Familial thyroid cancer: a dual perspective from institutional outcomes and a population-based cohort study

Lee, Cho Rok

Department of Medicine

Graduate School

Yonsei University

Familial thyroid cancer: a dual perspective from institutional outcomes and a population-based cohort study

Advisor Nam, Kee-Hyun

A Dissertation Submitted
to the Department of Medicine
and the Committee on Graduate School
of Yonsei University in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy in Medical Science

Lee, Cho Rok

June 2025

Familial thyroid cancer: a dual perspective from institutional outcomes and a population-based cohort study

This Certifies that the Dissertation of Lee, Cho Rok is Approved

Committee Chair	**Choi, Jong Rak**
Committee Member	**Nam, Kee-Hyun**
Committee Member	**Yoon, Jong Ho**
Committee Member	**Jo, Yong Suk**
Committee Member	**Seo, Jun-Young**

Department of Medicine
Graduate School
Yonsei University
June 2025

ACKNLEDGEMENTS

I would like to express my deepest gratitude to my advisor, Professor Kee-Hyun Nam, for his invaluable guidance, unwavering support, and continuous encouragement throughout the completion of this doctoral dissertation.

I am also sincerely thankful to Professor Jong Rak Choi, Jong Ho Yoon, Young Suk Jo, and Jun-Young Seo for taking time out of their busy schedules to serve on my dissertation committee and for their insightful feedback and valuable advice.

I would like to extend my heartfelt appreciation and respect to Professor Woong Youn Chung, Jong Ju Jeong, Sang-Wook Kang, and Jandee Lee, whose mentorship has been instrumental in guiding me on the right path as a surgeon and specialist in endocrine surgery.

Lastly, I sincerely thank my family for their unwavering love and faith. My parents' warm affection and steadfast support have been the most significant source of strength throughout this journey.

I am truly grateful to everyone who contributed to the successful completion of this study.

July, 2025
Lee, Cho Rok

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Familial thyroid cancer: a dual perspective from institutional outcomes and a population-based cohort study

Introduction: In recent years, the incidence of thyroid cancer has increased rapidly worldwide. Many studies have investigated the relationship between thyroid cancer and familial aggregation of thyroid cancer. This study aimed to investigate the prevalence, clinical characteristics, and long-term outcomes of familial non-medullary thyroid cancer (FNMTC) in a large institutional cohort of nonmedullary thyroid cancer (NMTC) patients. Additionally, using the Korean Genome and Epidemiology Study (KoGES) and institutional cohort data, we analyzed sociodemographic and clinical factors related to familial thyroid cancer to identify potential contributors to familial risk.

Methods: In this study, 42,743 patients were classified as having sporadic NMTC (SNMTC) and 3,829 (8.2%) as having FNMTC based on family history. Clinicopathological characteristics at diagnosis and surgery were compared, and prognostic outcomes were analyzed in patients with follow-up data. Using the KoGES data from 172,479 individuals, 941 patients with thyroid cancer were identified. Sociodemographic and lifestyle factors were compared between the thyroid cancer group and cancer-free controls, and within the thyroid cancer group, further analysis was conducted based on family history. Among the institutional data from 11,143 thyroid cancer patients, 885 (7.9%) and 10.258 (92.1%), were classified as F-TC and S-TC, respectively, based on family history. Sociodemographic factors were compared between the two groups.

Results: Among 46,572 patients with NMTC, 8.2% (n = 3,829) had FNMTC. FNMTC was found to be more prevalent in women and tends to occur at a younger age than SNMTC. Over time, the proportion of FNMTC among all thyroid cancer cases gradually increased, with the highest prevalence observed in the 35–59 age group.

Patients with FNMTC exhibited a higher frequency of bilateral tumors (23.5% vs. 17.5%, $p < 0.001$), multifocality (39.0% vs. 30.5%, $p < 0.001$), and central lymph node metastasis (41.5% vs. 38.8%, $p = 0.001$) than SNMTC. Despite having smaller tumors on average (0.9 ± 0.7 cm vs. 1.0 ± 0.9 cm, $p < 0.001$), patients with FNMTC showed more aggressive clinicopathologic features. Recurrence rates were comparable (1.9% vs. 2.3%, $p = 0.1$), but overall survival was significantly higher in the

FNMTC group (99.6% vs. 98.6%, $p < 0.001$). Multivariate Cox regression analysis identified family history, extracapsular extension, lymph node metastasis, and tumor size as independent predictors of recurrence. Risk-stratified survival analyses demonstrated that family history significantly affected recurrence-free survival in the intermediate-to-high-risk groups (HR = 1.65, $p < 0.001$) but not in low-risk patients. In the national cohort analysis, a history of thyroid disease and current alcohol consumption were more significantly associated with thyroid cancer than in individuals without a history of cancer. Fatty liver disease and alcohol consumption have been identified as factors associated with familial thyroid cancer. In the institutional cohort analysis, hypertension was a negative predictor of familial thyroid cancer (OR = 0.667, $p = 0.040$).

Conclusions: FNMTC exhibits aggressive clinical characteristics and is a significant risk factor for disease recurrence. Factors associated with the occurrence of thyroid cancer and family history of thyroid cancer, as identified through large-scale cohort and institutional analyses, did not show consistent results. Due to the complex interplay of genetic predisposition, metabolic factors, and environmental influences, it is difficult to identify a single risk factor for familial thyroid cancer. In the future, personalized prognostic assessments and management strategies will be necessary for patients with a family history of thyroid cancer.

Keywords: nonmedullary thyroid cancer, family history, recurrence, thyroid cancer, prevalence, prognosis

1. INTRODUCTION

Over the past 20 years, the incidence of thyroid cancer has increased in different populations worldwide (Figure 1) (1, 2). This trend is particularly pronounced in South Korea. Although thyroid cancer can occur in individuals of any sex, women account for approximately 75% of all patients with thyroid cancer (3). Thyroid cancer can occur across a range of ages; however, the median age at diagnosis is in the early 50s. Thyroid cancer is the most common malignancy in adolescents and adults aged 16–33 years (4).

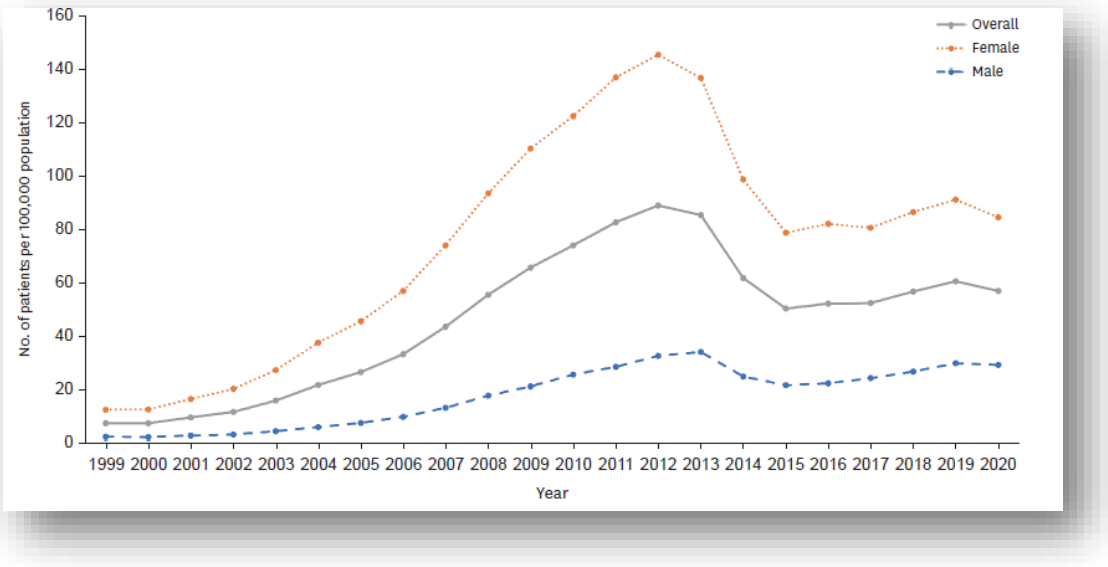


Figure 1. Trends in the crude rate of thyroid cancer in Korean men and women from 1999 to 2020. Adopted from Changed in the Trends of Thyroid Cancer Epidemiology According to South Korean Nationwide Database, 1999-2020 J Endocr Surg. 2024 Jun:24(2):31-38

According to the 2022 National Cancer Registry Statistics, thyroid cancer is the most commonly diagnosed cancer in South Korea regardless of sex. The most frequently occurring cancers in both sexes combined were thyroid cancer (12.0%), colorectal cancer (11.8%), lung cancer (11.5%), breast cancer (10.5%), stomach cancer (10.5%), prostate cancer (7.4%), and liver cancer (5.3%).

When analyzed separately according to sex, the most common cancers in men were lung cancer (14.7%), prostate cancer (14.1%), colorectal cancer (13.3%), stomach cancer (13.3%), liver cancer

(7.4%), and thyroid cancer (5.8%). Among women, breast cancer was the most prevalent (21.8%), followed by thyroid cancer (18.8%), colorectal cancer (10.0%), lung cancer (7.9%), stomach cancer (7.4%), and pancreatic cancer (3.5%). From 1999 to 2021, the age-standardized incidence rates showed that thyroid cancer exhibited the highest annual percentage change. Additionally, as of 2022, thyroid cancer had the highest prevalence among significant cancer types, accounting for 21.4%. This is attributable to its high incidence and exceptionally high survival rate (5, 6). Therefore, appropriate management (surgery and follow-up) of thyroid cancer is essential.

Thyroid cancer can be broadly classified into three categories based on histological characteristics. (1) Differentiated thyroid carcinoma (DTC), which includes papillary, follicular, and oncocytic carcinomas. (2) Medullary thyroid carcinoma (MTC) originates from the parafollicular C cells. (3) Anaplastic carcinoma, which arises from differentiated thyroid cancer and has an extremely high mortality rate (7).

The incidence of thyroid cancer subtypes varies across countries. However, in South Korea, differentiated thyroid carcinoma accounts for more than 95% of all cases. Many studies have reported that the worldwide increase in the incidence of thyroid cancer is due to the increased diagnosis of small low-risk papillary thyroid carcinomas, which coincides with the widespread use of high-resolution ultrasound. (8, 9) The cause of thyroid cancer remains unclear, it is accepted that genetic and environmental factors affect the risk. Previous studies have reported that various risk factors for Papillary Thyroid Carcinoma(PTC), such as radiation exposure, female sex, benign thyroid disease, high iodine intake, obesity, and a family history of PTC, are responsible for the increased prevalence of thyroid cancer (10-13).

Recent clinical practice guidelines for thyroid cancer have been revised in a more de-escalated direction in response to concerns regarding the overdiagnosis and overtreatment of asymptomatic thyroid cancer. Although the incidence of thyroid cancer has increased sharply, the mortality rates remain stable. The most common type of PTC is indolent, making active surveillance a new management option instead of immediate surgery (14). The 2015 American Thyroid Association (ATA) Management Guidelines endorsed active surveillance as an alternative to immediate surgery (15). The most recently published ‘Korean Thyroid Association Guidelines on the Management of Differentiated Thyroid Cancers’ also state that active surveillance may be considered for adult patients diagnosed with low-risk papillary thyroid microcarcinoma (tumor size ≤1 cm, without lymph node metastasis or extrathyroidal extension). This has led to increased detection of patients

with low-risk DTC, and conservative treatment has been proposed for patients with sporadic non-medullary thyroid cancer (NMTC) (8, 16). However, the exact extent of familial non-medullary thyroid cancer (FNMTC) remains controversial.

A family history of PTC is reported as a risk factor for thyroid cancer. A thorough and precise family history of cancer is crucial for assessing cancer risk, because it captures the intricate interplay between inherited genetic predispositions and common environmental and lifestyle factors (17). Approximately 20% of patients with cancer have a family history of cancer without meeting the specific criteria for hereditary cancer syndromes, placing them at a moderately higher risk compared to the general population. These familial cancers are characterized by the occurrence of the same type of cancer in at least two first-degree relatives, despite the absence of identified germline mutations (18). Individuals with a family history of certain cancers may have an increased risk of developing this disease. Numerous studies have shown that those with a family history of cancer are two to three times more likely to develop the same type of cancer than individuals without such a history (19).

FNMTC constitutes 3–9% of all thyroid cancers (20, 21). FNMTC is further classified as nonsyndromic or syndromic, depending on whether the thyroid cancer component is the main cancer (nonsyndromic) in relatives or as part of one of many constellations of tumors (syndromic) in relatives. Syndromic FNMTC occurs as a minor feature of familial cancer syndromes, such as familial adenomatous polyposis, Gardner syndrome, and Cowden disease. Most susceptibility genes for syndromic FNMTC are known, but the susceptibility gene(s) for nonsyndromic FNMTC are unknown. Moreover, nonsyndromic FNMTC is much more common than syndromic FNMTC (22).

In 1955, Robinson and Orr first reported isolated familial papillary thyroid cancer in 24-year-old identical twins (23). Since then, many studies have reported on the presence of relatives with differentiated thyroid cancer (DTC), suggesting the real existence of a familial form of non-medullary thyroid cancer. FNMTC is defined as differentiated thyroid cancer that occurs in at least two first-degree relatives, including the index patient, without other predisposing causes of thyroid cancer (24). However, owing to the increasing incidence of thyroid cancer in the general population, some researchers have argued that the presence of NMTC in only two first-degree relatives within a family could be a coincidental occurrence rather than evidence of a hereditary predisposition. (25) Additionally, because the susceptibility genes for nonsyndromic FNMTC have not yet been identified, determining whether a genetic predisposition exists remains challenging when only two

first-degree relatives are affected. Charkes et al., who applied exact probability measures to a series of first-degree family members with FNMTC, suggested that only two affected members in relatives may represent a fortuitous association with the disease. According to his mathematical simulation, 62–69% of 2-hit families are sporadic occurrences. Thus, only families with three or more affected first-degree relatives should be considered for clinical and genetic investigation of FNMTC. (25) Another study evaluating the risk of thyroid cancer based on the number of FNMTC cases within a family assessed genetic predisposition through clinical screening (thyroid ultrasound and physical examination), as no genetic testing is currently available to identify at-risk family members of FNMTC, and susceptibility genes for nonsyndromic FNMTC have not yet been identified. In this study, a prospective screening approach using thyroid ultrasound and physical examination was conducted in at-risk family members from those with at least two first-degree relatives affected by FNMTC. The results showed that thyroid cancer was diagnosed in 4.6% of individuals from families with two affected first-degree relatives, whereas the detection rate increased to 22.7% in families with three or more affected first-degree relatives. Based on these findings, the authors suggested that because clinically insignificant, asymptomatic, and low-risk thyroid cancers exist in the general population, screening should only be performed in families with three or more affected first-degree relatives to prevent overdiagnosis and overtreatment.(26) However, a recent study from the Swedish Family Cancer database that included 14.7 million individuals was used to estimate familial cancer risk for the 25 most common cancer sites and has been highlighted as the first-degree relatives of patients affected by small intestines; thyroid and testicular cancers are the most at risk of developing the same cancer (19). If a parent had thyroid cancer, the risk in the offspring was three-fold.

