Population-based big data analysis and institution-specific data verification of secondary cancer risk according to thyroid cancer in patients with lipid metabolic disease

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Population-based big data analysis and institution-specific data verification of secondary cancer risk according to thyroid cancer in patients with lipid metabolic disease

Directed by Professor Jandee Lee

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Because thyroid cancer has a good prognosis and many long-term survivors, the management of these patients is very important. Based on the previous study that the occurrence of secondary cancer increased in those patients with lipid metabolism disease, it was confirmed that the risk of secondary cancer increased when thyroid cancer occurred in patients with lipid metabolism disease. In addition, it was confirmed that the risk of secondary cancer may vary depending on the duration and dose of thyroid hormone taken after thyroid cancer surgery. It is important to manage the risk of thyroid cancer and secondary cancer in patients with lipid metabolism disease, and setting an appropriate hormone intake period in thyroid cancer patients can be an important factor in managing cancer survivors.

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ABSTRACT

Population-based big data analysis and institution-specific data verification of secondary cancer risk according to thyroid cancer in patients with lipid metabolic disease

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Lipid metabolism diseases, such as non-alcoholic fatty liver disease and dyslipidemia, are continuously increasing due to lifestyle changes, and many studies have reported that the incidence of other cancers increases in these diseases. Thyroid cancer occurs frequently, and its prognosis is good; therefore, there are many survivors. Lipid metabolic diseases and thyroid cancer are recognized for their association with high-lipid states and obesity. In the author's previous study, dyslipidemia was found to increase the risk of secondary cancer in patients with thyroid cancer, and there are many obesity-related secondary carcinomas. In this study, we aimed to confirm whether thyroid cancer itself affects the risk of secondary cancer in patients with lipid metabolic disease and the factors affecting this risk through analysis of institutional data and big data from the Korea National Health Insurance system. In both institutional and big data, patients were extracted through the diagnosis of lipid metabolic disease, and the risk of secondary cancer was compared according to the presence or absence of thyroid cancer. In the analysis of institutional data, the risk of secondary cancer increased by approximately two-fold compared to that in patients without thyroid cancer. Interestingly, the risk of secondary cancer was not significantly increased in the patient group with both non-alcoholic fatty liver disease and dyslipidemia. Thyroid cancer increases the risk of secondary cancer in patients with lipid metabolic diseases such as non-alcoholic fatty liver disease and dyslipidemia. When the two diseases coexist, there is no further increase in the risk of secondary cancers. In the nationwide cohort, univariate

and multivariate analyses indicated that hazard ratios of thyroid cancer were 1.329 (95% confidence interval [CI], 1.153–1.533) and 1.301 (95% CI, 1.115–1.517), respectively. In the risk analysis of individual cancers, lip, tongue, mouth, lung, bone, joints, soft tissue, skin, brain, and male cancers and lymphoma showed significantly increased hazard ratios after the occurrence of thyroid cancer.

As a result of analysis according to thyroid hormone replacement, which can be an external factor affecting the occurrence of secondary cancer in patients with thyroid cancer, analysis of institutional data showed that the risk of secondary cancer decreased with long-term use. In the population-based cohort analysis, 261,598 patients who underwent surgery for thyroid cancer were included. Among them, 11,790 patients had a second primary cancer and 47,160 patients without secondary primary cancer were matched. The average dose of thyroid hormone also increased the adjusted odds ratio (OR) in both low (≤ 50 μg, OR 1.29, CI 1.12–1.48) and high (> 100 μg, OR 1.24, CI 1.12–1.37) doses. Analyzing over time, the adjusted OR of second primary cancer was increased compared to patients without thyroid hormone administration, especially in short (≤ 1 year) duration, 1.29 (CI, 1.12–1.48), and long (> 5 years) duration, 1.24 (CI, 1.12–1.37). Thyroid cancer in patients with dyslipidemia or non-alcoholic fatty liver disease might be a valuable factor for predicting the development of other cancers, and insufficient and excessive thyroid hormone replacement might be linked to increased secondary cancer in patients undergoing thyroidectomy.

Key words : NAFLD, dyslipidemia, thyroid cancer, secondary cancer, obesity, thyroid hormone replacement, population based national cohort

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I. INTRODUCTION

The number of patients with lipid metabolism diseases, such as non-alcoholic fatty liver disease (NAFLD) and dyslipidemia, is increasing owing to changes in diet and lifestyle. These trends are reflected in Western and many Eastern countries. According to a meta-analysis of the Asian population, the incidence of NAFLD continues to increase as it gets closer in recent years, resulting in worse outcomes such as liver cancer and death.(1) A similar trend was evident in the Korean population.(2-4) Lipid metabolism diseases frequently coexist with other diseases, and once diagnosed, continuous management and follow-up are essential. NAFLD causes not only liver-related diseases but also extrahepatic

manifestations and comorbidities in various organs. Diseases, such as obstructive sleep apnea, osteoporosis, psoriasis, periodontitis, hypothyroidism, and even malignant tumors, such as colorectal cancer, may occur simultaneously.(5, 6) Studies have been published that dyslipidemia is associated with the development of various carcinomas. Kevin et al. reviewed the association between high cholesterol levels and the risk of prostate cancer.(7) Hao et al. reported that dyslipidemia increases the risk of non-small cell lung cancer in a Chinese population-based data analysis.(5)

Thyroid cancer is the most common endocrine cancer, and the number of patients with thyroid cancer has increased rapidly worldwide over the past 20 years.(8-11) Even in Korea, thyroid cancer is a malignancy with a high incidence, and despite the controversy over overtreatment in the early 2010s, it was the sixth most common cancer in men and the second most common cancer in women as of 2017 **(Figure 1)**.(12, 13)

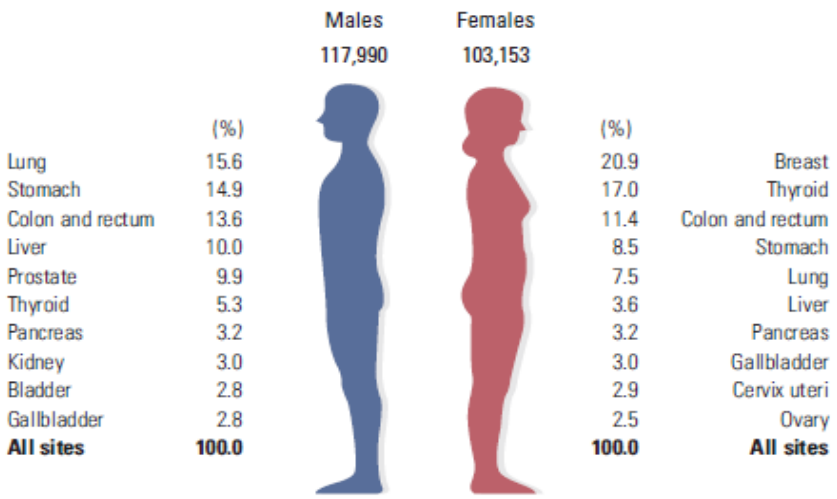
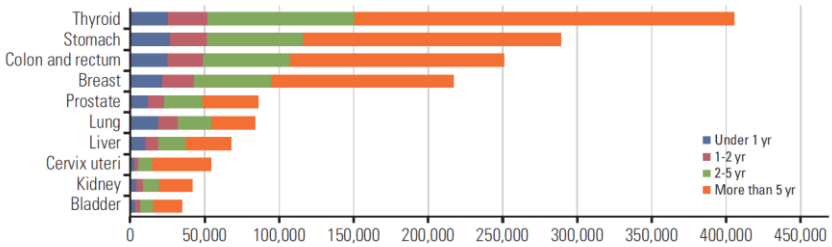


Figure 1. Prevalences of cancers in Korea.
Adopted from *Prediction of Cancer Incidence and Mortality in Korea, 2017. Cancer Res Treat. 2017 Apr;49(2):306-312.*

In addition, because thyroid cancer has a good prognosis, there are more survivors with a longer period after diagnosis than for other cancer types (**Figure 2**). Thyroid cancer is characterized by a large number of long-term survivors, because it occurs at a relatively young age and has a good prognosis. The management of comorbidities or secondary cancers occurring in long-term survivors is important. Many studies have reported the incidence of secondary cancer in thyroid cancer survivors, and some studies have reported an increase in secondary cancer incidence in thyroid cancer survivors compared to the general population.(14-16)



Cancer prevalent cases

Time since diagnosis	Thyroid	Stomach	Colon and rectum	Breast	Prostate	Lung	Liver	Cervix uteri	Kidney	Bladder	All cancers
Under 1 yr	26,026	26,971	25,621	22,125	12,491	19,905	11,260	3,303	4,938	4,027	204,451
1-2 yr	26,111	24,917	23,165	21,236	11,075	12,807	8,427	3,187	4,446	3,544	176,867
2-5 yr	97,944	64,680	58,903	51,603	25,102	22,178	17,874	8,656	10,724	8,355	446,428
More than 5 yr	254,951	172,655	143,374	122,239	37,767	29,352	30,516	39,768	22,405	19,659	1,039,659
Total	405,032	289,223	251,063	217,203	86,435	84,242	68,077	54,914	42,513	35,585	1,867,405

Figure 2. Cancer survivors and periods after diagnosis by cancer type
Adopted from *Prediction of Cancer Incidence and Mortality in Korea, 2017. Cancer Res Treat. 2017 Apr;49(2):306-312.*

In addition, radioactive iodine treatment (RAIT) is a representative factor affecting the incidence of secondary cancer,(17-20) and the author's previous large-scale cohort study also reported that the presence of RAIT and dyslipidemia in thyroid cancer survivors increased the incidence of secondary cancer. In the author's previous study, the incidence

of secondary cancer in patients with thyroid cancer was confirmed using data from the Health Insurance Review & Assessment (HIRA), which has accumulated medical information for the entire Korean population. From the data, 527,451 adult patients diagnosed with thyroid cancer between 2008 and 2018 were extracted. Among them, 269,604 patients were finally analyzed, excluding patients with a washout period of 2 years, patients without a cancer-exempted calculation code, patients with a previous history of other cancers, and patients who had received external beam radiation therapy. Among the extracted patients, 20,699 who developed secondary cancer and those whose age, sex, and index date were matched 1:5 were extracted, and the effects of RAIT and dyslipidemia on the occurrence of secondary cancer were analyzed. As a result of comparing the cancer incidence statistics of the Korea Central Cancer Registry for the entire Korean population and the incidence of secondary cancer in patients with thyroid cancer, the overall risk of developing second cancer was higher in patients with thyroid cancer than in the general population (SIR 3.83; 95% CI, 3.77–3.89). The risk of secondary cancer according to the presence or absence of RAIT, which has been confirmed to have an influence on the occurrence of secondary cancer in various previous studies, was found to be higher in the group of patients receiving RAIT than in the group without RAIT (OR 1.133; 95% CI, 1.091–1.176). Finally, it was confirmed that the risk of secondary cancer was higher in the patient group with dyslipidemia than in the non-dyslipidemia group (OR 1.247; 95% CI, 1.200–1.295).(21) In the data used in a previous study, there was no other information such as blood test results or past history of the patient group. Therefore, dyslipidemia was found to increase the risk of secondary cancer in patients with thyroid cancer, but there was a limitation in that influencing factors could not be further analyzed.

