 ± 8.0	76.3 ± 7.0	86.0 ± 7.3	< 0.001
SBP (mmHg)	120 ± 15	119 ± 14	125 ± 14	< 0.001
DBP (mmHg)	75 ± 10	75 ± 10	74 ± 9	< 0.001
Fasting glucose (mg/dL)	100 ± 28	98 ± 25	110 ± 35	< 0.001
Total cholesterol (mg/dL)	206 ± 38	205 ± 37	211 ± 40	< 0.001
Triglyceride (mg/dL)	125 ± 81	117 ± 75	156 ± 98	< 0.001
HDL-C (mg/dL)	58 ± 27	59 ± 28	54 ± 25	< 0.001
LDL-C (mg/dL)	125 ± 37	124 ± 36	128 ± 39	< 0.001
AST (IU/L)	25 ± 14	24 ± 13	28 ± 17	< 0.001
ALT (IU/L)	22 ± 18	19 ± 12	36 ± 28	< 0.001
γGTP (IU/L)	27 ± 37	24 ± 34	40 ± 46	< 0.001
Hypertension	49,319 (40.6)	36,719 (37.3)	12,600 (54.7)	< 0.001
T2DM	28,356 (23.3)	19,613 (19.9)	8,743 (38.0)	< 0.001
Dyslipidemia	25,843 (21.3)	19,805 (20.1)	6,038 (26.2)	< 0.001
Current smoking	7,101 (5.8)	4,931 (5.0)	2,170 (9.4)	< 0.001
Non-alcoholic	96,379 (79.3)	79,051 (80.3)	17,328 (75.2)	< 0.001
Low income (lower 25%)	38,141 (31.5)	31,140 (31.8)	7,001 (30.5)	< 0.001

Values are presented as number (%) or mean ± standard deviation.
MASLD, metabolic dysfunction-associated steatotic liver disease; HSI, Hepatic Steatosis Index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, γ-glutamyl transpeptidase; T2DM, type 2 diabetes mellitus.

(54 ± 25 mg/dL vs. 59 ± 28 mg/dL, $p < 0.001$).

Compared with the normal group, the MASLD group had a significantly higher prevalence of hypertension (54.7% vs. 37.3%, $p < 0.001$), T2DM (38.0% vs. 19.9%, $p < 0.001$), dyslipidemia (26.2% vs. 20.1%, $p < 0.001$), current smoking (9.4% vs. 5.0%, $p < 0.001$), and alcohol consumption (24.8%% vs. 19.7%, $p < 0.001$), and a significantly lower prevalence of low-income status (30.5% vs. 31.8%, $p < 0.001$).

Risk of thyroid cancer according to MASLD status

The risk of thyroid cancer according to MASLD status is shown in Table 2. The IR of thyroid cancer was higher in the MASLD group than in the normal group (IR, 3.92 per 1,000 person-years vs. 3.70 per 1,000 person-years). In the unadjusted model (Model 1), the risk of thyroid cancer was higher in the MASLD group than in the normal group (HR 1.06, 95% CI 0.98–1.14); however, this increased risk was not statistically significant ($p = 0.13$). In Model 2, which adjusted for age and sex, the risk of thyroid cancer was significantly higher in the MASLD group than in the normal group (HR 1.19, 95% CI 1.11–1.29, $p < 0.001$).

Risk of thyroid cancer in MASLD according to age and BMI

In an analysis of the risk of thyroid cancer stratified by age group (Table 3), among participants aged 65 years or older, the risk of thyroid cancer was higher in the MASLD group than in the normal group (HR 1.31, 95% CI 1.00–1.72, *p*

Table 2. The risk of thyroid cancer in MASLD

	Number	Events	Person-year	IR[a)]	Unadjusted HR model (95% CI)	*p* value	Adjusted HR model (95% CI)	*p* value
Normal	98,444	3,357	907,546	3.70	1.00 (reference)		1.00 (reference)	
MASLD	23,035	833	212,285	3.92	1.06 (0.98–1.14)	0.13	1.19 (1.11–1.29)	< 0.001

Adjusted HR model (95% CI) was adjusted for age and sex.
MASLD, metabolic dysfunction-associated steatotic liver disease; IR, incidence rate; HR, hazard ratio; CI, confidence interval.
[a)]Per 1,000 person-years, the reference hazard ratio 1.0 as normal group.