Despite strong evidence indicating a genetic predisposition, no definitive susceptibility locus has been identified for isolated FNMTC and no germline mutations have been confirmed. The genetic basis of FNMTC is complex and heterogeneous. However, recent studies utilizing linkage analysis, whole-genome sequencing, and whole-exome sequencing in families with nonsyndromic FNMTC have identified rare germline variants that may contribute to this disease. Nevertheless, independent studies have not validated these findings or explained most nonsyndromic FNMTC cases. Some limitations of these studies may stem from the inclusion of incompletely characterized families or those with only two affected members. Additionally, classifying all cases under the umbrella of nonsyndromic FNMTC may obscure the presence of distinct subtypes and underlying genetic factors.

Furthermore, alternative modes of inheritance such as epigenetic modifications remain largely unexplored and may play a role in the development of nonsyndromic FNMTC (24, 27-29).

The natural progression of syndromic FNMTC resembles that of sporadic FNMTC. However, the aggressiveness of nonsyndromic FNMTC compared to that of sporadic NMTC remains a topic of debate. While some studies suggest that nonsyndromic FNMTC exhibits a more aggressive clinical course, others report no significant differences in disease severity, recurrence risk, or mortality compared to sporadic NMTC. The authors spreviously reported that in a study comparing the biological aggressiveness of 149 patients with FNMTC measuring less than 1 cm and 2,265 patients with sporadic FNMTC, FNMTC exhibited a higher rate of central lymph node metastasis and local recurrence (30). Zhou et al. conducted a meta-analysis to compare whether the second generation of parent/offspring type FNMTC exhibited greater aggressiveness and worse prognosis than its first-generation counterparts. Their analysis concluded that second generation of parent/offspring type FNMTC has a higher risk than its first-generation counterpart (31). Another meta-analysis of FNMTC studies comparing the extent of disease and outcomes in sporadic versus nonsyndromic FNMTC found that nonsyndromic FNMTC was associated with a younger age at diagnosis, a higher rate of multifocal and bilateral tumors, extrathyroidal invasion, lymph node metastasis, and recurrence. (32) Most studies have reported more aggressive disease at presentation, leading to worse outcomes in the FNMTC group (33, 34). However, several studies have reported more aggressive disease at presentation, with similar outcomes at the end of follow-up, or similar baseline characteristics with similar or worse outcomes (35-39). Multiple studies have shown that patients with FNMTC tend to present with a more advanced disease at diagnosis, which often leads to a more aggressive initial treatment. However, there is currently no evidence to suggest that patients with FNMTC respond differently to surgery or radioactive iodine therapy (RAIT) than patients with sporadic thyroid cancer. Nevertheless, it is crucial to consider that while treatment trends for sporadic differentiated thyroid cancer (DTC) are shifting toward less aggressive approaches, there is a lack of research evaluating the applicability of these changes to families with FNMTC.

In this study, we examined familial histories of thyroid cancer in 46572 patients who visited our institution and investigated the prevalence and clinical characteristics, including long-term outcomes of FNMTC, among a relatively large group of patients with NMTC. In addition, using data from the Korean Genome and Epidemiology Study (KoGES) and institutional cohort data, we analyzed

various sociodemographic and clinical characteristics related to a family history of thyroid cancer to identify factors influencing familial risk.

2. MATERIALS AND METHODS

2.1. Clinical outcome of FNMTC

2.1.1. Study patients

This study included patients who were pathologically confirmed to have differentiated thyroid carcinoma between January 1990 and December 2024 and were followed up at Severance Hospital in Yonsei University College of Medicine. We retrospectively surveyed the family history of differentiated thyroid carcinoma and directly asked patients whether they had any first-degree relatives who had been diagnosed with thyroid cancer. First-degree relatives included the patients, offspring, and siblings. The FNMTC group included patients whose first-degree relative(s) was(were) confident that their first-degree relative(s) had been diagnosed with thyroid cancer after surgery or needle (fine or core) aspiration biopsy. Patients with prior radiation exposure and coexisting anaplastic thyroid carcinoma, poorly differentiated thyroid carcinoma, medullary thyroid carcinoma, or other inherited familial cancer syndromes (e.g., familial adenomatous polyposis, Gardner's syndrome, or Cowden's disease) were excluded from this study. Among the 46,572 patients, 42,743 had sporadic NMTC, and 3,829 had FNMTC.

To compare the clinicopathological characteristics of FNMTC and sporadic NMTC, the following parameters were examined and analyzed: age at the time of diagnosis of NMTC, sex, histopathology, tumor size, lymph node metastasis, multiplicity, extrathyroidal extension, combined thyroid disease, treatment with radioactive iodine, staging, recurrence risk stratification, survival, and recurrence. Recurrence was defined as locoregional or distant, which was confirmed through histology or a whole-body scan and serum thyroglobulin following radioactive iodine therapy. We subdivided FNMTC into sibling FNMTC, parent-offspring FNMTC, and patient-offspring-sibling FNMTC. Patient-offspring and patient-offspring-sibling FNMTC was divided into two groups as well.

The Institutional Review Board of the Yongin Severance Hospital approved this study (IRB No: 9-2024-0159).

2.1.2. Statistical analysis

All continuous variables were expressed as mean ± standard deviations (SDs). Statistical analyses were performed using Pearson's chi-square test to compare categorical variables between the groups. One-way analysis of variance (ANOVA) was performed to assess the differences in means among the groups. Recurrence-free survival curves were drawn using the Kaplan-Meier method and statistically analyzed using the log-rank test. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 18.1 (Stata Corp LLC, College Station, TX, USA).

2.2. National Cohort Analysis

2.2.1. Participants and clinical parameter measurement

In addition to analyzing data from institutions, domestic population-based big data analysis is being conducted. Data were obtained using bioresources from CODA in the National Biobank of Korea, the Agency for Disease Control and Prevention. KoGES recruited 172479 participants from 2004 to 2016 among men and women aged 40–79 years who visited health examination centers in metropolitan and mid-sized city hospitals across 15 urban areas, including Seoul, Busan, Incheon, and Gyeonggi. In addition to biological samples (blood, saliva, and urine), demographic and anthropometric data were collected. The administration of questionnaires further supported detailed physical and physiological measurements. Participants were asked whether they had been diagnosed with thyroid cancer by a physician, and those who responded affirmatively were considered to have the disease. Participants were also asked if they had any cancer, and they specified the type of cancer among those who answered "yes."

Information regarding age, education, income, smoking history, outdoor activities, alcohol consumption, and physical exercise was collected during the health interviews. Education level was divided into four categories: elementary or lower, middle, high, and college or higher. Family income (won/month) was categorized into <1 million, 1-2 million, 2-4 million, and > 4 million. Smoking status was categorized into current smoker, past smoker, and never-smoker. Alcohol consumption was classified into never drinker, past drinker, and current drinker. Height, body weight, and waist circumference were measured using the same light clothes and bare feet according to a standardized procedure. Body mass index (BMI) was calculated by dividing the body weight

(kg) by the square of height (m^2). Blood was collected with and without anticoagulants from participants after fasting for > 12 hours. The plasma and serum samples were separated using centrifugation. Lipid profiles and glucose, creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) concentrations were measured in plasma and serum samples using an automatic analyzer. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times with the participant in a sitting position with the right arm at the same height as the heart, and the average values were used (40).

Data from 172,479 individuals in the national cohort were analyzed by classifying them into two levels of comparison:

1. Thyroid cancer group vs. non-cancer group: Individuals diagnosed with thyroid cancer (n = 941) were compared to those with no history of any cancer (n = 167,210). To reduce selection bias due to the large differences in sample sizes between the groups, 1:5 propensity score matching (PSM) was performed. Individuals diagnosed with thyroid cancer were matched with non-cancer controls at a ratio of 1:5, based on age and sex. This matching procedure was conducted using data from the CODA cohort and resulted in a matched dataset comprising 941 thyroid cancer patients and 4,705 non-cancer individuals, allowing for a more balanced comparison between groups.
2. Familial vs. sporadic thyroid cancer group: Among the patients with thyroid cancer, individuals with a family history of thyroid cancer (F-TC, n = 54) were compared to those without a family history (sporadic thyroid cancer, S-TC, n = 887).

2.2.2. Statistical Analysis

Data are presented as the mean ±SD for normally distributed continuous variables and as proportions for categorical variables (e.g., sex and smoking status) according to the family history of thyroid cancer. Statistical analyses were performed using Pearson's chi-square test to compare categorical variables between the groups. One-way ANOVA was performed to assess the differences in means among the groups. Conditional logistic regression was performed to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI). A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 18.1 (Stata Corp LLC, College Station, TX, USA).

2.3. Institutional Cohort Analysis

2.3.1 Participants and clinical parameter measurement

Patient data were extracted using the Severance Clinical Research Analysis Portal program. Patients who underwent surgery for thyroid cancer between 2005 (the start of electronic medical records) and 2016 were included. Only adults aged 40–79 years were selected, resulting in 11,143 patients. To assess the impact of family history on thyroid cancer, patients were divided into two groups: S-TC (n = 10,258, 92.1%) and F-TC (n = 885, 7.9%). Baseline characteristics including age, sex, body mass index (BMI), and blood pressure were compared. In addition, blood test results, including glucose, hemoglobin (Hb), creatinine (Cr), AST, ALT, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were analyzed to identify relevant clinical differences and associated factors.

2.3.2. Statistical Analysis

Data are presented as the mean ±SD for normally distributed continuous variables and as proportions for categorical variables (e.g., sex and hypertension) according to the family history of thyroid cancer. Statistical analyses were performed using Pearson's chi-square test to compare categorical variables between the groups. One-way ANOVA was performed to assess the differences in means among the groups. Conditional logistic regression was performed to estimate the OR and corresponding 95% CI. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 18.1 (StataCorp LLC, College Station, TX, USA).

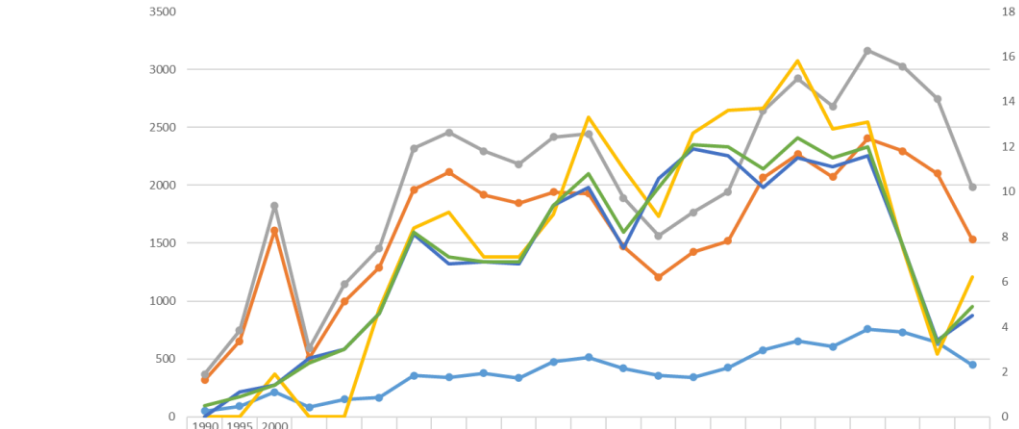
3. RESULTS

3.1. Clinical outcome of FNMTC

3.1.1. Trends in thyroid cancer surgery, sex ratio, and FNMTC proportion (1990-2024)

Figure 2 presents the annual number of patients who underwent surgery for thyroid cancer, male-to-female ratio, and proportion of FNMTC patients from 1990 to 2024. The number of patients with thyroid cancer increased sharply from the early 2000s and then showed a significant decline from 2014. However, approximately five years later, in 2018, the number of patients with thyroid cancer increased again. In 2024, the number of surgeries decreased due to the unique medical crisis in Korea's medical policy. Additionally, the proportion of patients with FNMTC has gradually increased since the late 2000s. After 2014, when the total number of surgeries decreased, the proportion of FNMTC cases increased significantly, but started to decline again in the 2020s. Regarding the sex ratio, the proportion of FNMTC cases has been consistently higher in both sexes.

Figure 2. Trends in thyroid cancer surgery, sex ratio, and FNMTC proportion (1990-2024)



	1990-94	1995-99	2000-04	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Male(N)	51	92	214	82	151	168	356	341	378	336	476	513	420	358	341	425	578	653	608	758	731	644	450
female(N)	318	653	1612	509	995	1290	1962	2115	1916	1845	1941	1930	1471	1207	1425	1520	2066	2268	2072	2405	2294	2102	1532
Total(N)	369	745	1826	591	1146	1458	2318	2456	2294	2181	2417	2443	1891	1565	1766	1945	2644	2921	2680	3163	3025	2746	1982
Male prevalence(FNMTC)	0	0	1.9	0	0	4.8	8.4	9.1	7.1	7.1	9	13.3	11	8.9	12.6	13.6	13.7	15.8	12.8	13.1	7.5	2.8	6.2
Female prevalence(FNMTC)	0	1.1	1.4	2.6	3	4.6	8.1	6.8	6.9	6.8	9.4	10.2	7.5	10.6	11.9	11.6	10.2	11.5	11.1	11.6	7.6	3.4	4.5
Total prevalence(FNMTC)	0.5	0.9	1.4	2.4	3	4.6	8.2	7.1	6.9	6.9	9.4	10.8	8.2	10.2	12.1	12	11	12.4	11.5	12	7.6	3.3	4.9

3.1.2. Prevalence of FNMTC

Among the total 46,572 patients with NMTC, 3,829 had a family history of NMTC, resulting in a prevalence of FNMTC of 8.2% (3,829/46,572). As seen in Table 1, both FNMTC and SNMTC are more prevalent in women than in men. The peak age of thyroid cancer occurrence is 35–44 years for both FNMTC and SNMTC. After the age of 55, the prevalence declined significantly in both groups, with very few cases observed after 75 years of age. FNMTC showed a slightly younger peak than SNMTC, with the highest prevalence occurring in the 35–59 age group, while SNMTC peaked in the 40–44 age group. These findings suggest that familial thyroid cancer tends to occur at a younger age than sporadic thyroid cancer, with a higher proportion of cases observed in women.