Many studies have shown that cancer development is associated with high fat content and

obesity in the body.(22-24) Kitahara et al. reported that overweight and obesity may have contributed significantly to the rapid increase in the incidence of papillary thyroid cancer.(25) Ulmer et al. reported that serum triglyceride concentrations are involved in the pathogenesis of lung, rectal, thyroid, prostate, and gynecological cancers.(26) According to these findings, there is a possibility that secondary cancer occurring in patients with obesity-related thyroid cancer also occurs because of obesity or lipid metabolism disorder. In a previous study, carcinomas with an increased incidence due to dyslipidemia in thyroid cancer survivors were also obesity-related.(21) In patients with high fat or obesity due to problems with lipid metabolism, the accumulation of lipids affects the incidence of cancer, and especially if thyroid cancer occurs in this patient, it may act as a factor that increases the incidence of other secondary cancers.

Patients with thyroid cancer take thyroid hormones after surgery, and the dose and duration of the hormones taken by thyroid cancer survivors vary depending on the scope of surgery and the patient's body requirements. To determine the risk of secondary cancer in thyroid cancer survivors, it is necessary to evaluate the effect of hormones taken in addition to RAIT administered after surgery, along with the patient's organic background, such as the patient's past history and general condition. There is controversy regarding the duration of hormone therapy after thyroid cancer surgery, and there are a number of studies on the risk of cancer caused by thyroid dysfunction and thyroid hormone replacement (THR).(27-30)

This study aimed to determine whether thyroid cancer itself affects the occurrence of secondary cancer in cancer development in patients with dyslipidemia and NAFLD and to identify other factors affecting it. In addition, we attempted to identify external factors that may act in addition to genetic and environmental factors affecting the development of

secondary cancer in these patients. To confirm the possibility of the influence of the drug, which can be considered a representative external factor, the risk of secondary cancer occurrence according to the duration of hormonal drug use after thyroid surgery will be analyzed. In addition, through a large-scale population-based cohort study, we aimed to check whether it is possible to present a predictive model for factors that are likely to have an impact.

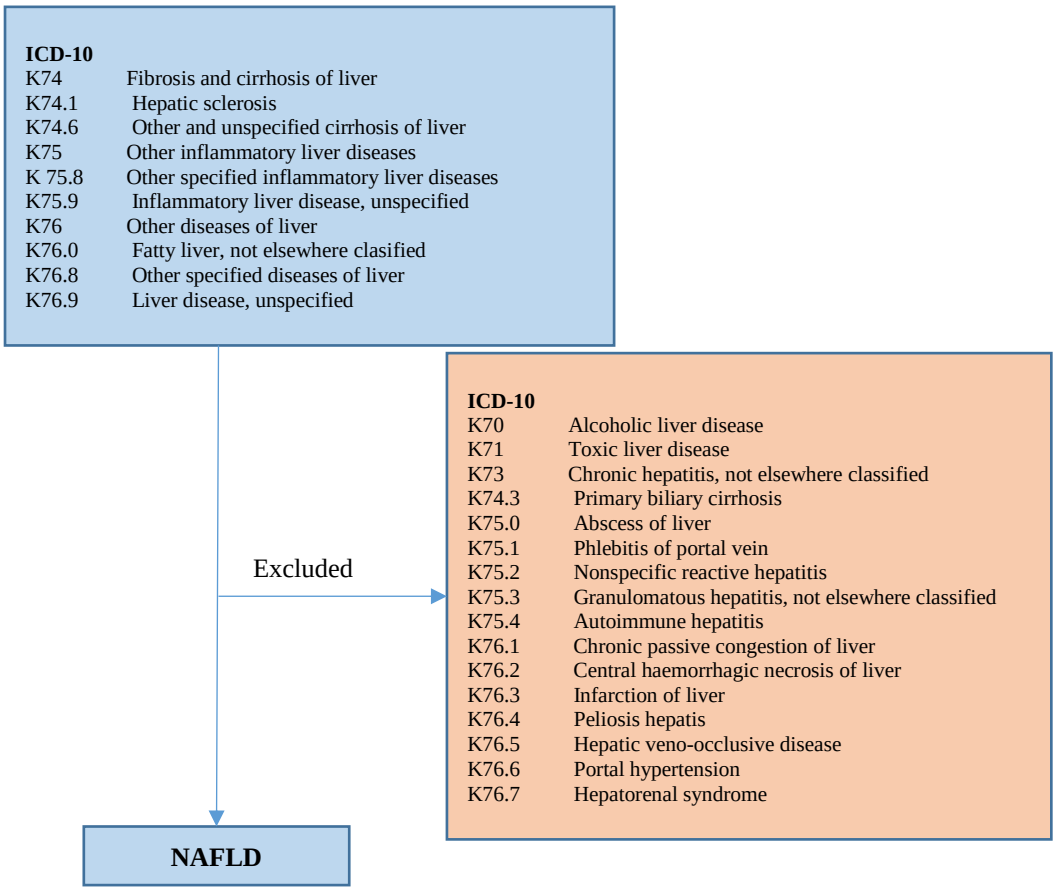


Figure 3. Flowchart of identification of patients with NAFLD in the medical record system. NAFLD, non-alcoholic fatty liver disease

II. MATERIALS AND METHODS

1. Impact of thyroid cancer on the risk of second cancer in dyslipidemia and/or NAFLD patients.

1-1. Institutional data analysis

A. Study Patients

Data on patients were extracted using an in-hospital patient information search program. Patients from September 2004, when the medical records began to be used, to 2020 were included, and patients were extracted based on their diagnosis. All in-hospital patients whose diagnosis was confirmed at least once were included, and in the case of dyslipidemia, the diagnosis was used as-is. In the case of NAFLD, patients with inflammatory liver disease, fatty liver, and cirrhosis were included. Patients with alcoholic, toxic, chronic hepatitis, liver abscess, and biliary cirrhosis were excluded, and patient groups were finally extracted. **Figure 3** summarizes the set of patient groups according to diagnosis based on the ICD-10 standard.(31) Moreover, in the case of thyroid cancer and secondary cancer, patients with a diagnosis were included.

Adults aged 20 to 79 years were extracted, and after a washout period of 1 year, patients from September 2005 were finally extracted. Patients with a prior diagnosis of thyroid cancer were excluded (**Figure 4**). The patient morbidity period was set from the date of initial diagnosis to the date of secondary cancer, and for patients who did not develop secondary cancer, it was set until May 2021. For patients with dyslipidemia and NAFLD at the same time, the morbidity period was set from the date of diagnosis of a later disease. To evaluate the risk of developing secondary cancer due to thyroid cancer in patients with lipid metabolic disease, and to identify factors that affect it, baseline characteristics such as age, sex, waist circumference, and body mass index (BMI) were assessed. The blood test

results for glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were confirmed. For each result, the value of the test period closest to the diagnosis period of NAFLD and dyslipidemia was used. For patients with both diseases, values close to the time of diagnosis of the later diagnosed disease were used.

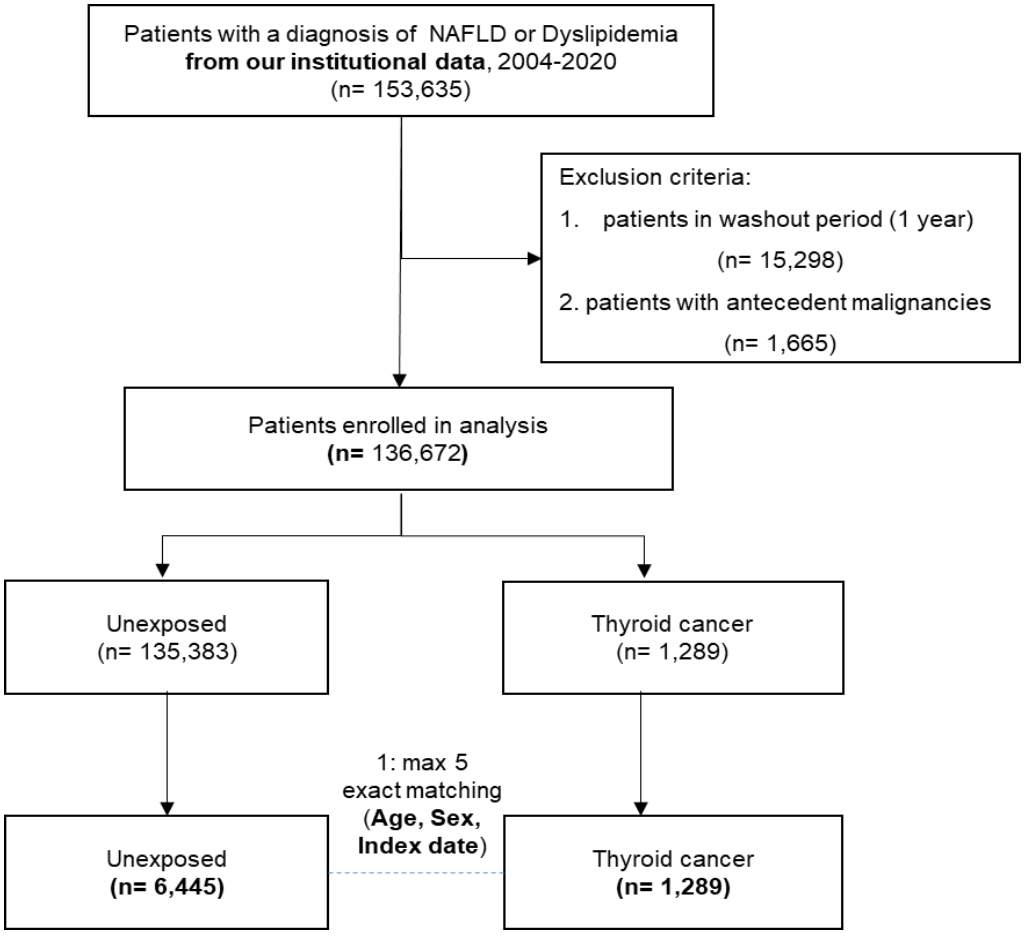


Figure 4. Schematic flow of study design using our institutional cohort.
Abbreviations**:** NAFLD, non-alcoholic fatty liver disease

The effects of thyroid cancer on the incidence of secondary cancers in the entire cohort were analyzed, as well as the effects of the aforementioned clinical characteristics and blood test results.