Table 3. The risk of thyroid cancer in MASLD according to age and BMI

		Number	Events	HR (95% CI)	*p* value	*p* for interaction
Age (yr)						< 0.05
< 65	Normal group	80,199	3,055	1.00 (reference)		
	MASLD group	16,660	793	0.97 (0.89–1.04)	0.37	
≥65	Normal group	21,576	276	1.00 (reference)		
	MASLD group	3,044	66	1.31 (1.00–1.72)	0.05	
BMI						0.57
Underweight	Normal group	3,116	73	1.00 (reference)		
	MASLD group	3	0	NA	NA	
Normal BMI	Normal group	45,928	1,564	1.00 (reference)	0.95	
	MASLD group	972	33	0.99 (0.70–1.40)		
Overweight	Normal group	29,923	1,035	1.00 (reference)	0.09	
	MASLD group	3,613	105	0.84 (0.69–1.03)		
Obesity	Normal group	17,892	659	1.00 (reference)	0.68	
	MASLD group	20,032	721	0.98 (0.88–1.09)		

The reference hazard ratio 1.0 as HSI < 36.
MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; HR, hazard ratio; CI, confidence interval; NA, not applicable.

= 0.05). In contrast, in participants younger than 65 years, the risk of thyroid cancer was not associated with MASLD (HR 0.97, 95% CI 0.89–1.04, $p = 0.37$). The interaction between MASLD and age in modifying the risk of thyroid cancer was statistically significant (p for interaction < 0.05). In a subgroup analysis of the risk of thyroid cancer according to MASLD status stratified by BMI, MASLD was not associated with an increased risk of thyroid cancer in the normal BMI (HR 0.99, 95% CI, 0.70–1.40, $p = 0.95$), overweight (HR 0.84, 95% CI, 0.69–1.03, $p = 0.09$), or obese (HR 0.98, 95% CI 0.88–1.09, $p = 0.68$) subgroups.

DISCUSSION

MASLD has been shown to be associated with an increased risk of various cancers. However, the association between MASLD and thyroid cancer has received limited attention. This study demonstrated that the IR of thyroid cancer was higher in participants with MASLD than in those without MASLD. Although the association was not statistically significant in the unadjusted analysis, the risk of thyroid cancer was 19% higher in the MASLD group than in the non-MASLD group after adjusting for age and sex. In the age-stratified analysis, MASLD was associated with a significantly increased risk of thyroid cancer in individuals aged 65 years or older, but was not associated with an increased risk of thyroid cancer in individuals aged younger than 65 years,

https://doi.org/10.3904/kjim.2025.006

suggesting that the effect of MASLD on thyroid cancer risk may be age-dependent. Aging is associated with progressive metabolic dysfunction, chronic low-grade inflammation, and oxidative stress, all of which have been implicated in cancer development [13]. The significant interaction between MASLD and age supports the hypothesis that prolonged exposure to metabolic disturbances may increase susceptibility to thyroid carcinogenesis in older individuals.

In a recent study, the IRs for all cancers combined and thyroid cancer were significantly higher in the MASLD group than in the non-MASLD group [14]. A cohort study conducted in China, in which NAFLD was diagnosed using abdominal ultrasonography, found that NAFLD was associated with an increased risk of thyroid cancer [15]. In these previous studies, the HRs for thyroid cancer in relation to MASLD/NAFLD were higher than that found in this study. This may be attributable to several factors, including differences in the study population, methods of diagnosing MASLD/NAFLD, and the duration of follow-up. The results of a nationwide cohort study in South Korea by Moon et al. [16], published in 2025, provide further evidence supporting an association between MASLD and thyroid cancer. Similar to our study, the authors observed a significant increase in thyroid cancer risk among individuals with MASLD. However, the two studies have some key methodological differences. Our study included only individuals who underwent at least three health examinations during the study period, whereas the study by Moon et al. [16] included all individuals aged 40 years and older who underwent a single examination. Unlike the study by Moon et al. [16], our study captured long-term metabolic health trends, thereby reducing potential biases related to transient metabolic changes. Second, Moon et al. [16] examined both MASLD and metabolic and alcohol-related liver disease in relation to thyroid cancer, whereas our study focused on the differential impact of MASLD on the risk of thyroid cancer in different age groups and excluded individuals with alcohol-related liver disease. Our study found that MASLD was associated with thyroid cancer only in individuals aged 65 years or older. The study by Moon et al. [16] did not report age-stratified results.