Table 1. Age and sex distribution of familial and sporadic non-medullary thyroid cancer

					FNMTC				SNMTC			
		Total		Male		Female		Total		Male		Female	
Age	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
5~9	1	0.03	0	0	1	0.03	8	0.02	4	0.05	4	0.01
10~14	4	0.1	0	0	4	0.14	45	0.11	14	0.17	31	0.09
15~19	24	0.63	5	0.57	19	0.64	268	0.63	31	0.38	237	0.69
20~24	97	2.53	19	2.18	78	2.64	1068	2.5	159	1.93	909	2.64
25~29	265	6.92	55	6.3	210	7.1	3402	7.96	531	6.44	2871	8.32
30~34	473	12.35	101	11.57	372	12.58	5480	12.82	1130	13.7	4350	12.61
35~39	584	15.25	161	18.44	423	14.31	6339	14.83	1377	16.69	4962	14.39
40~44	570	14.88	136	15.58	434	14.68	6459	15.11	1321	16.01	5138	14.9
45~49	490	12.82	103	11.91	387	13.09	5557	13	1061	12.86	4496	13.04
50~54	481	12.56	101	11.57	380	12.85	5056	11.83	850	10.3	4206	12.19
55~59	382	9.97	88	10.08	294	9.94	3871	9.06	718	8.7	3153	9.14
60~64	253	6.61	49	5.61	204	6.9	2654	6.21	506	6.13	2148	6.23
65~69	115	3	30	3.44	85	2.87	1442	3.37	307	3.72	1135	3.29
70~74	54	1.41	12	1.37	42	1.42	742	1.74	162	1.96	580	1.68
75~79	32	0.84	10	1.15	22	0.74	268	0.63	59	0.72	209	0.61
80~84	3	0.08	1	0.11	2	0.07	61	0.14	17	0.21	44	0.13
85~89	1	0.03	1	0.11	0	0	13	0.03	3	0.04	10	0.03
>=90	0	0	0	0	0	0	9	0.02	1	0.01	8	0.02
Total	3,829	100	872	100	2957	100	42,742	100	8,251	100	34,491	100

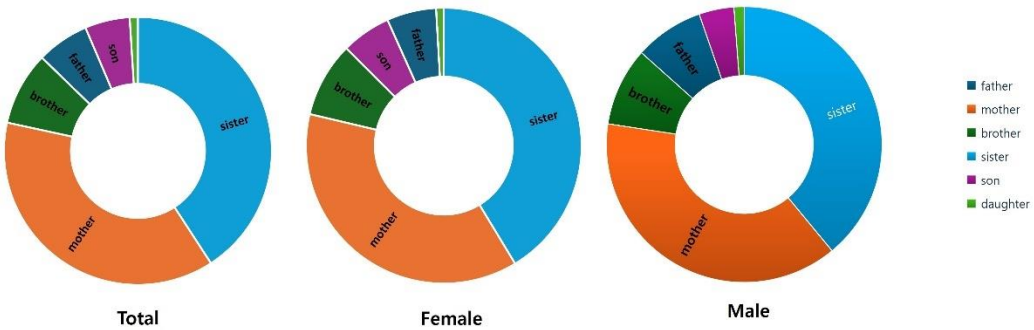
3.1.3. Familial relationship distribution analysis based on the affected family members count

Most FNMTC cases involve female first-degree relatives (sisters and mothers). Moreover, male patients had a slightly higher proportion of affected fathers and brothers than female patients. The prevalence of affected sons was lower among male patients than among female patients, whereas daughters had the lowest overall proportion. These findings suggest that one family affected by FNMTC was more commonly linked to female relatives, particularly sisters and mothers, regardless of the patient's sex(Table 2, Figure 3).

Table 2. Distribution of FNMTC based on one affected family member and sex

	Total		Female		Male	
Relashion	N	%	N	%	N	%
father	216	5.8	155	5.8	61	8.1
mother	1283	37.3	992	37.3	291	38.4
brother	303	8.8	233	8.8	70	9.2
sister	1395	41.3	1099	41.3	296	39
son	185	5.8	154	5.8	31	4.1
daughter	34	0.9	25	0.9	9	1.2
Total	3416	100	2658	100	758	100

Figure 3. Distribution of FNMTC based on one affected family member and sex

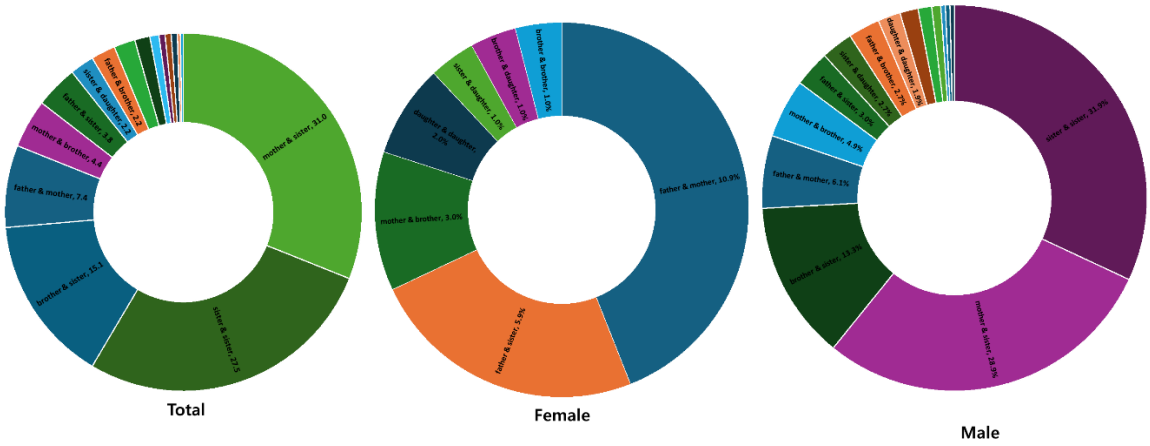


In Table 3 and Figure 4, we have analyzed the familial relationships of cases involving two affected family members. The most frequently affected pair was mother & sister (31.0%), followed by sister & sister (27.5%) and brother & sister (15.1%). Paternal combinations (father & mother, 7.4%; mother & brother, 4.4%) were observed in a smaller proportion of cases. Sibling-sibling (sister & sister, brother & sister) combinations were common in both male and female patients. Parent-child combinations were rare, particularly father-daughter (0.3%) and mother-daughter (0.5%).

Table. 3 Distribution of FNMTC based on two family members and sex

Relashion	Total		Female		Male	
	N	%	N	%	N	%
father & mother	27	7.4%	16	6.1%	11	10.9%
father & brother	8	2.2%	7	2.7%	1	1.0%
father & sister	14	3.8%	8	3.0%	6	5.9%
father & daughter	1	0.3%	0	0.0%	1	1.0%
mother & brother	16	4.4%	13	4.9%	3	3.0%
mother & sister	113	31.0%	76	28.9%	37	36.6%
mother & daughter	2	0.5%	2	0.8%	0	
mother & son	2	0.5%	1	0.4%	1	1.0%
brother & brother	5	1.4%	4	1.5%	1	1.0%
brother & sister	55	15.1%	35	13.3%	20	19.8%
brother & daughter	2	0.5%	1	0.4%	1	1.0%
sister & sister	100	27.5%	84	31.9%	16	15.8%
sister & daughter	8	2.2%	7	2.7%	1	1.0%
sister & son	1	0.3%	1	0.4%	0	0
daughter & daughter	7	1.9%	5	1.9%	2	2.0%
daughter & son	3	0.8%	3	1.1%	0	0
Total	364	100%	263	100	101	100%

Figure 4. Distribution of FNMTC based on two affected family members and sex



In the distribution of those with three affected family member (Figure 5, Table 4), the most frequently affected combination was three sisters (23.9%), followed by mother & brother & sister (15.2%) and mother & sister & sister (13.0%). Brother & two sisters (13.0%) and father & mother & sister (8.7%) were also observed at notable frequencies. The least common triads were father & mother & brother (2.2%) and two daughters & son (2.2%). These findings suggest that familial thyroid cancer most frequently affects female siblings (sisters), whereas male patients more often have affected parents in addition to siblings.

Figure 5. Distribution of FNMTC based on three affected family members and sex

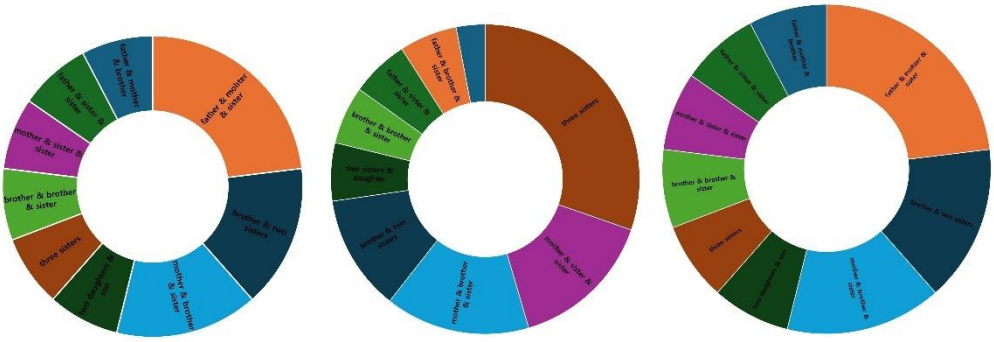


Table. 4 Distribution of FNMTC based on three affected family members and sex

Relashion	Total		Female		Male	
	N	%	N	%	N	%
father & mother & brother	1	2.2	0	0	1	7.7%
father & mohter & sister	4	8.7	1	3	3	23.1%
father & brother & sister	2	4.30%	2	6.1	0	0.0%
father & sister & sister	3	6.50%	2	6.1	1	7.7%
mother & brother & sister	7	15.20%	5	15.2	2	15.4%
mother & sister & sister	6	13.00%	5	15.2	1	7.7%
brother & brother & sister	3	6.50%	2	6.1	1	7.7%
brother & two sisters	6	13.00%	4	12.1	2	15.4%
three sisters	11	23.90%	10	30.3	1	7.7%
two sisters & daughter	2	4.30%	2	6.1	0	0.0%
two daughters & son	1	2.20%	0	0	1	7.7%
Total	46	100.00%	33		13	

3.1.4. Comparison of clinicopathological characteristics of FNMTC and SNMTC

A comparative analysis was conducted to evaluate the clinicopathological characteristics of the patients with FNMTC and SNMTC in Table 5. The proportion of male patients was significantly higher in the FNMTC group than in the SNMTC group (22.8% vs. 19.3%, $p<0.001$). The mean age did not differ significantly between groups (45.0 ± 12.1 vs. 44.7 ± 12.3 years, $p=0.068$), and the age distribution was comparable ($p=0.3$). Regarding surgical approaches, robot-assisted surgery was slightly more common in the FNMTC group (23.7% vs. 22.7%), whereas open thyroidectomy remained the predominant method in both groups ($p=0.018$). There were no significant differences in the extent of surgery between the groups ($p=0.2$). Tumor size was significantly smaller in patients with FNMTC (0.9 ± 0.7 cm vs. 1.0 ± 0.9 cm, $p<0.001$), with a higher proportion of microcarcinomas (≤10 mm) in the FNMTC group (71.8% vs. 68.0%, $p<0.001$). However, FNMTC was associated with a higher frequency of bilaterality (23.5% vs. 17.5%, $p<0.001$), multifocality (39.0% vs. 30.5%, $p<0.001$), and extracapsular extension (53.7% vs. 51.1%, $p=0.002$).

Histological subtype distribution showed a slightly higher proportion of papillary carcinoma in FNMTC (99.1% vs. 98.5%, p=0.007), although aggressive histology did not differ significantly. Central lymph node (CN) metastasis was more frequent in the FNMTC group (41.5% vs. 38.8%, p=0.001), whereas lateral lymph node (LLN) and distant metastasis rates were similar.

The proportion of patients receiving RAIT was identical in both groups (34.9%), although high-dose RAIT was more common in FNMTC (13.5% vs. 12.3%, p=0.035). There was no difference in the response to RAIT.

The recurrence rates were comparable between the two groups (1.9% in FNMTC vs. 2.3% in SNMTC; p=0.1), and most recurrences were locoregional in both groups. Notably, the all-cause mortality rate was significantly lower in the FNMTC group (0.4% vs. 1.4%, p<0.001), although the thyroid cancer-specific mortality did not differ (p=0.6). The mean follow-up duration was significantly shorter in FNMTC (44.6 ± 29.5 months) than in SNMTC (55.7 ± 42.2 months, p<0.001).

Table. 5 Clinicopathological characteristics, treatment modalities, and outcomes of SNMTC versus FNMTC

	Overall N = 46,572	SNMTC N = 42,743	FNMTC N = 3,829	p-value
Sex				<0.001
Male	9,124 (19.6%)	8,251 (19.3%)	873 (22.8%)	
Female	37,448 (80.4%)	34,492 (80.7%)	2,956 (77.2%)	
Age	44.7 ± 12.3	44.7 ± 12.3	45.0 ± 12.1	0.068
Age(group)				0.3
< 55 years	36,680 (78.8%)	33,691 (78.8%)	2,989 (78.1%)	
≥ 55 years	9,892 (21.2%)	9,052 (21.2%)	840 (21.9%)	
Thyroid_function abnormal				0.2
Hypothyroidism	636 (1.4%)	575 (1.4%)	61 (1.6%)	
Hyperthyroidism	303 (0.7%)	284 (0.7%)	19 (0.5%)	
OP_method				0.018
Open	28,709(61.6%)	26,392 (61.7%)	2,317 (60.5%)	
Minimal incision	6,342 (13.6%)	5,792 (13.6%)	550 (14.4%)	
Endoscopic	889 (1.9%)	836 (2.0%)	53 (1.4%)	
Robot	10,632 (22.8%)	9,723 (22.7%)	909 (23.7%)	
OP_name				0.2
Lobectomy	20,889 (44.9%)	19,197 (44.9%)	1,692 (44.2%)	
Lobectomy + partial or subtotal	5,871 (12.6%)	5,413 (12.7%)	458 (12.0%)	
Bilateral total	19,812(42.5%)	18,133 (42.4%)	1,679 (43.8%)	

Tumor_size	1.0 ± 0.9	1.0 ± 0.9	0.9 ± 0.7	<0.001
Tumor_size group				<0.001
≤ 10mm	31,797 (68.3%)	29,048 (68.0%)	2,749 (71.8%)	
10~20mm	10,829 (23.3%)	9,962 (23.3%)	867 (22.6%)	
20~40mm	3,255 (7.0%)	3,075 (7.2%)	180 (4.7%)	
> 40mm	691 (1.5%)	658 (1.5%)	33 (0.9%)	
Bilaterality	8,385 (18.0%)	7,486 (17.5%)	899 (23.5%)	<0.001
Multiplicity	14,515 (31.2%)	13,020 (30.5%)	1,495 (39.0%)	<0.001
Extracapsular extension	23,879 (51.3%)	21,824 (51.1%)	2,055 (53.7%)	0.002
Pathology_result				0.007
Papillary ca.	45,888 (98.5%)	42,095 (98.5%)	3,793 (99.1%)	
Follicular ca.	581 (1.2%)	547 (1.3%)	34 (0.9%)	
Oncocytic ca.	103 (0.2%)	101 (0.2%)	2 (0.1%)	
Aggressive pathology*	420 (0.9%)	390 (0.9%)	30 (0.8%)	0.4
CLN† metastasis	18,171 (39.0%)	16,583 (38.8%)	1,588 (41.5%)	0.001
LLN‡ metastasis	4,482 (9.6%)	4,119 (9.6%)	363 (9.5%)	0.8
Distant metastasis				0.7
None	46,372 (99.6%)	42,558 (99.6%)	3,814 (99.6%)	
Synchronous	139 (0.3%)	130 (0.3%)	9 (0.2%)	
Metachronous	61 (0.1%)	55 (0.1%)	6 (0.2%)	
Distant_metastasis organ				0.5
Lung	169 (82.4%)	157 (83.1%)	12 (75.0%)	
Bone	25 (12.2%)	22 (11.6%)	3 (18.8%)	

Brain	3 (1.5%)	3 (1.6%)	0 (0.0%)	
Multiple	5 (2.4%)	4 (2.1%)	1 (6.3%)	
Other	3 (1.5%)	3 (1.6%)	0 (0.0%)	
RAIT§	16,233 (34.9%)	14,897 (34.9%)	1,336 (34.9%)	>0.9
RAIT dose				0.035
Low dose	10,515 (22.8%)	9,693 (22.9%)	822 (21.6%)	
High dose	5,718 (12.4%)	5,204 (12.3%)	514 (13.5%)	
RAIT result				0.3
No & minimal uptake	16,151 (99.4%)	14,823 (99.5%)	1,328 (99.3%)	
Hot uptake	91 (0.6%)	81 (0.5%)	10 (0.7%)	
Recurrence	1,038 (2.2%)	967 (2.3%)	71 (1.9%)	0.1
Recurrence site				0.6
Local	953 (91.8%)	887 (91.7%)	66 (93.0%)	
Distant	51 (4.9%)	48 (5.0%)	3 (4.2%)	
Local + distant	34 (3.3%)	32 (3.3%)	2 (2.8%)	
Survival				<0.001
Alive	30,605(98.7%)	28,080 (98.6%)	2,525 (99.6%)	
Death	413 (1.3%)	402 (1.4%)	11 (0.4%)	
Cause of Death				0.6
Thyroid cancer	90 (21.3%)	89 (21.6%)	1 (9.1%)	
Other cause	333 (78.7%)	323 (78.4%)	10 (90.9%)	
Follow-up duration	54.7 ± 41.4	55.7 ± 42.2	44.6 ± 29.5	<0.001