There are limitations in collecting and analyzing the blood test results of the entire patient group, and to accurately analyze the influence of factors excluding the influence of other variables, a group of patients whose age-sex propensity score was calculated in a 1:5 ratio compared to patients with thyroid cancer was extracted. For the test results or factors analyzed to have an effect on the patient group extracted by matching, we attempted to further analyze the entire patient group (**Figure 4**).

This study was approved by the Institutional Review Board of Severance Medical Center (Seoul, South Korea) and conducted in accordance with the recommendations of the Institutional Review Board (4-2020-0777), which waived the requirement for informed consent because of the retrospective nature of this study.

B. Statistical Analysis

Data are presented as the mean ± standard deviation for normally distributed continuous variables and as proportions for categorical variables. Multivariate Cox regression analysis was performed to determine the hazard ratio (HR) and confidence interval (CI) of the factors affecting the relationship between thyroid cancer and secondary cancer. Conditional logistic regression was performed to estimate the HR and corresponding 95% CI. A p-value of .05 or less was considered statistically significant. All statistical analyses were performed using Statistical Product and Service Solutions, version 25.0, for Windows (SPSS Inc., Chicago, Illinois, USA).

1-2. National Cohort Analysis

A. Study Patients

In addition to analyzing data within the institution, a domestic population-based big data analysis is being conducted. Data from the National Health Insurance System (NHIS), which has accumulated medical information for the entire domestic population, were used. Using data available from 2002 to 2015, patient groups were extracted using a method similar to that used for in-hospital data. To increase the accuracy of the patient group in the representative data, patients with medical records for which the corresponding diagnosis was entered twice or more were extracted. Dyslipidemia was extracted from confirmed patients with ICD 10 code E78.0-78.9 at least twice. For NAFLD, patient groups were extracted using the same diagnostic criteria inclusion and exclusion methods as those extracted from the in-hospital data (**Figure 3**).

A washout period of 1 year was established to exclude the effects of previous diseases, and only adults were included, except for patients under 19 years of age or over 80 years of age. Patients diagnosed with cancer before the diagnosis of NAFLD and dyslipidemia were excluded, and from the thyroid cancer patient group, patients diagnosed with other cancers before the diagnosis of thyroid cancer were excluded.

A nested case-control study was conducted to exclude lead time bias in these patients. Secondary cancers in both groups were identified by extracting the patient group with thyroid cancer and matching age, sex, and index date 1:5 (**Figure 5**). To evaluate the risk of thyroid cancer on cancer occurrence in patients with metabolic diseases and identify factors that affect it, the baseline characteristics and blood test results of the patients were collected. For each result, the value of the test period closest to the diagnosis period of NAFLD and DL was used. For patients with both diseases, values close to the time of

diagnosis of the later diagnosed disease were used.

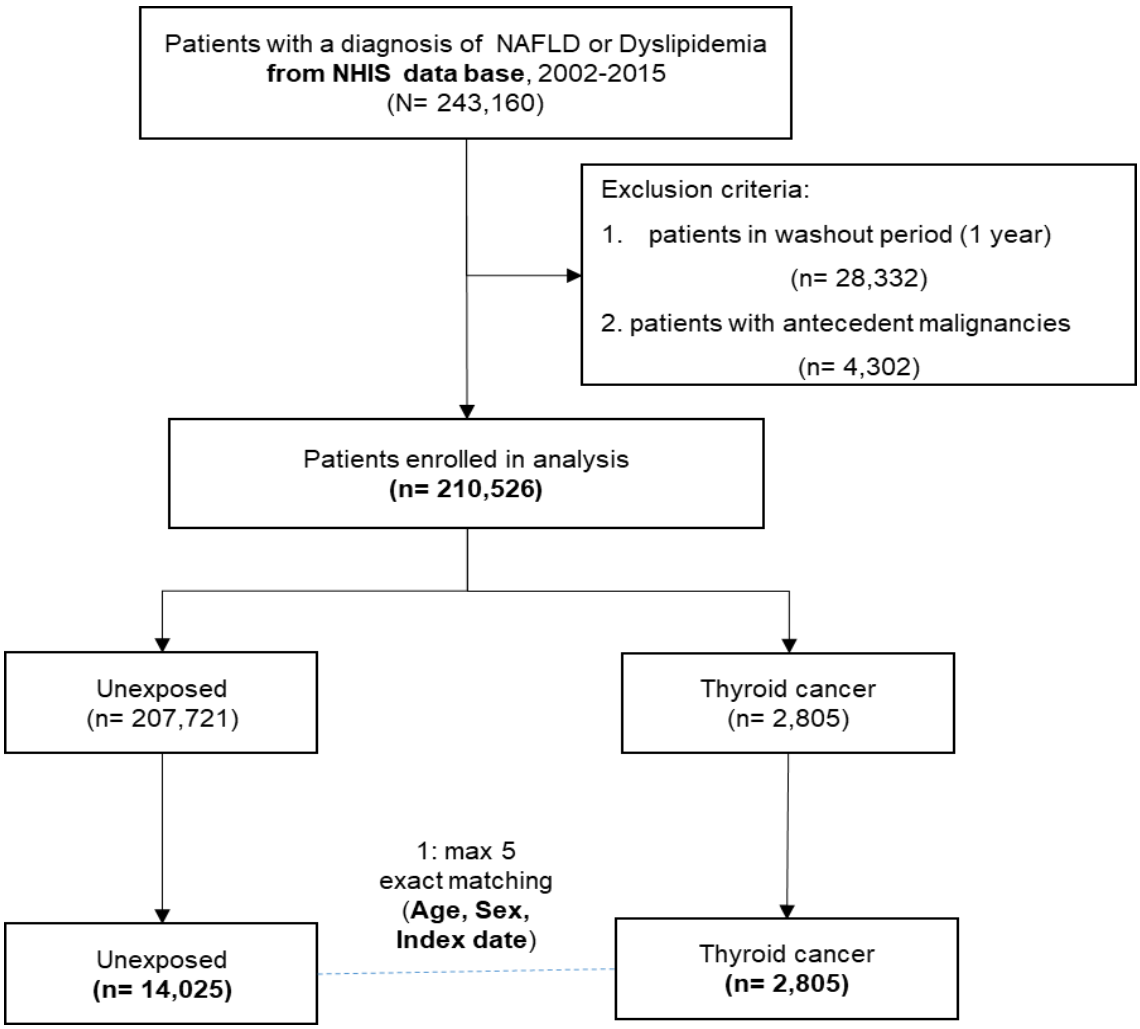


Figure 5. Schematic flow of study design using Korean national cohort.
Abbreviations: NAFLD, non-alcoholic fatty liver disease

B. Statistical Analysis

Data are presented as the mean ± standard deviation for normally distributed continuous variables and as proportions for categorical variables. We investigated factors related to

cancer development in patients with thyroid cancer using a nested case-control analysis to avoid length bias, wherein patients were matched for age, sex, index date of lipid metabolism disorder diagnosis, and follow-up duration. Stratified Cox proportional hazard regression was performed to estimate HRs and corresponding 95% CI. Statistical significance was set at $p < 0.05$. SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

2. Impact of thyroid hormone on the risk of second cancer after thyroidectomy

2-1. Institutional data analysis

A. Study Patients

To determine the external factors affecting the incidence of secondary cancer in patients with thyroid cancer, patients who underwent hemithyroidectomy between 2005 and 2020 were extracted. Patients under 19 years of age and over 80 years of age and patients with a history of other cancers before surgery were excluded. To analyze the effect of hormone intake on the occurrence of secondary cancer without length bias, patients with secondary cancer and patients with age, sex, operation date, and follow-up duration matched 1: max 5 were extracted (**Figure 6**).

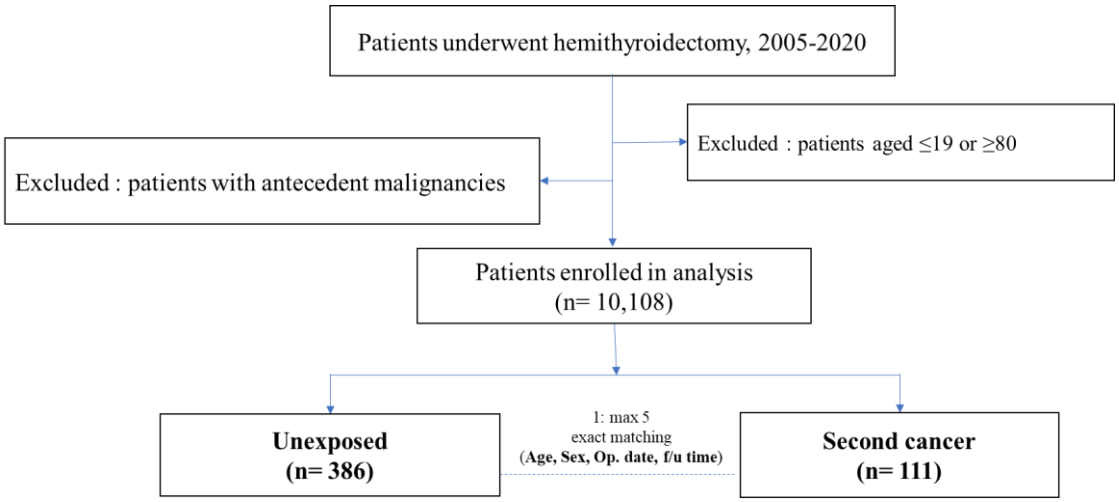


Figure 6. Schematic flow of study design using our institutional cohort.

All patients started taking hormonal drugs on the day of surgery, and all test values were the results of the last test performed. Based on the duration of hormonal medication, patients who took the drug for a short period of less than 5 years and the group of patients who took it for more than 6 years were compared. BMI, glucose, LFT, uric acid, total cholesterol, and TFT test results were analyzed to determine the factors affecting the incidence of secondary cancer in the patient.

B. Statistical Analysis

Data are presented as the mean ± standard deviation for normally distributed continuous variables and as proportions for categorical variables. Multivariate Cox regression analysis was performed to determine the HR and CI of the factors affecting the relationship between the duration of thyroid hormone use and secondary cancer. Conditional logistic regression was performed to estimate the HR and corresponding 95% CI. A p-value of .05 or less was considered statistically significant. All statistical analyses were performed using Statistical

Product and Service Solutions, version 25.0, for Windows (SPSS Inc., Chicago, Illinois, USA).