The method used to define MASLD in this study differed from those used in some previous studies [14,15]. In clinical practice, noninvasive indices such as the HSI and the Fatty Liver Index (FLI) are widely used as simple and rapidly assessed measures of MASLD [11,16-18]. In this study, MASLD was diagnosed based on the HSI. The HSI was originally developed in a Korean population and has shown high accuracy in diagnosing MASLD in East Asian populations [11]. The HSI is more accurate than the FLI at detecting fatty liver disease [19]. Although ultrasonography and liver biopsy are valuable diagnostic tools, the HSI used in this study offers several advantages, particularly in large epidemiological studies, because it is less resource-intensive and more accessible.

This study revealed that the association between MASLD and thyroid cancer risk differs by age. Specifically, among participants aged 65 years or older, MASLD was associated with a 31% increased risk of thyroid cancer, with borderline statistical significance. In contrast, no association was observed between MASLD and the risk of thyroid cancer in participants younger than 65 years. This finding suggests that older adults with MASLD, but not younger adults with MASLD, have a higher risk of thyroid cancer, potentially due to the cumulative effects of chronic metabolic dysfunction over time, which may exacerbate inflammation and other carcinogenic processes. Aging is associated with cellular senescence [20]. Cellular senescence is exacerbated by various factors, including DNA damage, alterations in gene expression, oxidative stress, and mitochondrial dysfunction [21]. These factors collectively contribute to the deterioration of cellular and tissue function, which can increase the likelihood of developing cancer as individuals age. In younger participants, the absence of an association between MASLD and thyroid cancer may reflect a greater capacity for cellular repair and a more robust response to metabolic challenges [22,23]. A nationwide cohort study of adults aged 20 to 39 years in South Korea, in which MASLD was measured using the FLI [24], found that MASLD was associated with an increased risk of thyroid cancer in young adults, with a higher risk in participants with higher FLI scores and cumulative FLI points. However, the study focused on a restricted age group and had an insufficient follow-up period to capture the long-term cancer risk associated with MASLD, particularly in younger individuals who may develop cancer later in life.

Obesity exacerbates metabolic disturbances such as insulin resistance, hyperinsulinemia, and chronic low-grade inflammation, all of which are linked to both MASLD and an increased risk of various cancers, including thyroid cancer [25-27]. Recent studies have demonstrated that obesity is associated with a significantly increased risk of thyroid cancer [28-30]. A five-point increase in BMI has been shown

to be associated with a 30% increase in the risk of thyroid cancer [30]. In this study, the association between MASLD and thyroid cancer varied across BMI categories. While MASLD was linked to an increased risk of thyroid cancer in the overall analysis, the BMI-stratified analysis showed HR values below 1 in all BMI subgroups. However, the smaller sample sizes in these subgroups may have increased variability and reduced statistical power, making HR values below 1 a natural statistical phenomenon.. Since the overall analysis (Table 2) confirmed that MASLD significantly increases the risk of thyroid cancer, we believe this does not have a major impact on the study's main conclusions. This paradoxical finding may result from BMI being both a key component of MASLD and an independent risk factor for thyroid cancer. Stratification by BMI may have led to over-adjustment, weakening the observed association. Additionally, residual confounding cannot be ruled out, as BMI alone does not fully account for the metabolic complexities of MASLD. Future studies should use MASLD definitions that exclude BMI to better assess its independent impact on thyroid cancer risk [31].

This study has several strengths. The large cohort size of over 120,000 participants provided high statistical power and enabled detailed subgroup analyses. The long follow-up period of up to 20 years enabled the long-term risk of thyroid cancer associated with MASLD to be assessed. The use of the HSI, a noninvasive index, to diagnose MASLD made it feasible to conduct a large epidemiological study.