Aggressive pathology* : Hobnail, Tall cell, Columnar cell, Diffuse sclerosing variant

CLN† : Central lymph node LLN‡ :Lateral lymph node RAIT§ : Radioactive iodine treatment

We performed a subgroup analysis according to the affective family members and family member relationships of the patients with FNMTC. As seen in Table 6, among the 3,829 patients with FNMTC, a subgroup analysis was performed based on the number of affected first-degree relatives: 3,321 patients had two affected relatives (FNMTC-2), 409 had three (FNMTC-3), and 63 had four or more (FNMTC-4+). The mean tumor size was comparable across subgroups (0.9 ± 0.6 cm in FNMTC-3, 0.8 ± 0.6 cm in FNMTC-4+, vs. 0.9 ± 0.7 cm in FNMTC-2; p = 0.087), and the distribution of tumor size groups showed no significant difference (p = 0.8). However, bilaterality was significantly more frequent in the FNMTC-3 group (30.2%) than in FNMTC-2 (22.6%) or FNMTC-4+ (26.2%) (p = 0.002). Multiplicity also tended to be higher in FNMTC-3 and FNMTC-4+ (44.1% and 43.1%, respectively) than in FNMTC-2 (38.3%), although this did not reach statistical significance (p = 0.06). There were no significant differences in the rates of extracapsular extension (p = 0.9), cervical lymph node metastasis (p = 0.5), or lateral lymph node metastasis (p = 0.6) among the groups. Similarly, the occurrence of distant metastasis and the distribution of metastatic organs were not significantly different. RAIT was administered more frequently to FNMTC-3 (41.5%) than to FNMTC-2 (34.2%) or FNMTC-4+ (30.8%) (p = 0.011). The use of low-dose RAIT was more common in the FNMTC-3 group (27.1%) than in the other groups (p = 0.037). The response to RAIT, including the rate of minimal or no uptake, showed no significant difference (p = 0.2). Recurrence rates were low and not significantly different among the subgroups (1.7% for FNMTC-2, 2.7% for FNMTC-3, and 3.1% for FNMTC-4+; p = 0.2), with local recurrence being the predominant pattern. Overall survival was excellent across all groups, exceeding 99%. and disease-specific mortality was rare, with only one thyroid cancer–related death reported in FNMTC-2 (p > 0.9). The mean follow-up duration was slightly longer in FNMTC-3 (47.5 ± 31.1 months) than in FNMTC-2 and FNMTC-4+, but this difference was not statistically significant (p = 0.2).

Table 6. Clinicopathological characteristics, treatment modalities, and outcomes of FNMTC based on the affected family members

Characteristics	Overall N = 3,829	one affected N = 3,354	two affected N = 410	three or more affected N = 65	p-value
Sex					0.041
Male	873 (22.8%)	744 (22.2%)	109 (26.6%)	20 (30.8%)	
Female	2,956 (77.2%)	2,610 (77.8%)	301 (73.4%)	45 (69.2%)	
Age	45.0 ± 12.1	45.0 ± 12.2	44.9 ± 11.3	43.8 ± 11.4	0.8
Age(group)					0.083
< 55 years	2,986 (78.0%)	2,597 (77.4%)	337 (82.2%)	52 (80.0%)	
≥ 55 years	843 (22.0%)	757 (22.6%)	73 (17.8%)	13 (20.0%)	
Thyroid function abnormal					0.6
Hypothyroidism	61 (1.6%)	56 (1.7%)	5 (1.2%)	0 (0.0%)	
Hyperthyroidism	19 (0.5%)	19 (0.6%)	0 (0.0%)	0 (0.0%)	
OP method					0.7
Open	2,317 (60.5%)	2,026 (60.4%)	247 (60.2%)	44 (67.7%)	
Minimal incision	550 (14.4%)	478 (14.3%)	62 (15.1%)	10 (15.4%)	
Endoscopic	53 (1.4%)	45 (1.3%)	8 (2.0%)	0 (0.0%)	

Robot	909 (23.7%)	805 (24.0%)	93 (22.7%)	11 (16.9%)	
OP name					0.3
Lobectomy	1,692 (44.2%)	1,502 (44.8%)	160 (39.0%)	30 (46.2%)	
Lobectomy + partial or subtotal	458 (12.0%)	399 (11.9%)	51 (12.4%)	8 (12.3%)	
Bilateral total	1,679 (43.8%)	1,453 (43.3%)	199 (48.5%)	27 (41.5%)	
Tumor size	0.9 ± 0.7	0.9 ± 0.7	0.9 ± 0.6	0.8 ± 0.6	0.087
Tumor size group					0.8
≤ 10mm	2,749 (71.8%)	2,397 (71.5%)	303 (73.9%)	49 (75.4%)	
10~20mm	867 (22.6%)	767 (22.9%)	86 (21.0%)	14 (21.5%)	
20~40mm	180 (4.7%)	158 (4.7%)	20 (4.9%)	2 (3.1%)	
>40mm	33 (0.9%)	32 (1.0%)	1 (0.2%)	0 (0.0%)	
Bilaterality	899 (23.5%)	758 (22.6%)	124 (30.2%)	17 (26.2%)	0.002
Multiplicity	1,495 (39.0%)	1,286 (38.3%)	181 (44.1%)	28 (43.1%)	0.06
Extracapsular extension	2,055 (53.7%)	1,800 (53.7%)	222 (54.1%)	33 (50.8%)	0.9
Pathology result					0.13
Papillary ca.	3,793 (99.1%)	3,321 (99.0%)	409 (99.8%)	63 (96.9%)	
Follicular ca.	34 (0.9%)	31 (0.9%)	1 (0.2%)	2 (3.1%)	
Oncocytic ca.	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	

Aggressive pathology*	30 (0.8%)	26 (0.8%)	4 (1.0%)	0 (0.0%)	0.8
CLN† metastasis	1,588 (41.5%)	1,380 (41.1%)	181 (44.1%)	27 (41.5%)	0.5
LLN‡ metastsis	363 (9.5%)	314 (9.4%)	44 (10.7%)	5 (7.7%)	0.6
Distant metastasis					>0.9
None	3,814 (99.6%)	3,340 (99.6%)	409 (99.8%)	65 (100.0%)	
Synchronous	9 (0.2%)	8 (0.2%)	1 (0.2%)	0 (0.0%)	
Metachronous	6 (0.2%)	6 (0.2%)	0 (0.0%)	0 (0.0%)	
Distant metastasis organ					0.4
Lung	12 (75.0%)	11 (78.6%)	1 (50.0%)	0 (NA%)	
Bone	3 (18.8%)	2 (14.3%)	1 (50.0%)	0 (NA%)	
Brain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (NA%)	
Multiple	1 (6.3%)	1 (7.1%)	0 (0.0%)	0 (NA%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (NA%)	
RAIT§	1,336 (34.9%)	1,146 (34.2%)	170 (41.5%)	20 (30.8%)	0.011
RAIT dose					0.037
Low dose	822 (21.6%)	698 (21.0%)	111 (27.1%)	13 (20.0%)	
High dose	514 (13.5%)	448 (13.5%)	59 (14.4%)	7 (10.8%)	
RAIT result					0.2
No & minimal uptake	1,328 (99.3%)	1,140 (99.3%)	169 (99.4%)	19 (95.0%)	
Hot uptake	10 (0.7%)	8 (0.7%)	1 (0.6%)	1 (5.0%)	

Recurrence	71 (1.9%)	57 (1.7%)	12 (2.7%)	2 (3.1%)	0.2
Recurrence site					>0.9
Local	66 (93.0%)	52 (91.2%)	12 (100.0%)	2 (100.0%)	
Distant	3 (4.2%)	3 (5.3%)	0 (0.0%)	0 (0.0%)	
Local +distant	2 (2.8%)	2 (3.5%)	0 (0.0%)	0 (0.0%)	
Survival					>0.9
Alive	2,525 (99.6%)	2,203 (99.5%)	280 (99.6%)	42 (100.0%)	
Death	11 (0.4%)	10 (0.5%)	1 (0.4%)	0 (0.0%)	
Unknown	1,293	1,141	129	23	
Cause of Death					>0.9
Thyroid cancer	1 (9.1%)	1 (10.0%)	0 (0.0%)	0 (NA%)	
Other cause	10(90.9%)	9 (90.0%)	1 (100.0%)	0 (NA%)	
Follow-up duration	44.6 ± 29.5	44.3 ± 29.3	47.5 ± 31.1	41.7 ± 28.6	0.2

Aggressive pathology* : Hobnail, Tall cell, Columnar cell, Diffuse sclerosing variant

CLN† : Central lymph node LLN‡ :Lateral lymph node RAIT§ : Radioactive iodine treatment

Table 7. Clinicopathological characteristics, treatment modalities, and outcomes of FNMTC based on the hereditary forms

	Overall N = 3,829	Parent /Offspring N = 1,762	Sibling N = 1,877	Parent /Offspring /Sibling N = 190	p-value
Sex					0.005
Male	873 (22.8%)	407 (23.1%)	405 (21.6%)	61 (32.1%)	
Female	2,956 (77.2%)	1,355 (76.9%)	1,472 (78.4%)	129 (67.9%)	
Age	45.0 ± 12.1	40.9 ± 12.7	48.9 ± 10.4	44.5 ± 10.4	0.001
Age(group)					0.001
< 55 years	2,986 (78.0%)	1,484 (84.2%)	1,346 (71.7%)	156 (82.1%)	
≥ 55 years	843 (22.0%)	278 (15.8%)	531 (28.3%)	34 (17.9%)	
Thyroid function_ abnormal					0.8
Hypothyroidism	61 (1.6%)	27 (1.6%)	33 (1.8%)	1 (0.5%)	
Hyperthyroidism	19 (0.5%)	9 (0.5%)	10 (0.5%)	0 (0.0%)	
OP method					0.001
Open	2,317 (60.5%)	944 (53.6%)	1,264 (67.3%)	109 (57.4%)	
Minimal incision	550 (14.4%)	281 (15.9%)	241 (12.8%)	28 (14.7%)	
Endoscopic	53 (1.4%)	25 (1.4%)	25 (1.3%)	3 (1.6%)	
Robot	909 (23.7%)	512 (29.1%)	347 (18.5%)	50 (26.3%)	
OP name					0.001
Lobectomy	1,692 (44.2%)	872 (49.5%)	738 (39.3%)	82 (43.2%)	
Lobectomy + partial or subtotal	458 (12.0%)	213 (12.1%)	218 (11.6%)	27 (14.2%)	

Bilateral total	1,679 (43.8%)	677 (38.4%)	921 (49.1%)	81 (42.6%)	
Tumor size	0.9 ± 0.7	0.9 ± 0.7	0.9 ± 0.7	0.8 ± 0.6	0.056
Tumor size group					0.6
≤ 10mm	2,749 (71.8%)	1,251 (71.0%)	1,361 (72.5%)	137 (72.1%)	
10~20mm	867 (22.6%)	406 (23.0%)	414 (22.1%)	47 (24.7%)	
20~40mm	180 (4.7%)	86 (4.9%)	88 (4.7%)	6 (3.2%)	
>40mm	33 (0.9%)	19 (1.1%)	14 (0.7%)	0 (0.0%)	
Bilaterality	899 (23.5%)	358 (20.3%)	494 (26.3%)	47 (24.7%)	0.001
Multiplicity	1,495 (39.0%)	655 (37.2%)	765 (40.8%)	75 (39.5%)	0.085
Extracapsular extension	2,055 (53.7%)	921 (52.3%)	1,041 (55.5%)	93 (48.9%)	0.063
Pathology result					0.6
Papillary ca.	3,793 (99.1%)	1,749 (99.3%)	1,856 (98.9%)	188 (98.9%)	
Follicular ca.	34 (0.9%)	12 (0.7%)	20 (1.1%)	2 (1.1%)	
Oncocytic ca.	2 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	
Aggressive pathology*	30 (0.8%)	15 (0.9%)	12 (0.6%)	3 (1.6%)	0.3
CLN† metastasis	1,588 (41.5%)	783 (44.4%)	728 (38.8%)	77 (40.5%)	0.003
LLN‡ metastsis	363 (9.5%)	168 (9.5%)	183 (9.7%)	12 (6.3%)	0.3
Distant metastasis					>0.9
None	3,814 (99.6%)	1,756 (99.7%)	1,868 (99.5%)	190 (100.0%)	
Synchronous	9 (0.2%)	4 (0.2%)	5 (0.3%)	0 (0.0%)	
Metachronous	6 (0.2%)	2 (0.1%)	4 (0.2%)	0 (0.0%)	
Distant metastasis organ					0.8

Lung	12 (75.0%)	4 (66.7%)	7 (77.8%)	1 (100.0%)	
Bone	3 (18.8%)	1 (16.7%)	2 (22.2%)	0 (0.0%)	
Brain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Multiple	1 (6.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
RAIT[§]	1,336 (34.9%)	541 (30.7%)	729 (38.8%)	66 (34.7%)	0.001
RAIT dose					0.001
Low dose	822 (21.6%)	302 (17.3%)	474 (25.4%)	46 (24.2%)	
High dose	514 (13.5%)	239 (13.7%)	255 (13.6%)	20 (10.5%)	
RAIT result					0.1
No & minimal uptake	1,328 (99.3%)	541 (99.8%)	721 (98.8%)	66 (100.0%)	
Hot uptake	10 (0.7%)	1 (0.2%)	9 (1.2%)	0 (0.0%)	
Recurrence	71 (1.9%)	38 (2.2%)	27 (1.4%)	6 (3.2%)	0.09
Recurrence site					0.4
Local	66 (93.0%)	35(94.7%)	25 (83.9%)	6 (100.0%)	
Distant	3 (4.2%)	2 (5.3%)	1 (3.2%)	0 (0.0%)	
Local +distant	2 (2.8%)	0 (0.0%)	2 (6.5%)	0 (0.0%)	
Survival					0.9
Alive	2,525 (99.6%)	1,140 (99.5%)	1,261 (99.6%)	124 (100.0%)	
Death	11 (0.4%)	6 (0.5%)	5 (0.4%)	0 (0.0%)	
Unknown	1,293	616	611	66	
Cause of Death					>0.9
Thyroid cancer	1 (9.1%)	0 (0.0%)	1 (20.0%)	0 (NA%)	
Other cause	10(90.9%)	6 (100%)	4 (80.0%)	0 (NA%)	
Follow-up duration	44.6 ± 29.5	42.4 ± 27.7	46.6 ± 30.8	44.7 ± 30.5	0.007

Aggressive pathology[*] : Hobnail, Tall cell, Columnar cell, Diffuse sclerosing variant

CLN[†] : Central lymph node LLN[‡] :Lateral lymph node RAIT[§] : Radioactive iodine treatment

Among the 3,829 patients with FNMTC, a subgroup analysis was performed based on familial relationships: 1,762 patients had parent–offspring involvement, 1,877 had sibling involvement, and 190 had a mixed pattern (both parent–offspring and siblings).