2-2. National Cohort Analysis

A. Study Patients

When using our institutional data, the patient group was extracted rather small; thus, big data from Korea's HIRA were used to analyze the patient group in the total population. HIRA's database contains medical records of the entire Korean population and reflects the medical use and results of the entire Korean population. From these data, adult patients aged 19 years or older and less than 80 years who underwent thyroid surgery at least once between January 2009 and June 2020 were extracted. Patients who underwent thyroidectomy twice or more, those with a history of other cancers before surgery, and those who died or developed secondary cancer within 2 months after thyroidectomy were excluded. In addition, patients with no thyroid cancer diagnosis code prior to thyroid surgery or with a difference of ≥ 1 year between the initial thyroid cancer diagnosis and surgery were excluded. Among the patients finally extracted, those with secondary cancers were extracted. A patient with secondary cancer was defined as a patient with both a diagnosis code and special calculation code. Patients with secondary cancer and those with age, sex, operation date, and follow-up duration of 1:4 were extracted (**Figure 7**).

B. Statistical Analysis

Data are presented as the mean ± standard deviation for normally distributed continuous variables and as proportions for categorical variables. A nested case-control analysis was

performed to exclude length bias to confirm the correlation between the duration of hormone drug administration, dose, and incidence of secondary cancer. Conditional logistic regression was performed to estimate the odds ratio (OR) and corresponding 95% CI. Statistical significance was set at $p < 0.05$. SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC) was used for all statistical analyses.

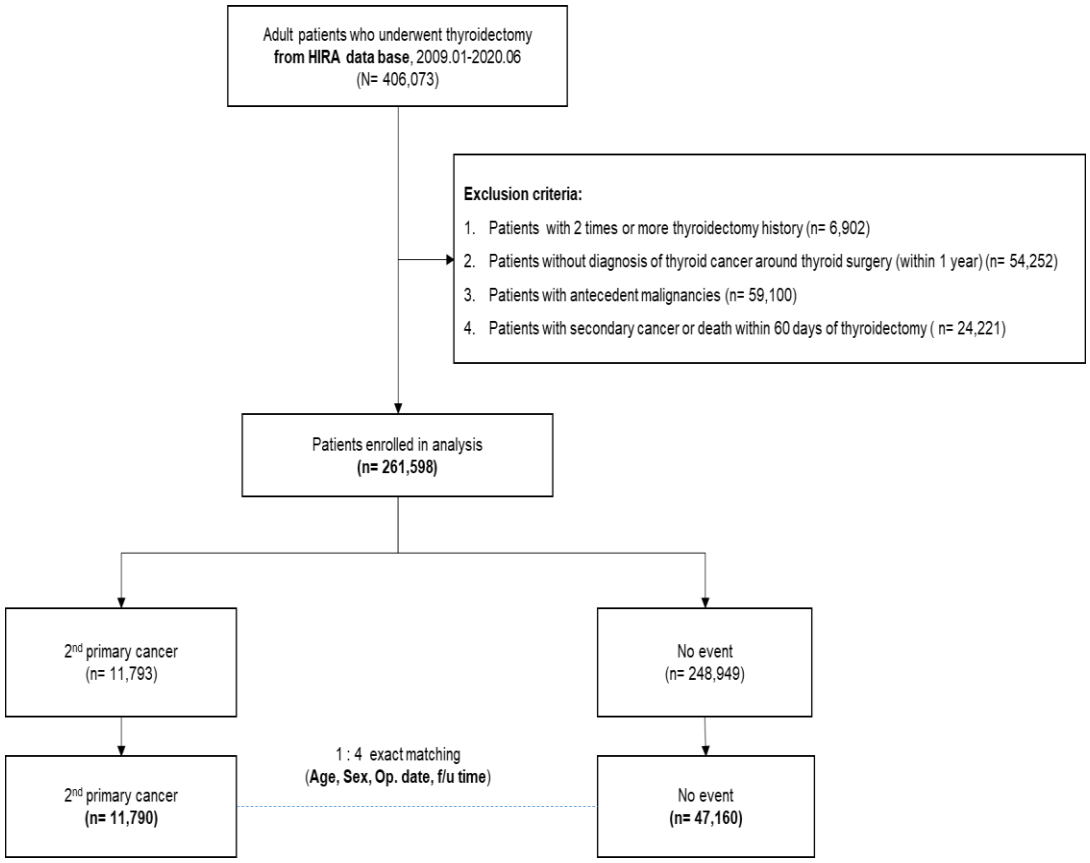


Figure 7. Schematic flow of study design using Korean national cohort.

III. RESULTS

1. Impact of thyroid cancer on the risk of second cancer in dyslipidemia and/or NAFLD patients.

1-1. Institutional data analysis

Based on our inclusion and exclusion criteria, 136,672 patients were finally included. (**Figure 4**). Next, we classified our institutional cohort into three groups: patients with NAFLD or DL, patients with NAFLD only, and patients with only DL. The baseline characteristics of the institutional cohort are summarized in Table 1. Briefly, 15,907 patients with NAFLD and 112,088 patients with DL were selected, and 1289 patients with NAFLD or DL developed thyroid cancer. The mean age of patients with NAFLD or DL was 52.8 ± 12.1, and the average follow-up period was 85.7 ± 59.5 months.

The propensity scores for age, sex, and index date were matched one-to-maximum five with patients without thyroid cancer in the total patient group, and 6445 patient groups were extracted (**Figure 4** and **Table 2**).

Although anthropometric variables such as BMI and waist circumference did not differ between the groups, patients with thyroid cancer showed higher total cholesterol and lower AST, ALT, and gamma-glutamyl transpeptidase (γGT) levels. Next, the effects of each variable measured in the patient group on the occurrence of other primary cancers were analyzed. Univariate analysis revealed that glucose and thyroid cancer increased the HR for cancer risk in the three cohorts (**Table 3**).

Table 1. Baseline characteristics in patients with NAFLD or dyslipidemia according to thyroid cancer in our institutional cohort before matching.

	Total	NAFLD only	DL only	NAFLD & DL
No of patients	136,672	15907	112088	8677
Age (yrs)	52.78 ± 12.07	49.56 ± 14.40	58.67 ± 11.98	52.77 ± 12.07
Sex				
Men	68830 (50.4%)	9764 (61.4%)	54155 (48.3%)	4911 (56.6%)
Women	67842 (49.6%)	6143 (38.6%)	57933 (51.7%)	3766 (43.4%)
Thyroid cancer	1289 (0.94 %)	147 (0.92 %)	1058 (1.34 %)	84 (0.97 %)
F/u periods (months)	85.66 ± 59.50	84.50 ± 67.10	87.39 ± 58.64	65.42 ± 51.34

NAFLD : Nonalcoholic fatty liver disease, DL : Dyslipidemia

Table 2. Baseline characteristics in patients with NAFLD or dyslipidemia according to thyroid cancer in our institutional cohort after matching.

	Thyroid cancer		P-value
	Absence (n=6,445)	Presence (n=1,289)	
Sex			
Male	1935 (30.02 %)	387 (30.02 %)	
Female	4510 (69.98 %)	902 (69.98 %)	
BMI	27.77 ± 6.55	29.28 ± 10.74	0.315
Waist circumference	90.66 ± 18.65	90.08 ± 15.49	0.234
Glucose	128.56 ± 70.42	138.35 ± 65.38	0.316
Total cholesterol	173.82 ± 63.81	210.30 ± 98.17	< .001
Triglyceride	154.21 ± 101.04	171.45 ± 90.99	0.981
HDL	47.91 ± 14.25	45.65 ± 13.45	0.108
LDL	101.43 ± 41.84	99.20 ± 40.27	0.400
AST	37.43 ± 47.31	27.05 ± 14.42	< .001
ALT	43.96 ± 70.68	29.55 ± 25.49	< .001
γGT	65.82 ± 46.20	52.39 ± 44.75	< .001

BMI : body mass index, HDL : high density lipoprotein, LDL : low density lipoprotein, AST : aspartate transaminase, ALT : alanine transaminase, γGT : gamma-glutamyl transpeptidase

For patients with NAFLD only, γGT also increased the HR, but the results were not consistent in the other two cohorts. Total and LDL cholesterol decreased the HR in patients with NAFLD or DL, but this result was not consistent in the other two groups. Multivariate analysis showed that only thyroid cancer had a statistically significant effect on the HR in all three cohorts (Table 4). As our data indicated that the presence of thyroid cancer in patients with NAFLD or DL increased the risk of other primary cancers, we compared the risks of individual cancers according to the presence or absence of thyroid cancer in this cohort (Table 5). The overall risk of cancer was higher in patients with thyroid cancer (127 out of 1,289 cases, 9.85%) than in those without (318 out of 6,445, 4.93%), indicating that the HR was 2.007 (95% CI, 1.597–2.522). In the risk estimation of individual cancer types, HRs increased in lung, bronchus, bone, joints, soft tissue cancers, and leukemia.

Table 3. Cancer risk estimation by univariable stratified cox regression analysis result after matching in our institutional cohort.

	HR (95% CI)		
Variables	**NAFLD or DL**	**NAFLD**	**Dyslipidemia**
BMI	0.99 (0.99-1.00)	0.99 (0.99-1.01)	0.99 (0.99-1.00)
Waist	0.98 (0.96-1.01)	0.98 (0.94-1.01)	1.00 (0.95-1.05)
Glucose	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Total cholesterol	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.99-0.99)
Triglyceride	1.00 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (1.00-1.00)
HDL	0.99 (0.99-1.01)	1.00 (0.99-1.02)	0.99 (0.98-1.00)
LDL	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.99-1.00)
AST	0.99 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.01)
ALT	0.99 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.01)
γGT	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Thyroid cancer (ref.=unexposed)	2.01 (1.60-2.52)	1.87 (1.07-3.25)	1.94 (1.49-2.53)

BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, AST: aspartate transaminase, ALT: alanine transaminase, γGT: gamma-glutamyl transpeptidase

Table 4. Cancer risk estimation by multivariable stratified cox regression analysis result after matching in our institutional cohort.

	HR (95% CI)		
	NAFLD or DL	**NAFLD**	**Dyslipidemia**
Glucose	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Total cholesterol	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.99-1.00)
LDL	1.00 (0.99-1.00)	0.99 (0.99-1.01)	1.00 (0.99-1.00)
γGT	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Thyroid cancer (ref=unexposed)	2.09 (1.55-2.83)	1.75 (1.04-3.66)	1.84 (1.30-2.62)

LDL: low density lipoprotein,, γGT : gamma-glutamyl transpeptidase.

1- 2. National Cohort Analysis

Our institutional cohort showed a small number of cancer occurrences among patients with thyroid cancer. We used population-based big data (NHIS) to validate our findings and investigate the risk estimation of individual cancers. Between 2002 and 2015, 243,160 patients with NAFLD or DL were identified. Among them, 210,526 patients were excluded based on our exclusion criteria. For the analysis of our institutional cohort, 1:5 exact matching was conducted on 2,805 patients with thyroid cancer and 14,025 patients without thyroid cancer, whose age, sex, and index year were matched (total 16,830 patients, **Figure 5**). The baseline characteristics of the patients in this cohort and the presence of thyroid cancer were related to a higher BMI (**Table 6**). However, other chemical variables, such as glucose, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, AST, and γGT, were higher in patients without thyroid cancer.