However, this study also has some limitations. The primary limitation is the potential misclassification of MASLD due to reliance on a noninvasive index. MASLD severity was assessed only through a binary classification (HSI $\geq$ 36), as the NHIS database lacks liver biopsy results, imaging-based steatosis quantification, and detailed biochemical markers, preventing a more precise evaluation. Second, BMI is an integral part of HSI, which may have influenced the observed association between MASLD and thyroid cancer. This overlap could attenuate the independent effect of MASLD. Although subgroup analyses were stratified by BMI, residual confounding cannot be ruled out. Ideally, adjusting for BMI as a separate covariate would clarify the independent association. However, this was not feasible due to the high correlation between BMI and HSI, which could introduce multicollinearity. Future studies should use MASLD definitions that exclude BMI to better assess its independent contribution to thyroid cancer risk. Another limitation is the possibility of residual confounding. The NHIS database lacks information on key metabolic and lifestyle factors, such as diet, genetic predisposition, family history of cancer, and other lifestyle behaviors. These missing variables could not be accounted for in our analysis. Lastly, as this study was conducted in a single country, the findings may not be generalizable to other populations with different metabolic and demographic profiles.

In conclusion, the results of this study support the hypothesis that MASLD increases the risk of thyroid cancer, with age acting as an effect modifier. These findings suggest that screening and prevention measures should target older adults with MASLD to mitigate the risk of thyroid cancer. Further research should explore the underlying mechanisms linking MASLD and thyroid cancer, particularly in older adults, to enable prevention measures to be enhanced and refined.

KEY MESSAGE

1. This retrospective cohort study investigated the risk of thyroid cancer associated with MASLD using a nationally representative sample of 121,479 adults from the Korean National Health Insurance database.
2. MASLD was defined using the HSI, which has been validated in the Korean population. In the age- and sex-adjusted analysis, MASLD was found to be associated with a significantly increased risk of thyroid cancer.
3. In the age-stratified analysis, MASLD was found to be associated with an increased risk of thyroid cancer in adults aged 65 years or older, but was not associated with thyroid cancer in adults aged younger than 65 years.

REFERENCES

1. Zhang XL, Fan JG, Wei L, Shi JP, Zheng MH; Chinese MAFLD Clinical Research Network. Promoting the term MAFLD: China in action. Lancet Gastroenterol Hepatol 2022;7:598.
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver

https://doi.org/10.3904/kjim.2025.006

Diseases. Hepatology 2018;67:328-357.
3. De A, Bhagat N, Mehta M, Taneja S, Duseja A. Metabolic dysfunction-associated steatotic liver disease (MASLD) definition is better than MAFLD criteria for lean patients with NAFLD. J Hepatol 2024;80:e61-e62.
4. Kim TY, Kim WG, Kim WB, Shong YK. Current status and future perspectives in differentiated thyroid cancer. Endocrinol Metab (Seoul) 2014;29:217-225.
5. Balajam NZ, Mousavian AH, Sheidaei A, et al. The 15-year national trends of endocrine cancers incidence among Iranian men and women; 2005-2020. Sci Rep 2023 10;13:7632.
6. Kitahara CM, Schneider AB. Epidemiology of thyroid cancer. Cancer Epidemiol Biomarkers Prev 2022;31:1284-1297.
7. Park JH, Choi M, Kim JH, et al. Metabolic syndrome and the risk of thyroid cancer: a nationwide population-based cohort study. Thyroid 2020;30:1496-1504.
8. Sawada K, Chung H, Softic S, Moreno-Fernandez ME, Divanovic S. The bidirectional immune crosstalk in metabolic dysfunction-associated steatotic liver disease. Cell Metab 2023;35:1852-1871.
9. Bruce KD, Byrne CD. The metabolic syndrome: common origins of a multifactorial disorder. Postgrad Med J 2009;85:614-621.
10. Kim MK, Han K, Lee SH. Current trends of big data research using the Korean National Health Information Database. Diabetes Metab J 2022;46:552-563.
11. Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42:503-508.
12. Han AL, Lee HK. Comparison of the diagnostic performance of steatosis indices for discrimination of CT-diagnosed metabolic dysfunction-associated fatty liver disease. Metabolites 2022;12:664.
13. Tan BL, Norhaizan ME, Liew WP, Sulaiman Rahman H. Antioxidant and oxidative stress: a mutual interplay in age-related diseases. Front Pharmacol 2018;9:1162.
14. Wei S, Hao Y, Dong X, et al. The relationship between metabolic dysfunction-associated fatty liver disease and the incidence rate of extrahepatic cancer. Front Endocrinol (Lausanne) 2023;14:985858.
15. Wang Z, Zhao X, Chen S, et al. Associations between nonalcoholic fatty liver disease and cancers in a large cohort in China. Clin Gastroenterol Hepatol 2021;19:788-796.e4.
16. Moon SY, Son M, Cho JH, et al. Association between metabolic dysfunction-associated steatotic liver disease and thyroid cancer. Thyroid 2025;35:79-86.
17. Lee YH, Bang H, Park YM, et al. Non-laboratory-based self-assessment screening score for non-alcoholic fatty liver disease: development, validation and comparison with other scores. PLoS One 2014;9:e107584.
18. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.
19. Hang Y, Lee C, Roman YM. Assessing the clinical utility of major indices for nonalcoholic fatty liver disease in East Asian populations. Biomark Med 2023;17:445-454.
20. López-Otín C, Pietrocola F, Roiz-Valle D, Galluzzi L, Kroemer G. Meta-hallmarks of aging and cancer. Cell Metab 2023;35:12-35.
21. Roger L, Tomas F, Gire V. Mechanisms and regulation of cellular senescence. Int J Mol Sci 2021;22:13173.
22. Zhu J, Thompson CB. Metabolic regulation of cell growth and proliferation. Nat Rev Mol Cell Biol 2019;20:436-450.
23. Ju SH, Song M, Lim JY, Kang YE, Yi HS, Shong M. Metabolic reprogramming in thyroid cancer. Endocrinol Metab (Seoul) 2024;39:425-444.
24. Kwon H, Han KD, Moon SJ, Park SE, Rhee EJ, Lee WY. Nonalcoholic fatty liver disease and the risk of thyroid cancer among young adults in South Korea. J Clin Endocrinol Metab 2024;109:e1095-e1104.
25. Manna P, Jain SK. Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies. Metab Syndr Relat Disord 2015;13:423-444.
26. Ibrahim MK, Simon TG, Rinella ME. Extrahepatic outcomes of nonalcoholic fatty liver disease: nonhepatocellular cancers. Clin Liver Dis 2023;27:251-273.
27. Jin X, Qiu T, Li L, et al. Pathophysiology of obesity and its associated diseases. Acta Pharm Sin B 2023;13:2403-2424.
28. Xu L, Port M, Landi S, et al. Obesity and the risk of papillary thyroid cancer: a pooled analysis of three case-control studies. Thyroid 2014;24:966-974.
29. Harikrishna A, Ishak A, Ellinides A, et al. The impact of obesity and insulin resistance on thyroid cancer: a systematic review. Maturitas 2019;125:45-49.
30. Matrone A, Ferrari F, Santini F, Elisei R. Obesity as a risk factor for thyroid cancer. Curr Opin Endocrinol Diabetes Obes 2020;27:358-363.
31. Trevellin E, Bettini S, Pilatone A, Vettor R, Milan G. Obesity, the adipose organ and cancer in humans: association or causation? Biomedicines 2023;11:1319.

Received : January 7, 2025
Revised : February 22, 2025
Accepted : March 11, 2025

Correspondence to
Hun-Sung Kim, M.D., Ph.D.
Department of Medical Informatics, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82-2-3147-8425, Fax: +82-0508-926-9080
E-mail: 01cadiz@hanmail.net
https://orcid.org/0000-0002-7002-7300

CRedit authorship contributions
Jeongmin Lee: conceptualization, methodology, data curation, formal analysis, writing - original draft, visualization; Jeongeun Kwak: data curation, formal analysis; Min-Hee Kim: data curation, formal analysis; Seung-Hwan Lee: writing - review & editing; Jae-Hyoung Cho: writing - review & editing; Dong-Jun Lim: writing - review & editing; Jung Min Lee: writing - review & editing; Sang-Ah Chang: writing - review & editing; Hun-Sung Kim: conceptualization, methodology, resources, investigation, data curation, formal analysis, validation, software, writing - original draft, supervision, project administration, funding acquisition

Conflicts of interest
The authors disclose no conflicts.

Funding
This study was supported by the Bio and Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. NRF-2019M3E5D3073104). This study was performed using the database from the National Health Insurance System; however, the results do not necessarily represent the views of the National Health Insurance Corporation.

Data availability
The data can be accessed on the National Health Insurance Data Sharing Service homepage of the NHIS (http://nhiss.nhis.or.kr).

https://doi.org/10.3904/kjim.2025.006