Sex distribution showed a significantly higher proportion of male patients in the mixed group (32.1%) than in the parent–offspring (23.1%) and sibling (21.6%) groups ($p = 0.005$). The mean age at diagnosis also differed significantly, with sibling group patients being older (48.9 ± 10.4 years) than the parent–offspring (40.9 ± 12.7 years) and mixed (44.5 ± 10.4 years) groups ($p = 0.001$). Accordingly, the proportion of patients <55 years was highest in the parent–offspring group (84.2%) and lowest in the sibling group (71.7%) ($p = 0.001$). There were significant differences in the surgical approaches among the groups. Robotic surgery was more frequently used in the parent–offspring group (29.1%) than in the sibling (18.5%) or mixed (26.3%) groups ($p = 0.001$). Conversely, open surgery was more common in the sibling group (67.3%) than in the parent–offspring (53.6%) and mixed (57.4%) groups. In terms of extent of surgery, lobectomy was more commonly performed in the parent–offspring group (49.5%), whereas bilateral total thyroidectomy was most frequent in the sibling group (49.1%) ($p = 0.001$). Tumor size was similar among groups (overall mean 0.9 ± 0.7 cm), with a non-significant trend toward smaller tumors in the mixed group ($p = 0.056$). The distribution of tumor size categories, extracapsular extension, and aggressive histological variants did not differ significantly. However, bilaterality was more prevalent in the sibling group (26.3%) than in the parent–offspring (20.3%) and mixed (24.7%) groups ($p = 0.001$). Central lymph node metastasis was significantly more frequent in the parent–offspring group (44.4%) than in the sibling (38.8%) and mixed (40.5%) groups ($p = 0.003$). Lateral neck node involvement and distant metastasis rates were low and comparable across all the groups.

Use of RAIT varied significantly among the groups, with the highest rate in the sibling group (38.8%) and the lowest in the parent–offspring group (30.7%) ($p = 0.001$). Low-dose RAIT was more commonly administered in the sibling and mixed groups ($p = 0.001$); however, the RAIT response (minimal vs. hot uptake) did not differ significantly. The recurrence rate showed a non-significant trend, being highest in the mixed group (3.2%) than in the parent–offspring (2.2%) and sibling (1.4%) groups ($p = 0.09$). Most recurrences are locoregional. Overall survival was excellent in all groups, with survival exceeding 99%. thyroid cancer–specific mortality was rare and not significantly different ($p = 0.9$). The mean follow-up duration differed slightly, being shortest in the parent–offspring group (42.4 ± 27.7 months) and longest in the sibling group (46.6 ± 30.8

months) (p = 0.007) (Table 7).

Table 8. Clinicopathologic characteristics, treatment modalities, and outcomes of SNMTC versus FNMTC in the low-risk group

Characteristics	Overall N = 16,894	SNMTC N = 15,582	FNMTC N = 1,312	p-value
Sex				0.2
Male	2,919 (17.3%)	2,677 (17.2%)	242 (18.4%)	
Female	13,975 (82.7%)	12,905 (82.8%)	1,070 (81.6%)	
Age	45.1 ± 11.6	45.1 ± 11.6	45.0 ± 11.5	0.9
Age(group)				0.8
< 55 years	13,358 (79.1%)	12,317 (79.0%)	1,041 (79.3%)	
≥ 55 years	3,536 (20.9%)	3,265 (21.0%)	271 (20.7%)	
Thyroid function abnormal				0.5
Hypothyroidism	152 (0.9%)	145 (1.0%)	7 (0.5%)	
Hyperthyroidism	341(2.0%)	324(2.1%)	17(1.3%)	
OP method				
Open	9,322 (55.2%)	8,613 (55.3%)	709 (54.0%)	
Minimal incision	3,041 (18.0%)	2,795 (17.9%)	246 (18.8%)	
Endoscopic	431 (2.6%)	406 (2.6%)	25 (1.9%)	
Robot	4,100 (24.3%)	3,768 (24.2%)	332 (25.3%)	
OP name				0.5
Lobectomy	10,072 (59.6%)	9,290 (59.6%)	782 (59.6%)	
Lobectomy + partial or subtotal	2,748 (16.3%)	2,548 (16.4%)	200 (15.2%)	
Bilateral total	4,074 (24.1%)	3,744 (24.0%)	330 (25.2%)	
Tumor size	0.7 ± 0.6	0.7 ± 0.6	0.7 ± 0.5	0.002
Tumor size group				0.085
≤ 10mm	14,274 (84.5%)	13,134 (84.3%)	1,140 (86.9%)	
10~20mm	2,022 (12.0%)	1,886 (12.1%)	136 (10.4%)	
20~40mm	588 (3.5%)	552 (3.5%)	36 (2.7%)	
>40mm	10 (0.1%)	10 (0.1%)	0 (0.0%)	

Bilaterality	1,650 (9.8%)	1,496 (9.6%)	154 (11.7%)	0.012
Multiplicity	3,611 (21.4%)	3,265 (21.0%)	346 (26.4%)	<0.001
Pathology result				0.11
Papillary ca.	16,796 (99.4%)	15,486 (99.4%)	1,310 (99.8%)	
Follicular ca.	84 (0.5%)	82 (0.5%)	2 (0.2%)	
Oncocytic ca.	14 (0.1%)	14 (0.1%)	0 (0.0%)	
CLN* metastasis	1,325 (7.8%)	1,205 (7.7%)	120 (9.1%)	0.067
RAIT†	2,018 (11.9%)	1,872 (12.0%)	146 (11.1%)	0.3
RAIT dose				0.5
No	14,701 (87.9%)	13,546 (87.9%)	1,155 (88.8%)	
Low dose	1,944 (11.6%)	1,802 (11.7%)	142 (10.9%)	
High dose	74 (0.4%)	70 (0.5%)	4 (0.3%)	
RAIT result				>0.9
No & minimal uptake	2,025 (100.0%)	1,877 (100.0%)	148 (100.0%)	
Hot uptake	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Recurrence	155 (0.9%)	143 (0.9%)	12 (0.9%)	>0.9
Recurrence site				0.2
Local	157 (94.6%)	144 (95.4%)	13 (86.7%)	
Distant	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Local + distant	1 (0.6%)	1 (0.7%)	0 (0.0%)	
Survival				0.2
Alive	10,747 (99.3%)	9,929 (99.3%)	818 (99.6%)	
Death	78 (0.7%)	75 (0.7%)	3 (0.4%)	
Cause of Death				>0.9
Thyroid cancer	9 (12.2%)	9 (12.5%)	0 (0.0%)	
Other cause	65 (87.9%)	63 (87.5%)	2 (100.0%)	
Follow-up duration	52.4 ± 40.3	53.2 ± 41.0	42.6 ± 29.3	<0.001

CLN* : Central lymph node RAIT† : Radioactive iodine treatment

Due to the complexity of analyzing a large heterogeneous cohort, patients were stratified according to ATA risk categories to facilitate more accurate and clinically relevant subgroup comparisons.

As seen in Table 8, among 16,894 patients classified as low-risk based on the ATA guidelines, 1,312 (7.8%) had FNMTC and 15,582 (92.2%) had sporadic NMTC (SNMTC). The baseline characteristics, including sex, age, and thyroid function, were comparable between the groups. The FNMTC group had significantly smaller tumors ($p = 0.002$) but showed higher rates of bilaterality (11.7% vs. 9.6%, $p = 0.012$) and multifocality (26.4% vs. 21.0%, $p<0.001$). Central lymph node metastasis was slightly more frequent in FNMTC (9.1% vs. 7.7%, $p = 0.067$). The surgical extent and RAIT usage did not differ significantly. Recurrence rates were equally low (0.9%), and no distant metastases were observed in either group. Overall survival exceeded 99% in both groups, with no thyroid cancer-related deaths among patients with FNMTC. However, the FNMTC group had a significantly shorter follow-up duration ($p<0.001$).

Among 29,678 patients classified as intermediate- to high-risk according to ATA guidelines, 2,517 (8.5%) had FNMTC and 27,161 (91.5%) had SNMTC. Patients with FNMTC were more likely to be male (25.1% vs. 20.5%, $p<0.001$) and slightly older at diagnosis ($p=0.016$). Tumors in patients with FNMTC were smaller on average (1.0 ± 0.8 cm vs. 1.2 ± 1.0 cm, $p<0.001$), but they showed significantly higher rates of bilaterality (29.6% vs. 22.1%, $p<0.001$) and multifocality (45.6% vs. 35.9%, $p<0.001$). The proportion of patients undergoing total thyroidectomy, the use of RAI therapy, and the extent of surgery were comparable between the groups. High-dose RAI was slightly more frequent in FNMTC (20.4% vs. 19.1%, $p=0.05$). The rates of extracapsular extension, central/lateral lymph node metastasis, and distant metastasis were similar in both groups. Although the overall recurrence rate was slightly lower in FNMTC (2.3% vs. 3.0%, $p=0.051$), this did not reach statistically significant. Most recurrences are locoregional. Importantly, overall survival was significantly higher in the FNMTC group (99.5% vs. 98.2%, $p<0.001$), with only 8 deaths in FNMTC patients, and only one attributed to thyroid cancer. The FNMTC group had a significantly shorter follow-up duration (45.6 ± 29.5 vs. 57.0 ± 42.8 months, $p<0.001$), which may limit long-term outcome comparisons (Table 9).

Table 9. Clinicopathologic characteristics, treatment modalities, and outcomes of SNMTC versus FNMTC in the intermediate-high-risk groups

Charateristics	Overall N = 29,678	SNMTC N = 27,161	FNMTC N = 2,517	p-value
Sex				<0.001
Male	6,205 (20.9%)	5,574 (20.5%)	631 (25.1%)	
Female	23,473 (79.1%)	21,587 (79.5%)	1,886 (74.9%)	
Age	44.5 ± 12.6	44.4 ± 12.6	45.0 ± 12.4	0.016
Age(group)				0.13
< 55 years	23,322 (78.6%)	21,374 (78.7%)	1,948 (77.4%)	
≥ 55 years	6,356 (21.4%)	5,787 (21.3%)	569 (22.6%)	
Thyroid function abnormal				
Hypothyroidism	151 (0.5%)	139 (0.5%)	12 (0.5%)	
Hyperthyroidism	615(2.1%)	572(2.1%)	43(1.7%)	
OP method				
Open	19,387 (65.3%)	17,779 (65.5%)	1,608 (63.9%)	
Minimal incision	3,301 (11.1%)	2,997 (11.0%)	304 (12.1%)	
Endoscopic	458 (1.5%)	430 (1.6%)	28 (1.1%)	
Robot	6,532 (22.0%)	5,955 (21.9%)	577 (22.9%)	
OP name				0.8
Lobectomy	10,817 (36.4%)	9,907 (36.5%)	910 (36.2%)	
Lobectomy + partial or subtotal	3,123 (10.5%)	2,865 (10.5%)	258 (10.3%)	
Bilateral total	15,738 (53.0%)	14,389 (53.0%)	1,349 (53.6%)	
Tumor size	1.2 ± 0.9	1.2 ± 1.0	1.0 ± 0.8	<0.001
Tumor size group				<0.001
≤ 10mm	17,523 (59.0%)	15,914 (58.6%)	1,609 (63.9%)	
10~20mm	8,807 (29.7%)	8,076 (29.7%)	731 (29.0%)	
20~40mm	2,667 (9.0%)	2,523 (9.3%)	144 (5.7%)	
>40mm	681 (2.3%)	648 (2.4%)	33 (1.3%)	
Bilaterality	6,735 (22.7%)	5,990 (22.1%)	745 (29.6%)	<0.001
Multiplicity	10,904 (36.7%)	9,755 (35.9%)	1,149 (45.6%)	<0.001

Extracapsular extension	23,879 (80.5%)	21,824 (80.4%)	2,055 (81.6%)	0.12
Pathology result				0.027
Papillary ca.	29,092 (98.0%)	26,609 (98.0%)	2,483 (98.6%)	
Follicular ca.	497 (1.7%)	465 (1.7%)	32 (1.3%)	
Oncocytic ca.	89 (0.3%)	87 (0.3%)	2 (0.1%)	
Aggressive pathology*	420 (1.4%)	390 (1.4%)	30 (1.2%)	0.3
CLN† metastasis	16,846 (56.8%)	15,378 (56.6%)	1,468 (58.3%)	0.1
LLN‡ metastasis	4,482 (15.1%)	4,119 (15.2%)	363 (14.4%)	0.3
Distant metastasis				0.6
None	29,478 (99.3%)	26,976 (99.3%)	2,502 (99.4%)	
Synchronous	139 (0.5%)	130 (0.5%)	9 (0.4%)	
Metachronous	61 (0.2%)	55 (0.2%)	6 (0.2%)	
Distant metastasis organ				0.5
Lung	168 (82.4%)	156 (83.0%)	12 (75.0%)	
Bone	25 (12.3%)	22 (11.7%)	3 (18.8%)	
Brain	3 (1.5%)	3 (1.6%)	0 (0.0%)	
Multiple	5 (2.5%)	4 (2.1%)	1 (6.3%)	
Other	3 (1.5%)	3 (1.6%)	0 (0.0%)	
RAIT§	14,215 (47.9%)	13,025 (48.0%)	1,190 (47.3%)	0.5
RAIT dose				0.05
No	15,204 (51.7%)	13,891 (51.6%)	1,313 (52.5%)	
Low dose	8,571 (29.1%)	7,891 (29.3%)	680 (27.2%)	
High dose	5,644 (19.2%)	5,134 (19.1%)	510 (20.4%)	
RAIT result				0.4
No & minimal uptake	14,126 (99.4%)	12,946 (99.4%)	1,180 (99.2%)	
Hot uptake	91 (0.6%)	81 (0.6%)	10 (0.8%)	
Recurrence	883 (3.0%)	824 (3.0%)	59 (2.3%)	0.051
Recurrence site				>0.9
Local	818 (90.2%)	763 (90.1%)	55 (91.7%)	
Distant	51 (5.6%)	48 (5.7%)	3 (5.0%)	
Local + distant	33 (3.6%)	31 (3.7%)	2 (3.3%)	

Survival				<0.001
Alive	19,858 (98.3%)	18,151 (98.2%)	1,707 (99.5%)	
Death	335 (1.7%)	327 (1.8%)	8 (0.5%)	
Cause of death				0.5
Thyroid cancer	81 (23.2%)	80 (23.5%)	1 (11.1%)	
Other cause	268 (76.8%)	260(76.5%)	8 (88.6%)	
Follow-up duration	56.0 ± 41.9	57.0 ± 42.8	45.6 ± 29.5	<0.001

Aggressive pathology* : Hobnail, Tall cell, Columnar cell, Diffuse sclerosing variant
CLN† : Central lymph node LLN‡ :Lateral lymph node RAIT§ : Radioactive iodine treatment

3.1.5. Recurrence-free survival analysis of FNMTC and SNMTC

Patients who underwent surgery between 1990 and 2019 were selected for recurrence-free survival analysis (N=32,976). Univariate and multivariate analyses were performed to identify factors associated with recurrence and determine the risk factors affecting disease-free survival (DFS).