Table 5. Risk estimation of cancer in patients with NAFLD or dyslipidemia according to thyroid cancer in our institutional cohort after propensity score matching.

	Thyroid cancer		
	Absence (n = 6,445)	Presence (n = 1,289)	
Cancer type	No. of cases (%)	No. of cases (%)	HR (95% CI)
Overall	**318 (4.93)**	**127 (9.85)**	**2.01 (1.60-2.52)**
Lip & Tongue & Mouth	1 (0.31)		
Oropharynx & Nasopharynx	2 (0.63)	1 (0.78)	1.75 (0.15 – 20.07)
Esophagus	2 (0.63)	2 (1.57)	3.15 (0.43 – 22.94)
Stomach	31 (9.75)	9 (7.09)	0.83 (0.39 – 1.74)
Small intestine	1 (0.31)	1 (0.78)	2.61 (0.16 – 41.74)
Colon	30 (9.43)	7 (5.51)	0.60 (0.25 – 1.44)
Anus, anal canal		1 (0.78)	
Liver	42 (13.21)	8 (6.30)	0.52 (0.25 – 1.12)
Pancreas	8 (2.52)	6 (4.72)	2.01 (0.70 – 5.80)
Lung, bronchus	20 (6.29)	24 (18.90)	3.25 (1.80 – 5.89)
Thymus, mediastinum, heart	2 (0.63)	2 (1.57)	2.69 (0.38 – 19.08)
Bone, joints & soft tissue	11 (3.46)	15 (11.81)	3.70 (1.69 – 8.07)
Skin, Melanoma	13 (4.09)	5 (3.94)	1.13 (0.40 – 3.18)
Breast	42 (13.21)	13 (10.24)	0.85 (0.46 – 1.59)
Uterus	17 (0.53)	1 (0.78)	0.17 (0.02 – 1.25)
Ovary	1 (0.31)	1 (0.78)	5.17 (0.32 – 82.74)
Prostate	8 (2.52)		
Kidney	22 (6.92)	7 (5.51)	0.83 (0.35 – 1.95)
Urinary bladder	14 (4.40)	1 (0.78)	0.20 (0.03 – 1.49)
Brain, CNS	9 (2.83)	3 (2.36)	0.93 (0.25 – 3.44)
Lymphoma	12 (3.77)	6 (4.72)	1.31 (0.49 – 3.49)
Multiple myeloma	6 (1.89)		
Leukemia	4 (1.26)	6 (4.72)	4.24 (1.18 – 15.18)
Others	20 (6.29)	8 (6.30)	1.09 (0.48 – 2.48)

Abbreviations: HR, hazard ratio; Total (%) = other primary cancer pts. / total pts. Cancer type (%) = specific type pts. / other primary cancer pts.

Univariate analysis confirmed that the levels of SBP, Hb, AST, and γGT and the occurrence of thyroid cancer increased the risk of secondary cancer in the entire patient group. Regarding LDL levels, the risk of secondary cancer was reduced in the entire patient group. In the NAFLD patient group, SBP, DBP, Hb, and thyroid cancer levels increased the risk of secondary cancer. In the dyslipidemia patient group, Hb and thyroid cancer increased the risk of secondary cancer, total cholesterol, and LDL. Numerical values reduced the risk of secondary cancer (**Table 7**). In the multivariable analysis, only Hb level and thyroid cancer incidence increased the risk of secondary cancer in the NAFLD patient group, DL patient group, and overall patient group (**Table 8**). Overall, other types of primary cancers occurred in 8.31% of patients with thyroid cancer and 6.37% of patients without thyroid cancer. When thyroid cancer occurred, the risk of cancer was increased compared to the case without thyroid cancer in patients with NAFLD or DL (HR, 1.329; 95% CI, 1.153–1.533). In this cohort, thyroid cancer increased the risk of lip, tongue, mouth, lung, bone, joints, soft tissue, skin, brain, and male cancers and lymphoma (**Table 9**).

Table 6. Baseline characteristics in patients with NAFLD or dyslipidemia according to thyroid cancer in Korean national cohort after matching.

	Thyroid cancer		P-value
	Absence (n=14,025)	Presence (n=2,805)	
Sex			
Male	2,630 (18.75)	526 (18.75)	
Female	11,395 (81.25)	2,279 (81.25)	
BMI	24.89 ± 3.13	25.03 ± 3.10	0.027
Waist circumference	82.57 ± 8.23	82.82 ± 8.32	0.122
SBP	135.77 ± 18.12	135.17 ± 17.33	0.125
DBP	85.14 ± 11.20	85.08 ± 10.85	0.840
Glucose	110.29 ± 37.45	108.29 ± 37.04	0.006
Total cholesterol	229.09 ± 40.72	227.27 ± 40.48	0.026
Triglyceride	164.07 ± 101.66	154.42 ± 93.25	< .001
HDL	51.37 ± 20.52	50.26 ± 11.94	< .001
LDL	140.24 ± 43.37	135.83 ± 40.60	< .001
Hb	13.95 ± 1.31	14.00 ± 1.32	0.061
Cr	1.03 ± 1.21	0.98 ± 0.93	0.060
AST	31.39 ± 22.71	30.17 ± 16.58	0.005
ALT	31.75 ± 28.40	31.40 ± 23.14	0.643
γGT	37.44 ± 47.30	33.60 ± 34.07	0.000
Urine protein	1.20 ± 0.64	1.23 ± 0.66	0.092

BMI: body mass index, SBP : systolic blood pressure, DBP : diastolic blood pressure, HDL : high density lipoprotein, LDL : low density lipoprotein, Hb : hemoglobin, Cr : creatinine, AST : aspartate transaminase, ALT : alanine transaminase, γGT : gamma-glutamyl transpeptidase

Table 7. Cancer risk estimation by univariable stratified cox regression analysis result after exact matching in Korean national cohort.

	HR (95% CI)		
	NAFLD or DL	**NAFLD**	**Dyslipidemia**
BMI	0.99 (0.97-1.01)	0.99 (0.97-1.02)	0.99 (0.97-1.01)
Waist circumference	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
SBP	1.00 (1.00-1.01)	1.01 (1.00-1.01)	1.00 (1.00-1.01)
DBP	1.00 (0.99-1.01)	1.01 (1.00-1.02)	1.00 (0.99-1.01)
Glucose	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)
Total cholesterol	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.99-1.00)
Triglyceride	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
HDL	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (0.99-1.00)
LDL	0.99 (0.99-0.99)	0.99 (0.99-1.00)	0.99 (0.99-1.00)
Cr	1.02 (0.97-1.07)	1.01 (0.95-1.08)	1.01 (0.95-1.06)
Hb	1.08 (1.03-1.14)	1.10 (1.04-1.17)	1.07 (1.02-1.13)
AST	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
ALT	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
γGT	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Urine protein	1.00 (0.91-1.10)	0.91 (0.78-1.06)	1.02 (0.92-1.12)
Thyroid cancer (ref=unexposed)	1.33 (1.15-1.53)	1.35 (1.11-1.64)	1.38 (1.18-1.60)

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, Hb: hemoglobin, Cr: creatinine, AST: aspartate transaminase, ALT: alanine transaminase, γGT: gamma-glutamyl transpeptidase

Table 8. Cancer risk estimation by multivariable stratified cox regression analysis result after exact matching in Korean national cohort.

	HR (95% CI)		
	NAFLD or DL	**NAFLD**	**Dyslipidemia**
BMI	0.98 (0.95-1.01)	0.98 (0.94-1.02)	0.98 (0.94-1.01)
Waist circumference	1.01 (0.99-1.02)	1.01 (0.99-1.02)	1.01 (0.99-1.02)
SBP	1.01 (1.00-1.01)	1.01 (1.00-1.02)	1.01 (1.00-1.01)
DBP	0.99 (0.98-1.00)	0.99 (0.98-1.01)	0.99 (0.98-1.00)
Glucose	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)
Total cholesterol	0.99 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (0.99-1.00)
Triglyceride	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
HDL	1.00 (0.99-1.01)	1.00 (1.00-1.01)	1.00 (0.99-1.01)
LDL	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.99-1.00)
Cr	1.01 (0.96-1.06)	1.00 (0.93-1.08)	0.99 (0.94-1.06)
Hb	1.08 (1.02-1.14)	1.09 (1.01-1.17)	1.07 (1.00-1.14)
AST	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
ALT	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.99-1.00)
γGT	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Urine protein	1.01 (0.92-1.12)	0.89 (0.76-1.05)	1.04 (0.94-1.15)
Thyroid cancer (ref=unexposed)	1.30 (1.12-1.52)	1.33 (1.08-1.64)	1.35 (1.15-1.59)

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, Hb: hemoglobin, Cr: creatinine, AST: aspartate transaminase, ALT: alanine transaminase, γGT: gamma-glutamyl transpeptidase

Table 9. Risk estimation of cancer in patients with NAFLD or dyslipidemia according to thyroid cancer in Korean national cohort.

	Thyroid cancer (N=16820)		
	Absence (n = 14,015)	Presence (n = 2,805)	
Cancer type	No. of cases (%)	No. of cases (%)	HR (95% CI)
Overall	**893 (6.37 %)**	**233 (8.31 %)**	**1.30 (1.12-1.52)**
Lip & Tongue & Mouth	3 (0.33 %)	1 (0.42 %)	3.95 (1.04-14.92)
Stomach	123 (13.77 %)	19 (8.15 %)	0.74 (0.441-1.23)
Small intestine	1 (0.11 %)	1 (0.42 %)	5.62 (0.16-202.86)
Colon	81 (9.07 %)	12 (5.15 %)	0.78 (0.41-1.47)
Liver	92 (10.30 %)	11 (4.72 %)	0.65 (0.33-1.26)
Pancreas	63 (7.05 %)	7 (3.00 %)	0.49 (0.21-1.13)
Lung, bronchus	106 (11.87 %)	35 (15.02 %)	1.64 (1.08-2.49)
Thymus, mediastinum, heart	4 (0.44 %)	5 (2.14 %)	4.81 (0.82-28.35)
Bone, joints & soft tissue	18 (2.02 %)	11 (4.72 %)	3.40 (1.61-7.20)
Skin, Melanoma	18 (2.02 %)	8 (3.43 %)	2.60 (1.08-6.23)
Kidney	28 (3.14 %)	8 (3.43 %)	1.09 (0.44-2.66)
Brain, CNS	32 (3.58 %)	21 (9.01 %)	3.15 (1.68-5.94)
Lymphoma	15 (1.68 %)	8 (3.43 %)	2.72 (1.11-6.65)
Multiple myeloma	10 (1.12 %)		
Leukemia	6 (0.66 %)	1 (0.42 %)	0.69 (0.07-6.77)
Male cancer	55 (6.16 %)	22 (9.44 %)	1.94 (1.18-3.18)
Female cancer	164 (18.36 %)	31 (13.30 %)	0.87 (0.57-1.31)
Others	156 (17.47 %)	43 (18.45 %)	1.39 (0.96-2.02)

Abbreviations: HR, hazard ratio; Total (%) = other primary cancer pts. / total pts. Cancer type (%) = specific type pts. / other primary cancer pts.