As seen in Table 10, a family history of thyroid cancer is independently associated with a significantly increased risk of recurrence (HR = 1.55, 95% CI: 1.16–1.91, p = 0.03). Among surgical extent categories, bilateral total thyroidectomy was associated with a significantly reduced risk of recurrence compared to lobectomy (HR = 0.27, 95% CI: 0.13–0.56, p < 0.001). In contrast, lobectomy with partial or subtotal completion did not show a significant difference (HR = 0.68, p = 0.4). Tumor size was also a significant risk factor, with increasing size correlating with higher recurrence risk (HR = 1.41, 95% CI: 1.10–1.82, p = 0.008). The presence of extracapsular extension demonstrated a strong association with recurrence (HR = 4.46, 95% CI: 1.70–11.7, p = 0.002), as did central lymph node metastasis (HR = 6.73, 95% CI: 2.88–15.7, p < 0.001), indicating these are potent independent predictors of poor DFS. Other variables, including sex, age, bilaterality, multiplicity, and lateral lymph node metastasis, were not statistically significant in the multivariate model.

Table 10. Cox proportional multivariate risk analysis of clinical and pathological variables for disease-free survivals in all patients

Total patients (N=32,976)	HR	p-value	95% CI	
Family history	1.55	0.03	1.16	1.91
Sex(female)	1.12	0.7	0.58	2.15
Age	0.47	0.12	0.19	1.21
Op range				
Lobectomy	Ref.			
Lobectomy + partial or subtotal	0.68	0.4	0.27	1.73
Bilatetal total	0.27	<0.001	0.13	0.56
Tumor size	1.41	0.008	1.10	1.82
Extracapsular extension	4.46	0.002	1.70	11.7
Bilaterality	0.68	0.5	0.25	1.85
Multiplicity	1.14	0.8	0.51	2.55
CLN* metastasis	6.73	<0.001	2.88	15.7
LLN† metastasis	1.69	0.2	0.79	3.58

CLN* : central lymph node LLN† : lateral lymph node

Table 11. Cox proportional multivariable competing risk analysis of clinical and pathological variables for disease-free survival in the low-risk group

Low-risk patients (N=11,416)	HR	p-value	95% CI	
Family history	1.94	0.075	0.93	4.03
Sex(female)	0.77	0.3	0.46	1.31
Age	1.08	0.8	0.66	1.77
Op range				
Lobectomy	Ref.			
Lobectomy + partial or subtotal	0.8	0.3	0.54	1.19
Bilatetal total	0.25	0.001	0.14	0.42
Bilaterality	0.81	0.6	0.34	1.94
Multiplicity	1.38	0.2	0.83	2.32
Lymph node metastasis	12.1	0.001	4.62	31.5

Table 12. Cox proportional multivariable competing risk analysis of clinical and pathological variables for disease-free survival in the intermediate-high-risk group

Indetermediate-high-risk patients (N=21,560)	HR	p-value	95% CI	
Family history	1.65	<0.001	1.23	2.21
Sex(female)	0.6	<0.001	0.51	0.71
Age	1.08	0.8	0.66	1.77
Op range				
Lobectomy	Ref.			
Lobectomy + partial or subtotal	0.66	0.002	0.50	0.86
Bilatetal total	0.52	<0.001	0.42	0.63
Extracapsular extension	1.47	<0.001	1.22	1.77
Bilaterality	1.26	0.06	0.99	1.61
Multiplicity	1.3	0.02	1.04	1.63
Lymph node metastasis	2.95	<0.001	2.43	3.58

To evaluate the recurrence risk according to the ATA risk category, multivariate Cox proportional competing risk analyses were performed separately in the low- and intermediate-to-high-risk groups (Tables 11 and 12). In the low-risk group (Table 11), total thyroidectomy was independently associated with a significantly lower risk of recurrence compared to lobectomy (HR = 0.25, p = 0.001). Lymph node metastasis was a strong predictor of recurrence (HR = 12.1, p = 0.001), whereas other factors—including family history, sex, age, bilaterality, and multiplicity—did not reach statistical significance.

Several variables were independently associated with recurrence in the intermediate-to-high-risk group (Table 12). Family history (HR = 1.65, p < 0.001), extracapsular extension (HR = 1.47, p < 0.001), multiplicity (HR = 1.30, p = 0.02), and lymph node metastasis (HR = 2.95, p < 0.001) were significant risk factors. Female sex was associated with a lower risk (HR = 0.60, p < 0.001), and both subtotal and total thyroidectomies were protective compared to lobectomies.

These findings suggest that the impact of certain risk factors such as family history and lymph node metastasis may differ in strength and significance depending on the underlying risk category, highlighting the importance of risk-adapted recurrence surveillance.

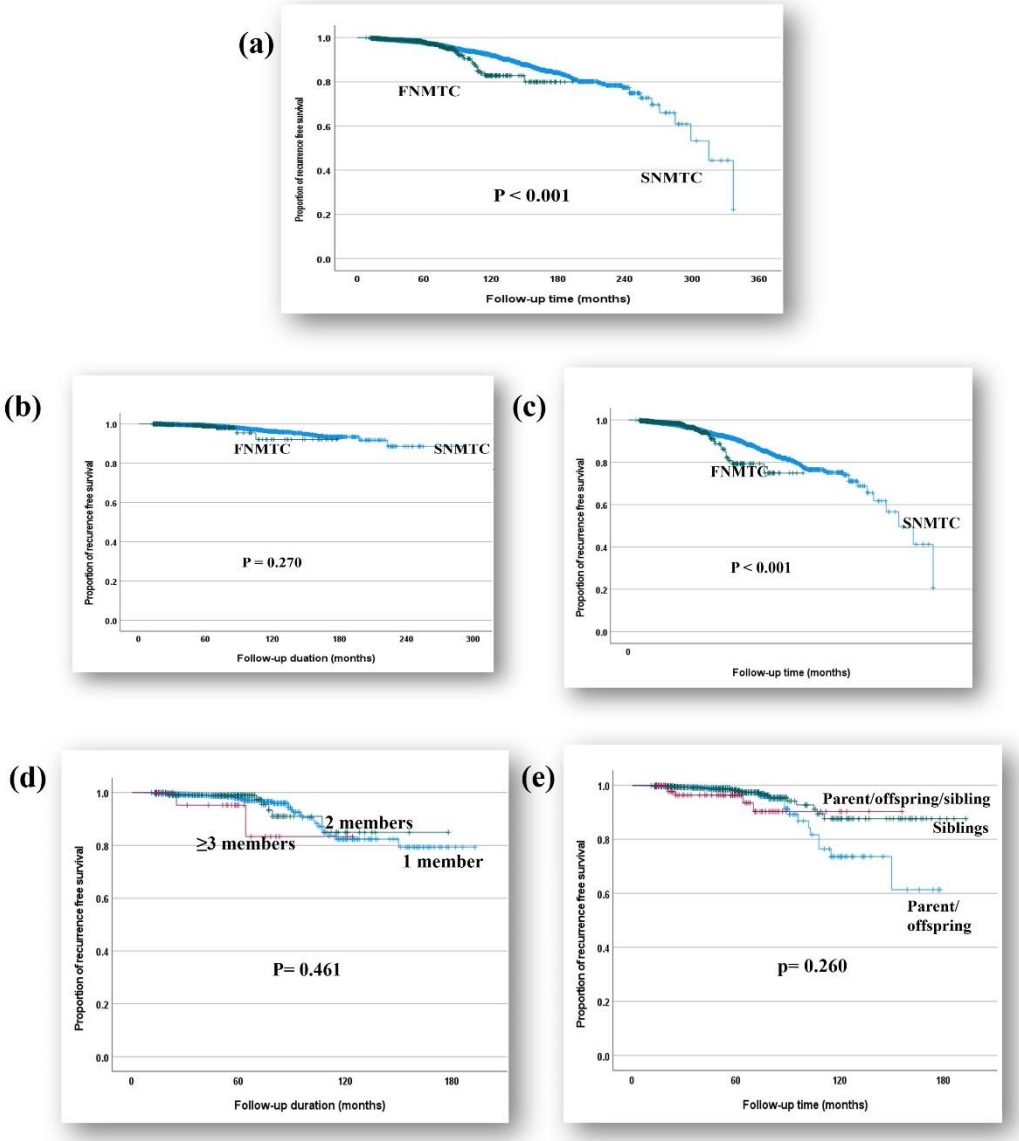


Figure 6 (a) Recurrence-free survival curves of FNMTC and SNMTC (b) Recurrence-free survival curves of the low-risk group (c) Recurrence-free survival curves of in the intermediate-high-risk group (d) Recurrence-free survival curves of the patient/offspring, sibling, and parent/offspring/sibling type patients with FNMTC (e) Recurrence-free survival curves of affected member type patients with FNMTC

3.2. National Cohort Analysis

3.2.1. Comparison of thyroid cancer group versus no history of any cancer group

Data from 172,479 individuals were analyzed to compare the sociodemographic and clinical characteristics of individuals with thyroid cancer (n = 941) and those without a history of cancer (n = 167,210). Given the substantial difference in sample sizes between the groups, PSM was performed at a 1:5 ratio based on age and sex, resulting in a matched cohort of 941 patients with thyroid cancer and 4,705 non-cancer controls.

Before matching, individuals with thyroid cancer differed significantly from the non-cancer controls in terms of multiple variables. They were shorter in height (158.4 ± 6.98 vs. 160.6 ± 8.12 cm, $p<0.0001$), weighed less (59.5 ± 8.68 vs. 61.9 ± 9.94 kg, $p<0.0001$), and had lower waist circumference, systolic and diastolic blood pressure, waist-to-hip ratio, and total cholesterol levels. They also had significantly lower rates of diabetes ($p = 0.0243$), hypertension ($p = 0.0499$), and myocardial infarction ($p = 0.0775$) but a higher prevalence of thyroid disease (24.3% vs. 4.5%, $p<0.0001$). Multiple laboratory markers, including creatinine, LDL, glucose, and albumin, were also significantly different between the groups.

After PSM, age and sex were balanced between the two groups (both $p>0.4$) and many of the previously observed differences were reduced or no longer significant. For example, BMI and waist circumference were comparable ($p=0.6434$ and 0.7235, respectively), and the differences in diabetes ($p = 0.2953$) and stroke ($p = 0.9996$) were no longer statistically significant. However, hypertension was significantly more prevalent in the thyroid cancer group (21.9% vs. 17.9%, $p = 0.0038$) than in hypercholesterolemia (8.3% vs. 4.8%, $p = 0.0002$). Total cholesterol, LDL, and HDL levels were also significantly higher in the non-cancer controls, even after matching.

Importantly, thyroid disease remained significantly more prevalent in the thyroid cancer group post-matching (24.3% vs. 6.3%, $p < 0.0001$), and the proportion of patients meeting 3–5 metabolic syndrome criteria was slightly higher in the cancer group, although this difference was modest ($p = 0.0447$). (Table 13).

As presented in Table 14, significant differences in lifestyle and health-related factors were observed between individuals with thyroid cancer and those without a history of cancer, both before and after PSM.

Table 13. Comparison of sociodemographics and clinical characteristics between thyroid cancer and no cancer history persons

	Before PSM*			After PSM		
	Thyroid cancer (n=941)	No cancer (n=167,210)	p-value	Thyroid cancer (n=941)	No cancer (n=4705)	p-value
Age(years)	52.97±7.48	53.02±8.36	0.8556	52.97±7.48	52.74±8.15	0.4195
Gender			<0.0001			1.000
Male	75 (7.97%)	57652 (34.48%)		75 (7.97%)	375 (7.97%)	
Female	866 (92.03%)	109558 (65.52%)		866 (92.03%)	4330 (92.03%)	
Height (cm)	158.4 ±6.98	160.6 ±8.12	<0.0001	158.4 ±6.98	157.4 ±6.24	<0.0001
Weight (kg)	59.51 ±8.68	61.88 ±9.94	<0.0001	59.51 ±8.68	58.76 ±8.47	0.0008
BMI(Kg/m$^{2)}$	23.79 ±2.89	23.85 ±2.91	0.0988	23.79 ±2.89	23.74±2.97	0.6434
Waist circumference (cm)	79.33 ±8.03	81.12 ±8.67	<0.0001	79.33 ±8.03)	79.23 ±8.39	0.7235
SBP(mmHg)	120.7 ±14.41	122.7 ±15.48	<0.0001	120.7 ±14.41	121.6 ±15.54	0.1092
DBP(mmHg)	74.56 ±9.41	76.28 ±10.05	<0.0001	74.56 ±9.41	76.28 ±10.04	0.0658
Wait-to-hip ratio	0.84 ±0.06	0.86 ±0.07	<0.0001	0.84 ±0.06	0.84 ±0.06	0.9075
Diabetes mellitus	45 (4.78%)	11051 (6.61%)	0.0243	45 (4.78%)	265 (5.63%)	0.2953

Hypertension	206 (21.89%)	32365 (19.36%)	0.0499	206 (21.89%)	841 (17.87%)	0.0038
Hypercholesterolemia	113 (4.78%)	11051 (6.61%)	0.0243	113 (4.78%)	389 (8.27%)	0.0002
Stroke	8 (0.85%)	2037 (1.22%)	0.3042	8 (0.85%)	40 (0.85%)	0.9996
Myocardiac infaction	15 (1.59%)	4168 (2.49%)	0.0775	15 (1.59%)	102 (2.17%)	0.2593
Fatty liver	55 (5.84%)	9806 (5.87%)	0.9772	55 (5.84%)	206 (4.38%)	0.0507
Laboratory result						
AST (IU/L)	23.04 ±13.90	23.87 ±18.19	0.0698	23.04 ±13.90	22.67 ±10.71	0.3675
ALT (IU/L)	22.36 ±28.67	22.52 ±21.95	0.8710	22.36 ±28.67	20.60 ±25.86	0.0634
Albumin g/dL	4.58 ±0.26	4.64 ±0.27	0.0001	4.58 ±0.26	4.61 ±0.26	0.0004
Total cholesterol (mg/dL)	190.0 ±35.14	197.6 ±35.59	0.0001	190.0 ±35.14	199.0 ±35.80	0.0001
Triglycerides (mg/dL)	114.0 ±66.32	127.0 ±90.02	0.0001	114.0 ±66.32	115.8 ±74.91	0.5076
HDL-cholesterol (mg/dL)	53.71 ±13.13	54.01 ±12.92	0.4887	53.71 ±13.13	55.64 ±12.93	0.0001
LDL(mg/dL)	113.7 ±30.92	119.0 ±31.93	0.0001	113.7 ±30.92	120.7 ±32.15	0.0001
Glucose (mg/dL)	93.55 ±14.79	95.19 ±21.63	0.0008	93.55 ±14.79	93.59 ±19.40	0.9514
Creatinine	0.73 ±0.20	0.82±0.23	0.0001	0.73 ±0.20	0.77 ±0.024	0.0001
Metabolic						

syndrome criteria						
1~2 factor	313 (33.26%)	57338 (34.29%)	0.5074	313 (33.26%)	1727 (36.71%)	0.0447
3~5 factor	628 (66.74%)	109872 (65.71%)		628 (66.74%)	2978 (63.29%)	
Thyroid disease diagnosis	229 (24.34%)	7544 (4.51%)	0.0001	229 (24.34%)	294 (6.25%)	0.0001
Thyroid disease			0.7260			0.4882
Hyperthyroidism	55 (51.40%)	1625 (53.12%)		55 (51.40%)	65 (56.03%)	
Hypothyroidism	52 (48.60%)	1434 (46.88%)		52 (48.60%)	51 (43.97%)	
Mean age at diagnosis	46.43 ±8.05	45.23 ±11.01	0.0335	46.43 ±8.05	44.48 ±10.96	0.0279

PSM* : Propensity Score Matching

Before matching, the thyroid cancer group had higher rates of regular physical activity (59.2% vs. 52.4%, $p < 0.0001$) and current alcohol consumption (69.3% vs. 50.4%, $p = 0.0001$) but lower rates of current smoking (1.8% vs. 12.0%, $p < 0.0001$). The thyroid cancer group also consumed less sodium (Na) and fat, and had lower levels of physical activity (e.g., fewer were classified as highly active). Despite these behavioral differences, energy, carbohydrate, and protein intake were comparable between the groups. However, after matching, some differences persisted. The thyroid cancer group continued to show significantly higher levels of regular physical activity (59.2% vs. 50.8%, $p < 0.0001$) and current alcohol consumption (69.3% vs. 61.7%, $p < 0.0001$). Notably, the differences in exercise frequency and physical activity levels were attenuated and no longer statistically significant. Sodium intake remained lower in the thyroid cancer group ($p = 0.0470$). The rate of prior cancer screening was significantly lower in the thyroid cancer group after matching (15.6% vs. 27.0%, $p = 0.0009$). Among reasons for screening, thyroid cancer patients more often reported abnormal symptoms as a triggers (23.5% vs. 12.7%, $p = 0.0013$), suggesting a more symptom-driven pathway to diagnosis.