2. Impact of thyroid hormone on the risk of second cancer after thyroidectomy

2-1. Institutional data analysis

After excluding patients according to the criteria, 10,108 patients who underwent hemithyroidectomy for thyroid cancer were included. Among them, 111 patients with secondary cancer were extracted, and 386 patients whose age, sex, date of operation, and follow-up period were matched by 1:max 5 were extracted. The baseline characteristics

of the two patient groups and blood test values at the time of surgery (glucose, AST, ALT, uric acid, cholesterol, T3, fT4, and TSH) were compared, and only medication duration showed a statistically significant difference (**Table 10**). The effects of each result on the risk of secondary cancer were analyzed. In the univariate analysis, medication duration and fT4 level were found to reduce the risk of secondary cancer (**Table 11**), and in the multivariable analysis, only medication duration was found to reduce the risk of secondary cancer (**Table 12**).

Table 10. Baseline characteristics in patients with thyroidectomy history according to secondary cancer in our institutional cohort after matching.

	Second cancer		P-value
	Second cancer(-) (n = 386)	Second cancer(+) (n = 111)	
Age (yrs)	46.01 ± 11.39	45.97 ± 13.48	
Sex (number of female, %)	449 (82.09 %)	92 (82.14 %)	
BMI (kg / m2)	23.46 ± 3.55	23.54 ± 2.73	0.102
Medication duration (months)	46.50 ± 31.78	36.21 ± 25.87	< .001
Glucose (mg/dL)	96.73 ± 14.28	97.82 ± 11.27	0.726
AST (IU/L)	30.73 ± 45.98	39.38 ± 78.44	0.128
ALT (IU/L)	30.63 ± 52.31	37.13 ± 78.47	0.252
Uric Acid (mg/dL)	5.21 ± 1.32	5.21 ± 1.26	0.054
Cholesterol (mg/dL)	209.56 ± 42.81	213.17 ± 39.48	0.212
T3 (ng/mL)	1.11 ± 0.25	1.08 ± 0.21	0.590
fT4 (ng/dL)	1.52 ± 0.34	1.62 ± 0.25	0.231
TSH (μIU/mL)	2.69 ± 2.83	2.72 ± 5.72	0.482

According to these results, the risk of secondary cancer was analyzed by dividing the medication duration into two groups: ≤ 5 years and > 5 years.

Secondary cancer occurred in 93 of 363 patients in the short-term group and in 18 of 134 patients in the long-term group. In total carcinoma, the risk of secondary cancer was reduced in the group over 5 years compared to the group 5 years or less (HR, 0.155; 95% CI, 0.076–0.314) (**Figure 8** and **Table 13**).

Table 11. Risk estimation of cancer in patients with hemithyroidectomy by Univariable cox regression analysis in our institutional cohort after matching.

	Total patients (n = 497)	
	HR (95% CI)	P-value
Medication duration (months)	0.14 (0.08–0.25)	< .001
BMI (kg / m2)	1.04 (0.99-1.10)	0.118
Glucose (mg/dL)	1.00 (0.99-1.01)	0.571
AST (IU/L)	1.00 (1.00-1.01)	0.078
ALT (IU/L)	1.00 (0.99-1.00)	0.194
Uric Acid (mg/dL)	1.14 (0.98-1.33)	0.086
Cholesterol (mg/dL)	0.99 (0.99-1.00)	0.091
T3 (ng/mL)	0.89 (0.35-2.29)	0.817
fT4 (ng/dL)	0.43 (0.23-0.81)	0.005
TSH (μIU/mL)	1.00 (0.98-1.03)	0.761

BMI : body mass index, AST : aspartate transaminase, ALT : alanine transaminase, TSH : thyroid stimulating hormone

Table 12. Risk estimation of cancer in patients with hemithyroidectomy by Multivariable cox regression analysis in our institutional cohort after matching.

	Total patients (n = 497)	
	HR (95% CI)	P-value
Medication duration (months)	0.14 (0.07-0.31)	< .001
BMI (kg / m2)	1.06 (0.96-1.16)	0.278
Glucose (mg/dL)	0.99 (0.97-1.02)	0.482
AST (IU/L)	1.01 (0.99-1.02)	0.510
ALT (IU/L)	0.98 (0.98-1.01)	0.731
Uric Acid (mg/dL)	1.20 (0.93-1.54)	0.160
Cholesterol (mg/dL)	0.99 (0.99-1.01)	0.821
T3 (ng/mL)	0.57 (0.10-3.28)	0.531
fT4 (ng/dL)	1.19 (0.54-2.61)	0.663
TSH (μIU/mL)	1.03 (0.99-1.07)	0.169

BMI : body mass index, AST : aspartate transaminase, ALT : alanine transaminase, TSH : thyroid stimulating hormone

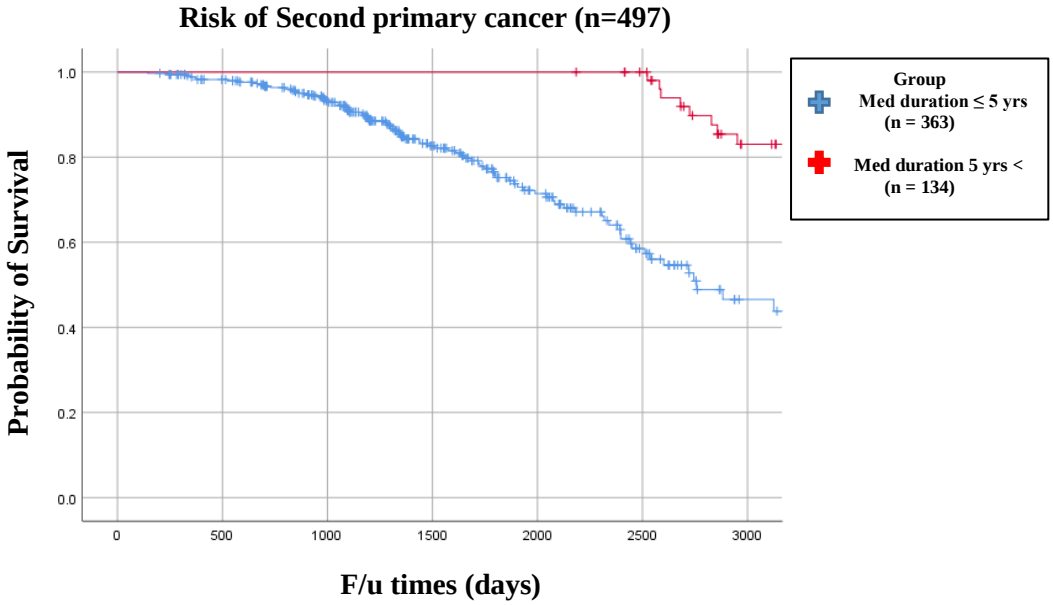


Figure 8. Second primary cancer free survival according to medication duration in our institutional cohort.

Table 13. Risk estimation of cancer in patients with hemithyroidectomy according to medication duration in our institutional cohort after matching.

	Medication ≤ 5 yrs (N = 363)	Medication 5 yrs < (N = 134)	
Cancer type	No. of cases (%)	No. of cases (%)	HR (95% CI)
Overall	**93 (25.62)**	**18 (13.43)**	**0.16 (0.08 – 0.31)**
Stomach	5 (5.38)	1 (5.56)	0.03 (0.00 – 88.33)
Colon	6 (6.45)	0	
Liver	3 (3.23)	0	
Pancreas	1 (1.08)	1 (5.56)	0.04 (0.00 – 76.45)
Lung, bronchus	11 (11.83)	2 (11.11)	0.35 (0.07 – 1.67)
Bone, joints & soft tissue	3 (3.23)	0	
Kidney	9 (9.68)	0	
Brain, CNS	2 (2.15)	2 (11.11)	1.58 (0.19 – 13.39)
Male cancer	5 (5.38)	2 (5.56)	0.15 (0.01 – 1.63)
Female cancer	43 (46.24)	9 (55.55)	0.20 (0.09 – 0.47)
Others	5 (5.38)	1 (5.56)	0.36 (0.04 – 3.216)

HR, hazard ratio; Total (%) = other primary cancer pts. / total pts. Cancer type (%) = specific type pts. / other primary cancer pts.

2-2. National data analysis

As a result of analyzing the institutional data, it was confirmed that the number of extracted patients and patients with secondary cancer was small, making it difficult to accurately analyze the data, and the entire population was analyzed using HIRA big data. A total of 261,598 patients who underwent surgery for thyroid cancer were extracted, excluding patients who met the above-mentioned criteria. Among them, 11,790 patients had secondary cancer, and 47,160 patients matched 1:4 with respect to age, sex, operation date, and follow-up duration were extracted (**Figure 7**). The average age of the two patient groups was 53.1 years, and the proportion of women was 80.49%. The hospital scale, hypertension, diabetes mellitus, and history of infection showed statistically significant differences between the two groups (**Table 14**).

Table 14. Baseline characteristics in patients with thyroidectomy history according to secondary cancer in Korean national cohort after matching.