Table 14. Comparison of lifestyle and health-related factors between thyroid cancer and no cancer history persons

	Before PSM*			After PSM		
	Thyroid cancer (n=941)	No cancer (n=167,210)	p-value	Thyroid cancer (n=941)	No cancer (n=4705)	p-value
Regular physical activity	556 (59.15%)	87163 (52.38%)	<0.0001	556 (59.15%)	2379 (50.75%)	<0.0001
Exercise Frequency			0.0115			0.2005
1-2 times per week	119 (21.76%)	23114 (27.61%)		119 (21.76%)	591 (25.76%	
3-4 times per week	219 (40.40%)	30858 (36.86%)		219 (40.40%)	845 (36.84%)	
5-6 times per week	118 (21.57%)	15496 (18.51%)		118 (21.57%)	461 (20.01%)	
Daily	91 (16.64%)	14259 (17.03%)		91 (16.64%)	397 (17.31%)	
Physical activity levels			0.0018			0.1626
Inactive	6(0.75%)	492 (0.48%)		6(0.75%)	14 (0.49%)	
Low activity	145 (18.15%)	20084 (15.94%)		145 (18.15%)	547 (19.24%)	
Active	72 (9.01%)	68798 (66.95%)		72 (9.01%)	322 (11.33%)	
Highly active	4 (2.72%)	13385 (13.03%)		4 (2.72%)	149 (11.73%)	
Nutrient consumption						
Energy intake (kcal)	1776.1 ±593.3	1811.9 ±599.3	0.0690	1776.1 ±593.3	1771.9 ±610.2	0.8486
Carbohydrate (g)	326.4 ±101.5	328.7 ±100.1	0.4860	326.4 ±101.5	323.2 ±103.3	0.3925

Protein (g)	57.20 ±24.47	58.30 ±26.32	0.1706	57.20 ±24.47	56.97 ±25.67	0.8063
Fat (g)	24.99 ±16.36	26.89 ±18.64	0.0004	24.99 ±16.36	25.82 ±18.73	0.1945
Na (mg)	1838.2 ±1129.3	1974.2 ±1190.3	0.0003	1838.2 ±1129.3	1920.4 ±1156.3	0.0470
Fiber (g)	25.08 ±10.48	24.63 ±10.31	0.1791	25.08 ±10.48	24.79 ±10.79	0.4373
Cholesterol (mg)	143.5 ±102.4	143.8±109.4	0.9248	143.5 ±102.4	141.0 ±107.9	0.5222
Smoking status			<.0001			0.1621
Never	204 (93.15%)	63639 (74.29%)		204 (93.15%)	2255 (92.00%)	
Past	11 (5.02%)	11764 (13.73%)		11 (5.02%)	93 (3.79%)	
Current	4 (1.83)	10261 (11.98%)		4 (1.83)	103 (4.20%)	
Alcohol behaviour			0.0001			<0.0001
Current	649 (69.34%)	83900 (50.38%)		649 (69.34%)	2885 (61.71%)	
Past	37 (3.95%)	6368 (3.83%)		37 (3.95%)	124 (2.65%)	
Never	250 (26.71%)	76162 (45.79%)		250 (26.71%)	1666 (35.64%)	
Previous cancer screening status (yes)	143 (15.60%)	27950 (16.73%)	<0.0001	143 (15.60%)	1270 (26.99%)	0.0009
Reason for cancer screening			0.0004			0.0013
Felt abnormal symptom	27 (23.48%)	3576 (12.79%)		27 (23.48%)	105 12.74%)	
No symptoms, but concerned about health	36 (31.30%)	10056 (35.98%)		36 (31.30%)	310 (37.62%)	
Notified by national health insurance	43(37.39 %)	11954 (42.77%)		43(37.39 %)	357 (43.33%)	

Workplace health check-up	4 (3.48%)	1733 (6.20%)	4 (3.48%)	35 (4.25%)
Recommended by doctor	4 (3.48%)	213 (0.76%)	4 (3.48%)	4 (0.49%)
Other	1 (0.87%)	418 (1.50%)	1 (0.87%)	2 (0.24%)

PSM* : Propensity Score Matching

Table 15. Risk estimation of thyroid cancer by multivariable stratified Cox regression analysis before propensity score matching(PSM)

	OR(95% CI)	p-value
Sex(female)	11.858 (7.794~17.635)	<.0001
Age	1.020 (1.009-1.031)	0.005
Weight	1.045 (1.024~1.065)	<.0001
BMI	0.906 (0.858~0.958)	<.0001
Hemoblobin	1.088 (1.011~1.171)	0.0242
Albumin	0.0660 (0.481~0.905)	0.0099
Creatinine	0.558 (0.287~1.082)	0.0844
Total cholesterol	0.993 (0.990~0.995)	<.0001

Multivariate stratified Cox regression analyses were conducted to identify independent risk factors for thyroid cancer both before (Table 15) and after (Table 16) PSM. Before PSM, several variables were found to be significantly associated with thyroid cancer. Being female was the strongest risk factor (OR, 11.86; 95% CI: 7.79–17.64, $p < 0.0001$). Increased age, weight, and hemoglobin levels were also positively associated with thyroid cancer, whereas higher BMI and albumin and total cholesterol levels were inversely associated with the risk. Creatinine levels showed a borderline inverse association ($p = 0.0844$). After PSM, the presence of a prior thyroid disease diagnosis remained a strong independent predictor of thyroid cancer (OR: 3.28, 95% CI: 2.51–4.29, $p < 0.001$). History of past alcohol consumption was inversely associated with thyroid cancer (OR: 0.70, $p < 0.001$), whereas current alcohol consumption showed a positive association (OR: 1.68, $p = 0.004$). Higher albumin levels continued to be associated with a reduced risk (OR: 0.69, $p = 0.049$). Other

variables including BMI, hypertension, smoking status, and metabolic disease were not significantly associated with thyroid cancer after matching.

These results suggest that, even after controlling for age and sex, factors such as thyroid disease history, alcohol consumption, and albumin levels remain significantly associated with thyroid cancer risk.

Table 16. Risk estimation of thyroid cancer by multivariable stratified Cox regression analysis after propensity score matching(PSM)

	OR(95% CI)	p-value
BMI	1.013(0.980-1.047)	0.431
Hypertension	1.164(0.924-1.466)	0.197
Smoke		
Never	Ref.	
Past	1.135(0.744-1.731)	0.190
Current	0.680(0.398-1.161)	0.114
Drink		
Never	Ref	
Past	0.695(0.568-0.852)	<0.001
Current	1.681(0.141-2.716)	0.004
Thyroid disease history	3.279(2.505-4.293)	<0.001
Albumin	0.688(0.475-0.998)	0.049
Creatinine	0.887(0.593-1.327)	0.559
Total cholesterol	0.998(0.989-1.006)	0.579
HDL cholesterol	0.997(0.987-1.006)	0.485
LDL cholesterol	0.997(0.988-1.005)	0.458
Metabolic disease	1.062(0.847-1.332)	0.601

3.2.2. Thyroid cancer group analysis

Among the 172479 individuals in the KoGES database, 941 were diagnosed with TC. Among them, 54 were F-TC and 887 were S-TC. F-TC cases were more prevalent in younger age groups (40-49), whereas S-TC cases were more prevalent in middle-aged individuals (50-59). The prevalence of thyroid cancer was higher in women in both F-CT and S-TC groups. F-TC cases were rare in individuals over 60 years old, whereas S-TC cases remained prevalent in older age groups (Table 17).

Table 17. Age-specific prevalence of familial and sporadic thyroid cancer (prevalence, %)

	F-TC			S-TC		
	Total	Male	Female	Total	Male	Female
Age	N	male	female	N	N	N
40~44	13(1.38)	1(1.33)	12(1.39)	131(13.92)	10(13.33)	121(13.97)
45~49	21(2.23)	1(1.33)	20(2.31)	161(17.11)	10(13.33)	151(17.44)
50~54	13(1.38)	0	13(1.5)	233(24.76)	13(17.33)	220(25.4)
55~59	5(0.53)	1(1.33)	4(0.46)	167(17.74)	10(13.33)	157(18.13)
60~64	1(0.11)	0	1(0.12)	124(13.18)	12(16)	112(12.93)
65~69	1(0.11)	0	1(0.12)	62(6.59)	14(18.67)	48(5.54)
70~74	0	0	0	9(0.96)	3(4)	6(0.69)
75~79	0	0	0	0	0	0
total	54(5.74)	3(4)	51(5.89)	887(94.26)	72(96)	815(94.11)

In Table 18, we describe the sociodemographic and clinical characteristics of the participants, including 54 patients with F-TC and 887 S-TC controls. We comprehensively compared sociodemographic and anthropometric characteristics, metabolic and clinical conditions, laboratory

findings, metabolic profiles, thyroid disease status, surgical history, and other cancers between the two groups. As a result of this comparison, within metabolic and clinical conditions, fatty liver was found in 12.96% of F-TC cases and 5.41% of S-TC cases, showing a significant difference (p=0.0216), suggesting a higher prevalence in sporadic thyroid cancer patients. Additionally, AST levels were significantly higher in S-TC cases (23.18±14.26 IU/L vs. 20.75±4.75 IU/L, p=0.0034). ALT levels were also higher in S-TC cases (22.54±29.46 IU/L vs. 19.40±8.04 IU/L, p=0.0359). No significant differences were observed in the prevalence of metabolic syndrome, blood lipid levels, history of thyroid disease, or prior cancer diagnosis. Both groups had similar clinical, anthropometric, and metabolic parameters. These results suggest that while F-TC and S-TC patients share similar metabolic and clinical profiles, certain liver-related factors (fatty liver, AST, and ALT) may differ. Further studies are required to explore the clinical significance of these findings.

No significant differences were observed in physical activity levels, exercise frequency, or dietary intake between the F-TC and S-TC groups. Smoking behavior was similar between the groups; however, alcohol consumption was significantly higher in the F-TC patients (p=0.0146). Most patients had undergone cancer screening, with no significant differences in screening history or reasons for screening. These findings suggest that lifestyle factors, including diet and physical activity, do not significantly differ between patients with sporadic and familial thyroid cancers. However, alcohol consumption may be more prevalent in familial thyroid cancer, warranting further investigation (Table 19).

Table. 18 Comparison of sociodemographics and clinical characteristics between sporadic(S-TC) and familial(F-TC) thyroid cancer patients.

	F-TC (n=54)	S-TC (n=887)	p-value
Age(years)	51.43(±6.40)	53.07(±7.53)	0.1177
Gender			0.7998
Male	3(5.56%)	72 (8.12%)	
Female	51(94.44%)	815(91.88%)	
Height (cm)	158.9 (±5.97)	158.3 (±7.04)	0.5363
Weight (kg)	59.87 (±9.40)	59.48 (±8.63)	0.7563
Body Mass Index (Kg/m^2)	23.83 (±3.24)	23.79 (±2.87)	0.9149
Waist circumference (cm)	77.94 (±8.27)	49.42 (±8.01)	0.1924
Systolic blood pressure (mmHg)	121.5 (±14.02)	120.6 (±14.44)	0.6583
Diastolic blood pressure (mmHg)	79.79 (±8.93)	74.48 (±9.44)	0.32
Wait-to-hip ratio	0.83 (±0.06)	0.84 (±0.06)	0.1185
Diabetes mellitus	1 (1.85%)	44 (4.96%)	0.2986
Hypertension	12 (22.22%)	194 (21.87%)	0.9517
Hypercholesterolemia	9 (16.67%)	104 (11.72%)	0.2781
Stroke	0 (0.0%)	8 (0.90%)	0.4834
Myocardial infarction	0 (0.0%)	15 (1.69%)	0.3354
Fatty liver	7 (12.96%)	48 (5.41%)	0.0216
Laboratory result			
AST (IU/L)	20.75 (±4.75)	23.18 (±14.26)	0.0034
ALT (IU/L)	19.40 (±8.04)	22.54 (±29.46)	0.0359
Albumin g/dL	4.56 (±0.24)	4.58 (±0.26)	0.7369
Total cholesterol (mg/dL)	187.3 (±30.40)	190.1 (±35.42)	0.5694
Triglycerides (mg/dL)	108.8 (±64.35)	114.3 (±66.46)	0.5529
HDL-cholesterol (mg/dL)	52.81 (±11.58)	53.77 (±13.22)	0.6044
LDL-cholesterol (mg/dL)	112.8 (±26.89)	113.8 (±31.16)	0.8104
Fasting blood glucose(mg/dL)	92.25 (±13.94)	93.63 (±14.84)	0.5081

Metabolic syndrome criteria			
1~2 factor	16 (29.63)	297 (33.48)	0.5595
3~5 factor	38 (70.37)	590 (66.52)	
Thyroid disease diagnosis	12 (22.22%)	217 (24.46%)	0.7093
Thyroid disease			
Hyperthyroidism	2 (28.57%)	53 (53.00%)	0.2113
Hypothyroidism	5 (71.43%)	47 (47.00%)	
Mean age at diagnosis	45.92 (±6.65)	46.46 (±8.14)	0.8212
Other operation history	14(33.3%)	235(35.07%)	0.2567
Cholecystectomy	2(14.28%)	4(1.70%)	
Liver	0	1(0.43%)	
Breast	0	13(5.53%)	
Prostate	0	1(0.43%)	
Other	12(85.71%)	211(89.78%)	
Other cancer (previous diagnosed)	1(1.85%)	38(4.28%)	0.655
Stomach	0	0	
Liver	0	0	
Colon & rectum	0	3(7.89%)	
Breast	0	19(50%)	
Uterus & cervix	0	9(23.68%)	
Lung	0	5(13.16%)	
Bladder	0	0	
other	1(100%)	2(5.26%)	

Table 19. Comparison of lifestyle and health-related factors between sporadic(S-TC) and familial(F-TC) thyroid cancer patients