	Second primary cancer		P-value
	Absence (n=47,160)	Presence (n=11,790)	
Age at surgery, mean ± SD	53.1 ± 11.4	53.1 ± 11.5	
≤ 40	5800 (12.30)	1450 (12.30)	
40 < & ≤ 60	27228 (57.74)	6807 (57.74)	
60 <	14132 (29.97)	3533 (29.97)	
Sex, n (%)			
Male	9212 (19.53)	2303 (19.53)	
Female	37948 (80.47)	9487 (80.47)	
Hospital scale* at surgery, n (%)			
Tertiary	30461 (64.59)	7261 (61.59)	
General	14209 (30.13)	3886 (32.96)	< 0.001
Community	1617 (3.43)	452 (3.83)	
Clinics	873 (1.85)	191 (1.62)	
Obesity, n (%)	84 (0.18)	21 (0.18)	1.000

Hypertension, , n (%)	16484 (34.95)	4450 (37.74)	< 0.001
Diabetes mellitus, n (%)	8671 (18.39)	2370 (20.10)	< 0.001
Dyslipidemia, n (%)	18203 (38.60)	4675 (39.65)	0.037
Infections[+], n (%)	2058 (4.36)	728 (6.17)	< 0.001
Duration of levothyroxine, n (%)			
Mean ± SD (days)	1187.0±916.8	1203.0±926.6	0.091
No	2674 (5.67)	580 (4.92)	0.009
≤ 1 year	7357 (15.60)	1877 (15.92)	
1 < & ≤ 5 years	26049 (55.24)	6493 (55.07)	
5 years <	11080 (23.49)	2840 (24.09)	
Daily average dose of levothyroxine, n (%)			
Mean ± SD	125.8±56.5	129.9±55.9	< 0.001
No	2674 (5.67)	580 (4.92)	< 0.001
≤ 50 μg	1626 (3.45)	450 (3.82)	
50 μg < & ≤ 100 μg	8489 (18.00)	1898 (16.10)	
100 μg <	34371 (72.88)	8862 (75.17)	
RAI cumulative dose, n (%)			
≤ 30mCi	35610 (75.51)	8560 (72.60)	< 0.001
30mCi < & ≤ 100mCi	5717 (12.12)	1425 (12.09)	
100mCi < & ≤ 150mCi	4261 (9.04)	1176 (9.97)	
150mCi <	1572 (3.33)	629 (5.34)	

* Classified according to the size of the bed, available departments, and location
[+] Epstein-barr virus(EBV), hepatitis B & C virus (HBV & HCV), human inmmunodeficiency virus (HIV), human papilloma virus(HPV), human T-cell leukemia/lymphoma virus type-1(HTLV-1), helicobacter pylori (H.pylori)

Patients were divided into three groups according to the duration of THR: less than 1 year (short-term), 1–5 years (mid-term), and > 5 years (long-term). There was no difference in the mean THR duration between the two groups, but the rate of second primary cancer was higher in patients in the short-term or long-term (>5 years) replacement group (P = 0.009, **Table 14**). In addition, patients were classified into three groups according to the daily average thyroid hormone dose: ≤ 50 μg (low dose), 50–100 μg (intermediate dose), and >

100 μg (high dose). The mean daily average dose was higher in patients with second primary cancer. However, secondary primary cancers occurred more frequently in patients in the low- and high-dose groups. As is well known, the cumulative RAI dose was higher in the group with second primary cancer (P < 0.001, **Table 14**).

Since the association of various factors with the risk of second primary cancer was confirmed, the relationship between the THR duration and the risk of second primary cancer was analyzed by adjusting for these factors. Compared to the group without replacement, all three groups showed an increased OR of second primary cancer **(Table 15).**

Table 15. Multivariable analysis for the association between duration of THR and secondary cancer risk

Duration	2nd primary cancer		Unadjusted OR (95% CI, P)	Adjusted OR (95% CI, P)
	Absence (n=47,160), no.(%)	Presence (n=11,790), no.(%)		
No	2674 (5.67)	580 (4.92)	Ref.	Ref.
≤ 1 years	7357 (15.60)	1877 (15.92)	1.20 (1.06-1.34, p = .003)	1.19 (1.06-1.34, p = .003)
1 < & ≤ 5 years	26049 (55.24)	6493 (55.07)	1.16 (1.05-1.28, p = .005)	1.15 (1.04-1.28, p = .006)
5 years <	11080 (23.49)	2840 (24.09)	1.27 (1.12-1.43, p <.001)	1.25 (1.10-1.41, p <.001)

Adjusted for obesity, hypertension, diabetes mellitus, dyslipidemia, infections.

However, a time-dependent increase in OR was not observed. We also performed another multivariate analysis adjusted for various factors to reveal the association between the daily dose of levothyroxine and second primary cancer. Interestingly, based on the no-replacement group, low and high doses showed significantly increased OR (**Table 16**). Interestingly, the low-dose group showed the highest unadjusted and adjusted ORs. As expected, the cumulative dose of RAI was also a significant risk factor for secondary

primary cancer in patients with papillary thyroid carcinoma (**Table 17**).

Table 16. Multivariable analysis for the association between dose of thyroid hormone and the risk of second primary cancer.

Daily dosage (avg. μg)	2nd cancer		Unadjusted OR (95% CI, P)	Adjusted OR (95% CI, P)
	Absence (n=47,160), no.(%)	Presence (n=11,790), no.(%)		
No	2674 (5.67)	580 (4.92)	Ref.	Ref.
≤ 50	1626 (3.45)	450 (3.82)	1.27 (1.11-1.47, p = <.001)	1.29 (1.12-1.48, p = .001)
50 < & ≤ 100	8489 (18.00)	1898 (16.10)	1.05 (0.95-1.17, p = .344)	1.07 (0.96-1.18, p = .233)
100 〈	34371 (72.88)	8862 (75.17)	1.26 (1.14-1.40, p = <.001)	1.24 (1.12-1.37, p = <.001)

Avg.; daily average, Adjusted for obesity, hypertension, diabetes mellitus, dyslipidemia, infections. cumulated dosage of radioactive iodine.

Table 17. Multivariable analysis for the association between cumulative dose of RAI and the risk of second primary cancer.

Cumulated dose of RAIT	2nd cancer		Unadjusted OR (95% CI, P)	Adjusted OR (95% CI, P)
	Absence (n=47,160), no.(%)	Presence (n=11,790), no.(%)		
≤ 30mCi	35610 (75.51)	8560 (72.60)	Ref.	Ref.
30mCi < & ≤100mCi	5717 (12.12)	1425 (12.09)	1.05 (0.98-1.12, p = .151)	1.03 (0.96-1.10, p = .385)
100mCi < & ≤150mCi	4261 (9.04)	1176 (9.97)	1.17 (1.09-1.26, p <.001)	1.14 (1.06-1.22, p <.001)
150mCi <	1572 (3.33)	629 (5.34)	1.70 (1.54-1.87, p <.001)	1.66 (1.50-1.83, p <.001)

Adjusted for obesity, hypertension, diabetes mellitus, dyslipidemia, infections. Abbreviations: RAI, Radioactive iodine; RAIT, Radioactive iodine therapy

Next, the OR of the THR duration for the occurrence of individual second primary cancers was analyzed. Most crude ORs increased with short- or long-term administration, but statistical significance was only observed in a small number of secondary carcinomas such as liver, lung, and brain cancers. Exceptionally, skin cancer and melanoma showed decreased ORs with THR (**Table 18**).

Table 18. The impact of the duration of thyroid hormone replacement on the risk of individual second primary cancer.

Duration	Crude OR (95% CI)						
	Lip & Tongue & Mouth	Stomach	Small intestine	Colon	Liver	Pancreas	Lung, bronchus
Second primary cases	44	923	45	704	795	515	1622
No	Reference						
≤ 1 years	2.25 (0.23-21.94)	1.31 (0.84-2.05)	1.16 (0.10-12.82)	1.16 (0.69-1.95)	**1.69 (1.12-2.55)**	1.34 (0.80-2.25)	**1.47 (1.07-2.02)**
1 < & ≤ 5 years	2.20 (0.21-22.73)	1.28 (0.87-1.88)	1.82 (0.31-10.53)	1.43 (0.92-2.25)	1.16 (0.80-1.70)	1.05 (0.67-1.66)	**1.40 (1.05-1.87)**
5 years 〈	4.04 (0.34-48.26)	1.36 (0.87-2.12)	3.47 (0.36-33.30)	1.34 (0.78-2.30)	1.02 (0.63-1.64)	1.47 (0.81-2.68)	1.27 (0.90-1.80)

Duration	Crude OR (95% CI)						
	Thymus, mediastinum, heart	Bone, joints & soft tissue	Skin, Melanoma	Breast	Uterus	Ovary	Prostate
Second primary cases	221	371	274	2455	229	264	332
No	Reference						
≤ 1 years	1.25 (0.56-2.77)	1.03 (0.54-1.96)	**0.38 (0.18-0.82)**	0.81 (0.63-1.04)	1.27 (0.57-2.84)	1.10 (0.51-2.35)	1.64 (0.84-3.20)
1 < & ≤ 5 years	1.99 (0.96-4.12)	1.07 (0.60-1.89)	**0.38 (0.22-0.69)**	0.87 (0.71-1.07)	1.27 (0.66-2.47)	1.29 (0.67-2.51)	1.24 (0.69-2.20)
5 years 〈	2.13 (0.80-5.70)	1.12 (0.54-2.33)	**0.37 (0.19-0.73)**	1.05 (0.82-1.34)	0.97 (0.42-2.20)	1.17 (0.52-2.67)	1.45 (0.75-2.80)

Duration	Crude OR (95% CI)					
	Kidney	Brain, CNS	Lymphoma	Multiple myeloma	Leukemia	Others
Second primary cases	373	785	215	74	168	1723
No	Reference					
≤ 1 years	1.32 (0.68-2.56)	**1.68 (1.04-2.73)**	0.99 (0.42-2.36)	1.26 (0.27-5.88)	1.14 (0.32-4.06)	1.30 (0.96-1.76)
1 < & ≤ 5 years	1.47 (0.84-2.59)	1.35 (0.87-2.09)	1.24 (0.60-2.56)	1.18 (0.31-4.47)	1.64 (0.59-4.56)	1.03 (0.79-1.34)
5 years 〈	1.56 (0.79-3.08)	1.29 (0.73-2.30)	1.12 (0.46-2.72)	2.02 (0.46-8.86)	2.68 (0.86-8.34)	1.31 (0.93-1.84)

IV. DISCUSSION

By comparing the risk of secondary cancer according to the presence or absence of thyroid cancer in patients with lipid metabolic disease, we found that the risk of secondary cancer increased when thyroid cancer occurred. It was confirmed that when thyroid cancer occurred, the incidence of secondary cancer increased by approximately two times compared to the case in which thyroid cancer did not occur.

Many previous studies have reported an increase in the incidence of cancer in patients with hyperlipidemia. Uzunlulu et al. reported that low HDL cholesterol levels were associated with an increased incidence of lung cancer and LDL cholesterol levels were associated with the development of hematologic malignancy.(32) Kim et al. reported that high TG and low HDL levels are associated with an increase in the incidence of prostate cancer.(33) Kitahara et al. reported that high total cholesterol levels could affect the increase in breast, colon, and prostate cancers.(34)

Many studies have been conducted from various perspectives to explain the relationship between high lipid profiles and cancer development.(35-37) For example, sex hormones can stimulate lipogenic gene expression and promote cancer cell growth.(38) Moreover, in nutritional studies, high-fat diets have been shown to promote tumor growth and metastasis.(35, 39) In addition, lipid-lowering drugs such as statins have been shown to reduce the formation and proliferation of metastatic cancer cell.(40, 41) Several mechanisms have also been proposed to explain the association between cholesterol and carcinogenesis. Lipids are key cell membrane components that are essential for various biological functions, including cell growth and division, which are necessary for the maintenance of cell integrity. Cholesterol is a precursor steroid hormone that can lead to increased tumor angiogenesis, increased tumor cell proliferation, and decreased tumor

apoptosis.(42) Another possible mechanism is that cholesterol also plays an important role in cell membranes, which can affect various signaling pathways, and may be associated with proteins such as the cell survival kinase Akt.(43, 44) These mechanisms or associations are ultimately caused by high lipid status, and among diagnosed patients, the more abnormal the lipid or cholesterol level, the higher the risk of secondary cancer.

In the patients of this study, waist circumference, BMI, lipid profile, and LFT at the time of NAFLD or dyslipidemia diagnosis were checked, and the effect of each factor on the incidence of secondary cancer was also analyzed. However, no significant influencing factors were identified.

Metabolic remodeling, a hallmark of cancer, has been firmly established.(45) Functionally lipid- and tumor-initiating cholesterol-related pathways have also been widely recognized and more frequently described during a series of remodeling processes.(46-48) Cholesterol and excess fat from cancer cells are stored in lipid droplets (LD), and high LD and cholesterol ester content in tumor cells are considered hallmarks of cancer aggression.(49-54) In view of these processes, among patients with lipid metabolic disease, those with thyroid cancer will have more active fat metabolism or a higher chance of metabolic remodeling. If so, it will be possible to establish a hypothesis that fat metabolism is activated through metabolic remodeling, resulting in a large number of tumor cells accumulating a lot of fat or cholesterol esters, thereby increasing the risk of secondary cancer. However, no significant difference was observed in lipid profiles or other tests in patients with lipid metabolic diseases who developed thyroid cancer.

In addition, in the case of secondary cancer occurring in a group of patients with thyroid cancer, which is well known as obesity-related cancer, such an association would be sufficient if there are more obesity-related cancers. In the author’s previous study, colon,

liver, pancreas, prostate, and kidney cancers, which are well-known obesity-related cancers among the secondary carcinomas, increased the risk of dyslipidemia in patients with thyroid cancer.(21) However, there was no noticeable increase in the incidence of these carcinomas in this study. This may be due to the relatively short follow-up period and small number of subjects. The most common carcinomas in patients with thyroid cancer are bone, joint, and soft tissue, which is thought to be because lymph nodes are included in these types of carcinomas.

Previous studies have concluded that there is an increased incidence of secondary cancer in patients with thyroid cancer. Meta-analysis of 70,844 patients with thyroid cancer showed a 20% increase in second cancer, which may be related to genetic predisposition or disease-specific treatments.(16) In genetic terms, thyroid cancer is reported to have relatively high heritability.(55) In addition, single nucleotide polymorphisms (SNPs) have been reported to be involved in cancer development. Certain SNPs, such as the MDM2-reference SNP 2279744 (rs2279744), significantly increase the risk of thyroid cancer, hepatocellular cancer, and leukemia.(56-58) The checkpoint kinase 2 (CHEK2) gene affects the DNA damage response, and I157T mutations (isoleucine substitution for threonine at position 157) have been identified in thyroid, breast, kidney, colon, and prostate cancers.(59) A patient who develops thyroid cancer with many of these genetic factors is likely to have a relatively genetic environment to develop other cancers as well. Likewise, the incidence of carcinoma to support the above hypothesis is insufficient, and large-scale population-based studies may be needed to further identify the increase in lipid metabolism, genetic environment-related carcinomas, or related factors. As such, additional large-scale studies are needed to determine whether the cause of the increase in secondary cancer incidence is the high-lipid state or whether the cancer itself is genetic or

molecular.

To determine the effect of external factors on the occurrence of secondary cancer in patients with thyroid cancer, we analyzed thyroid hormone intake after thyroidectomy. To date, no conclusions have been drawn regarding the effect of thyroid hormones on the incidence of cancer. According to institutional data, in patients who underwent hemithyroidectomy, the risk of secondary cancer was reduced in the long-term group when the two groups were compared according to the duration of hormonal drug administration based on 5 years. As only patients who underwent surgery for thyroid cancer were included in the analysis, this result could be explained by the hyperthyroidism induced by taking thyroid hormones to reduce the risk of recurrence after surgery. However, in the case of institutional data, the reliability of the analysis results may be lower because the total number of patients and the number of patients with secondary cancer were small.

As a result of population-based big data analysis that included a sufficient number of patients, the risk of secondary cancer was increased in patients who took thyroid hormones for a longer time and in high doses than in those who did not take thyroid hormones after thyroidectomy.

Analysis of the risk of secondary cancer according to hormone intake after thyroid surgery revealed a reason for the difference between institutional data and population-based big data. This may be due to the difference between the number of patients included in the analysis and the number of secondary cancers that occurred. Although 10,000 patients were extracted and analyzed from the institutional data, differences may have occurred from the analysis of the entire population. In addition, since our institution tends to more actively monitor recurrence and metastasis and conduct tests after surgery for thyroid cancer, it is thought that the patient group who took the drug for a short period showed a higher risk of

secondary cancer. When targeting the entire population, there is a difference in active surveillance in the postoperative management of thyroid cancer depending on the institution, and since these data include various institutions, it can be thought that the results were different from the analysis of our institutional data.

Several studies have reported that thyroid hormones affect cancer cell proliferation.(60, 61) A European population-based study reported that THR treatment increases the risk of all cancers, especially in women.(29) Several other studies have also reported that thyroid hormones are associated with the development of breast and lung cancers.(60, 62-64) Although the results of this study presented increased risks only in a small number of individual second primary cancers such as liver, lung, and brain cancers, when considered in combination with the results of other studies mentioned above, it can be confirmed that the risk of secondary cancer increases in the group of patients who took thyroid hormone compared to those who did not.

However, other studies have reported that thyroid dysfunction can increase cancer incidence and reduce cancer risk through THR.(28, 65) Through these other studies and the results of this study, there is a meaning that can serve as a touchstone for studies on the occurrence of second primary cancer and the appropriate discontinuation period, in addition to the effects of supplemental factors of levothyroxine in patients with thyroid cancer. In some carcinomas, the risk of occurrence was higher in the group using levothyroxine for a certain period than in the group without levothyroxine; in certain carcinomas, the risk was decreased regardless of the duration of use compared to the group without levothyroxine.

In population-based analysis, there are limitations in that the scope of surgery performed for thyroid cancer is not clear and the thyroid function status of each patient is not included. Future multicenter prospective studies are needed to establish an appropriate period of

thyroid hormone administration and evaluate the thyroid function status of patients.

V. CONCLUSION

In patients with NAFLD and dyslipidemia with a high prevalence and increased incidence, thyroid cancer increases the risk of secondary cancer. In patients with both diseases simultaneously, the effect on the incidence of secondary cancer was not significant. Long-term high-dose use of hormonal drugs in patients undergoing surgery for thyroid cancer slightly increases the risk of secondary cancer. The risk of recurrence of thyroid cancer, risk of secondary cancer, and symptoms according to the patient's thyroid function should be comprehensively reviewed and applied to the use of hormones.

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ABSTRACT(IN KOREAN)

지질대사질환 환자의 갑상선암에 따른 이차암 위험도 인구기반 빅데이터 분석 및 기관별 데이터 검증

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비알콜성 지방간염과 이상지질혈증과 같은 지방대사질환은 생활습관의 변화에 따라 지속적으로 증가하고 있으며, 이러한 질환 환자에서 암종의 발생이 증가한다는 것에 대한 다양한 연구들이 존재한다. 갑상선암은 흔하게 발생하고 예후가 상대적으로 좋기 때문에, 많은 수의 생존자가 존재한다. 지방대사질환과 갑상선암은 고지질상태와 비만과의 연관성이 확인된 질환이다. 저자의 이전연구에서 갑상선암 환자에서 이상지질혈증은 이차암 발생위험을 증가시키는 것을 분석하였고, 해당 암종들은 비만과 관련된 이차암종으로 확인되었다. 본 연구에서는 기관의 데이터와 건강보험공단의 인구기반 빅데이터의 분석을 통하여 지방대사질환 환자에서 갑상선암이 이차암 발생에 미치는 영향과 그에 영향을 미치는 요소들에 대한 분석하고자 한다.

기관 데이터와 인구기반 빅데이터에서 지방대사질환 진단을 통하여 환자를 추출하였고, 갑상선암의 유무에 따라 이차암 발생 위험을 분석하였다. 기관데이터 분석에서 갑상선암이 발생한 환자군에서 그렇지 않은 환자군에 비하여 이차암 발생위험이 증가하였다. 흥미롭게도 비알콜성 지방간염, 이상지질혈증이 동시에 있는 환자에서는 이차암 발생위험이 증가하지 않았다.

이상지질혈증이나 비알콜성지방간염과 같은 지방대사질환 환자에서 갑상선암은 이차암 발생위험을 증가시킨다. 두 질환이 동시에 있는

환자에서는 이차암 발생위험에 영향을 미치지 않는다. 인구기반 빅데이터에서의 단변량, 다변량 분석 결과, 갑상선암의 Hazard ratio는 각각 1.329 (95% CI, 1.153-1.533) , 1.301 (95% CI, 1.115-1.517) 로 확인되었다. 개별 암종에 대한 분석결과, 입술, 혀, 구강암, 폐암, 뼈, 관절 및 연부조직암, 피부암, 뇌암, 그리고 남성암, 림프종이 갑상선암 발생에 따라 발생위험이 증가하였다.

갑상선암 환자에서 이차암 발생에 영향을 미칠 수 있는 외부요인이 되는 갑상선 호르몬 복용에 따른 기관데이터 분석 결과 장기간 사용 환자 군에서 오히려 이차암 발생 위험이 감소하였다. 인구기반 빅데이터 분석결과, 갑상선 암으로 수술을 시행받은 총 261,598명의 환자가 추출되었다. 그 중 11,790 명의 이차암 발생환자와 그렇지 않은 47,160명의 매칭된 환자가 추출되었다. 갑상선 호르몬 일평균 용량 기준 50ug 이하, 그리고 100ug 초과 그룹 환자에서 이차암 발생위험이 증가하였다. 호르몬 복용기간 기준 1년이하, 그리고 5년 초과 그룹에서 이차암 발생위험이 증가하였다.

지방대사질환 환자에서 갑상선암은 이차암발생을 예측가능한 인자가 될 수 있으며, 갑상선암 수술을 시행받은 환자에서 부족하거나 과도한 갑상선 호르몬 보충요법은 이차암 발생 증가와 관련될 수 있다.

핵심되는 말 : 비알콜성지방간염, 이상지질혈증, 갑상선암, 이차암, 비만, 갑상선 호르몬 보충요법, 인구기반코호트