	F-TC (n=54)	S-TC (n=887)	p-value
Regular physical activity	30 (55.56%)	528 (59.37%)	0.58
Exercise Frequency			
1-2 times per week	5 (16.67%)	114 (22.05%)	0.562
3-4 times per week	15 (50.00%)	204 (39.46%)	
5-6 times per week	7 (23.33%)	111 (21.47%)	
Daily	3 (10.00%)	88 (17.02%)	
Physical activity levels			
Inactive	1 (2.00%)	5 (0.67%)	0.1731
Low activity	14 (28.00%)	131 (17.49%)	
Active	32 (64.00%)	544 (72.63%)	
Highly active	3 (6.00%)	69 (9.21%)	
Nutrient consumption			
Energy intake (kcal)	1785.2 (±485.3)	1775.5 (±599.4)	0.908
Carbohydrate (g)	330.1 (±86.27)	326.1 (±102.4)	0.7843
Protein (g)	56.53 (±19.22)	57.24 (±24.76)	0.8376
Fat (g)	24.51 (±14.47)	25.02 (±16.47)	0.8272
Na (mg)	1785.5 (±905.4)	1841.4 (±1141.8)	0.7267
Fiber (g)	24.93 (±8.91)	25.09 (±10.57)	0.9125
Cholesterol (mg)	135.4 (±73.45)	1440. (±103.9)	0.4259
Smoking status			
Never	10 (100.0%)	194 (92.82%)	0.6803
Past	0 (0.00)	11 (5.26%)	
Current	0 (0.00)	4 (1.91%)	
Alcohol behaviour			
Never	32 (59.26%)	617 (69.95%)	0.0146
Past	6 (11.11%)	31 (3.51%)	
Current	16 (29.63%)	234 (26.53%)	

Previous cancer screening status (yes)	8(100%)	135(97.12%)	0.6266
Reason for cancer screening			
Felt abnormal symptom	1 (14.29)	26 (24.07)	0.3314
No symptoms, but concerned about health	5 (71.43)	31 (28.70)	
Notified by the national health insurance	1 (14.29)	42 (38.89)	
Workplace health check-up	0 (0.00)	4 (3.70)	
Recommended by the doctor	0 (0.00)	4 (3.70)	
Other	0 (0.00)	1 (0.93)	

Table 20. Risk estimation of family history of thyroid cancer by multivariable stratified Cox regression analysis

	OR(95% CI)	p-value
Sex	1.04(0.99-1.10)	0.118
Age	1.00(1.00-1.01)	0.194
Fatty liver	2.20 (1.01~4.75)	0.0461
Alcohol consumption		
Never	Ref.	
Past	2.03 (1.03~4.02)	0.032
Current	0.94 (0.56~1.58)	0.1441
AST (IU/L)	0.96 (0.91~1.01)	0.1101
ALT (IU/L)	0.99 (0.95~1.02)	0.4302

As seen in Table 20, the significant risk factor analysis results are presented by comparing F-CT and S-TC based on variables identified in the univariate analysis. The fatty liver was associated considerably with F-TC (p = 0.0461), suggesting a potential metabolic link to F-TC. Past alcohol consumption was significantly associated with F-TC (OR = 2.03, 95% CI: 1.03–4.02, p = 0.032), whereas current alcohol consumption was not significantly different. These findings suggest that familial thyroid cancer is primarily driven by genetic predisposition and may be more influenced by metabolic factors such as fatty liver and post-alcohol consumption. Further studies are needed to explore the biological mechanisms underlying these associations.

3.3 Institutional cohort analysis: thyroid cancer group analysis

Comparison of baseline characteristics between F-TC (n = 885) and S-TC (n = 10,258) patients revealed several statistically significant differences. F-TC patients were significantly taller (p = 0.001) and heavier (p = 0.008) than S-TC patients, although BMI did not differ between the groups. The F-TC group had a significantly lower prevalence of diabetes mellitus (2.7% vs. 6.0%, p = 0.004) and hypertension (12.1% vs. 19.3%, p = 0.002). Hemoglobin levels were slightly higher in the F-TC group (13.56 vs. 13.41 g/dL, p = 0.001). No significant differences were observed in the blood pressure, liver enzymes (AST and ALT), lipid profile, fasting glucose, or creatinine levels. These findings suggest that patients with familial thyroid cancer may have a more favorable cardiometabolic profile at diagnosis than patients with sporadic thyroid cancer (Table 21).

As shown in Table 22, multivariate stratified Cox regression analysis was conducted to identify the clinical factors associated with a family history of thyroid cancer. Among the variables analyzed, hypertension was significantly associated with lower odds of having a family history of thyroid cancer (OR, 0.667; 95% CI, 0.454–0.981; p = 0.040), suggesting an inverse relationship.

Other variables—including height, weight, hemoglobin level, and diabetes mellitus—were not significantly associated with a family history of thyroid cancer. Diabetes showed a borderline association (OR, 0.624; p = 0.061), warranting further investigation in a larger cohort.

These findings suggest that traditional metabolic comorbidities, such as hypertension, may be less prevalent in familial thyroid cancer, supporting earlier results indicating a more favorable metabolic profile in this group.

Table 21. Comparison of baseline clinical and laboratory characteristics between familial(F-TC) and sporadic(S-TC) patients

	F-TC (n=885)	S-TC (n=10258)	p-value
Age(years)	51.98 (±8.04)	52.35 (±8.44)	0.364
Gender			0.072
Male	166 (18.8%)	1679 (16.4%)	
Female	719 (81.2%)	8579 (83.6%)	
Height (cm)	160.91 ±7.33	159.85 ±7.28	0.001
Weight (kg)	62.26 ±10.17	61.37 ±9.97	0.008
BMI (Kg/m^2)	23.98 ±3.01	23.97 ±3.16	0.741
Systolic blood pressure (mmHg)	125.79 ±15.28	125.24±15.34	0.421
Diastolic blood pressure (mmHg)	78.21 ±10.93	78.38 ±10.91	0.766
Diabetes Mellitus	24 (2.71%)	616 (6.01%)	0.004
Hypertension	107(12.10%)	1980 (19.30%)	0.002
Laboratory result			
Hemoglobin (g/dL)	13.56 (±1.42)	13.41 (±1.39)	0.001
AST (IU/L)	20.01 (±8.03)	20.32 (±8.38)	0.504
ALT (IU/L)	19.60 (±11.69)	20.43 (±13.96)	0.275
Total cholesterol (mg/dL)	188.42 (±32.61)	190.28 ±35.42)	0.123
Triglycerides (mg/dL)	126.96 (±51.49)	123.08 (±67.28)	0.286
HDL-cholesterol (mg/dL)	55.28 (±12.73)	52.00 (±12.49)	0.091
LDL-cholesterol (mg/dL)	120.96 (±33.29)	118.46 (±36.53)	0.461
Fasting blood glucose(mg/dL)	100.45 (±22.02)	99.22 (±19.10)	0.348
Creatinine(mg/dL)	0.76 (±0.37)	0.75 (±0.19)	0.243

Table 22. Risk estimation of family history of thyroid cancer by multivariable stratified Cox regression analysis

	OR(95% CI)	p-value
Height	1.021(0.987-1.058)	0.230
Weight	0.995(0.974-1.017)	0.656
Hemoblobin	0.960(0.832-1.106_	0.570
Hypertension	0.667(0.454-0.981)	0.040
DM	0.624(0.381-1.022)	0.061

4. DISCUSSION

With the increasing incidence of thyroid cancer, the number of patients with FNMTC has also increased. The present study showed that FNMTC accounted for a significant proportion of NMTC cases, with a prevalence of 8.2% in the total NMTC cohort. The reported prevalence of FNMTC is 3–9% of all thyroid cancers (18, 20, 24). Several large population-based studies have documented a higher risk of developing the same type of cancer in patients' relatives. In some cohorts, thyroid cancer has been reported to have the highest risk among all cancer types. FNMTC includes two or more first-degree relatives with NMTC without other known associated cancers (41). FNMTC is defined as differentiated thyroid cancer that occurs in at least two first-degree relatives, including the index patient, without other predisposing causes of thyroid cancer (24). However, this definition is controversial because in the case of only two affected members, there may present a cluster of 2 sporadic tumors with a probability of 62% to 66% (25). On the other hand, families with three or more affected members are rare and account for less than 5% of the major FNMTC series. In this study, patients were classified as having FNMTC if they had at least one first-degree relative with the disease. The prevalence of patients with two affected first-degree relatives, including the patient, was 7.31%, while the prevalence of those with three or more affected first-degree relatives was 0.8%. As reported by Park et al. and others, the diagnosis of thyroid cancer in Korea increased sharply in the early 2000s. However, after the debate on the overdiagnosis of thyroid cancer, which was

highlighted in the New England Journal of Medicine, the number of diagnoses temporarily declined. Since the late 2010s, its incidence has increased steadily. The number of thyroid cancer surgeries performed at our institution showed a similar trend. As the diagnosis of thyroid cancer has increased, the proportion of patients with FNMTC has also increased (2, 8). Our study also highlighted notable sex differences in the prevalence and inheritance of FNMTC. This disease is more common in women, which is consistent with the well-documented higher incidence of thyroid cancer in women. The proportion of FNMTC cases has also increased over time, particularly after 2014, although the total number of surgeries has decreased. This trend suggests that familial thyroid cancer cases may have remained relatively stable or even increased in incidence, highlighting the need for enhanced screening of at-risk individuals.

Our study also highlighted notable sex differences in the prevalence and inheritance of FNMTC. This disease is more common in women, which is consistent with the well-documented higher incidence of thyroid cancer in women. However, male patients with FNMTC exhibited a slightly higher proportion of affected fathers and brothers than female patients. The most common familial relationship patterns involved female first-degree relatives, particularly sisters and mothers. Analysis of familial relationship distribution revealed that mother-sister pairs were the most frequently affected combinations, followed by sister-sister and brother-sister pairs. Parent-child combinations were comparatively rare, with the father-daughter pair being the least frequent. When analyzing cases with three affected family members, the most common pattern involved three sisters, further emphasizing the female predominance in familial thyroid cancer. Estrogen is considered a possible risk factor, given that more than three-quarters of those who contract thyroid cancer are women. However, the association between estrogen and thyroid cancer has not yet been elucidated (42).

The biological characteristics of the disease, including the prognosis of patients with a family history of DTC, remain controversial. Most studies have reported more aggressive disease at presentation, leading to worse outcomes in the FNMTC group. (33, 34) However, several studies reported more aggressive diseases at presentation with similar outcomes at the end of follow-up or identical baseline characteristics with similar or worse outcomes (35-39). Studies recommending extensive treatment for patients with a family history of DTC have reported no difference in prognosis between patients with FNMTC and those with SNMTC (43, 44). While numerous studies on familial DTC have been conducted, most have included heterogeneous patient cohorts with

significantly smaller familial groups. These cohorts may have posed several limitations in the linear analysis. This study was conducted on a large patient population and is meaningful in that it not only compared aggressiveness at the time of diagnosis, but also followed up on recurrence. The results of this study showed that tumors in FNMTC tended to be smaller, with a higher proportion of PTMCs measuring less than 1 cm. Additionally, the proportions of bilateral and extracapsular extensions were lower, whereas the rates of multiplicity and central lymph node metastasis were higher. Previous studies have reported aggressiveness and outcomes based on the number of affected family members, and some have recommended more invasive surgery for patients with three or more first-degree relatives.(33, 34, 36, 45) When FNMTC cases were categorized based on the number of affected family members, it was observed that as the number of affected family members increased, the rates of bilaterality and multiplicity decreased.

To enhance the clinical relevance of our findings and reduce the potential heterogeneity inherent in large cohort studies, we stratified the patients with FNMTC and SNMTC according to the ATA risk stratification system (15). This approach allowed us to contextualize clinicopathological differences within clinically meaningful prognostic categories and examine whether family history exerted a differential influence depending on baseline recurrence risk. Risk stratification provides a more nuanced understanding of the behavior and outcomes of thyroid cancer. In the low-risk group, both FNMTC and SNMTC patients demonstrated excellent prognoses, with extremely low recurrence rates and no thyroid cancer-specific mortality. However, the significantly higher rates of bilaterality and multifocality in patients with FNMTC suggest that familial predisposition may contribute to more extensive local disease, independent of traditional prognostic indicators. In contrast, among intermediate-to high-risk patients, FNMTC was found to be associated with higher bilaterality and multifocality. Despite these locally invasive features, the tumor size is paradoxically smaller in patients with FNMTC. This observation may reflect earlier diagnosis due to increased surveillance in families with a known history of thyroid cancer or, alternatively, inherent differences in tumor growth dynamics. Extracapsular extension and central lymph node metastasis were also more common in patients with FNMTC in the overall cohort, although lateral lymph node and distant metastasis rates were comparable between the groups. These results suggest that, while FNMTC may present with more extensive local disease, the propensity for distant spread is similar to that of sporadic tumors.

There are three hereditary forms of FNMTC (parent/offspring, sibling, and parent/offspring/sibling), each with unique clinical characteristics. Park et al. reported that parent/offspring FNMTC exhibited more frequent extrathyroidal invasion and a higher recurrence rate than SNMTC in a classic study based on a large sample size. In contrast, sibling FNMTC exhibited a higher prevalence in women, smaller tumor size, and a higher incidence of Hashimoto's thyroiditis than SNMTC (33). Moreover, Cao et al. reported that despite an earlier onset of disease in the parent/offspring group, there were no other significant differences in the clinicopathological and outcome characteristics between the three hereditary forms of FNMTC (34). In this study, we divided patients with FNMTC according to their hereditary forms (parent/offspring, sibling, and parent/offspring/sibling types). There were no significant differences in the factors related to tumor aggressiveness. However, the sibling group had the highest average age and the parent/offspring/sibling group had the highest proportion of male patients.

There seems to be a lack of consensus concerning the impact of a family history of PTC on DFS. In this study, the recurrence-free survival analysis revealed that a family history of thyroid cancer was independently associated with an increased risk of recurrence across the entire cohort. This finding aligns with those of prior studies suggesting that familial tumors often exhibit multifocality, bilaterality, and a higher rate of local invasiveness, which may predispose them to recurrence even after initial treatment. When stratifying according to ATA risk categories, the impact of family history was more pronounced in the intermediate-to-high-risk group (HR =1.65, $p<0.001$) but was not statistically significant in the low-risk group (HR = 1.94, $p=0.075$). This suggests that the influence of familial predisposition on disease progression is more evident in the presence of other aggressive features. Consequently, patients with FNMTC in higher-risk strata may benefit from closer surveillance and more aggressive initial management strategies. Extracapsular extension, central lymph node metastasis, and multiplicity were identified as independent predictors of recurrence in both the general and intermediate-to-high-risk populations, consistent with the established prognostic models. Notably, lymph node metastasis had an exceptionally strong association with recurrence in low-risk patients (HR = 12.1, $p=0.0001$), indicating that even in this otherwise favorable subgroup, the presence of lymph node metastasis warrants careful postoperative follow-up.

Our results also revealed that certain risk factors exerted different influences depending on the baseline ATA risk category. While family history and multiplicity were significant in the

intermediate-to-high-risk group, they did not reach significance in the low-risk group. This finding underscores the importance of risk-adapted recurrence surveillance strategies and suggests tailoring the follow-up intensity and therapeutic planning, particularly for patients with familial disease.

In this large-scale, population-based cohort study using the KOGES dataset, we investigated the clinical and metabolic profiles of individuals with thyroid cancer compared to non-cancer controls and further delineated the differences between familial and sporadic cases of thyroid cancer. Individuals with thyroid cancer exhibit a distinctive metabolic and clinical profile compared to those without any history of cancer. Even after adjusting for age and sex using PSM, patients with thyroid cancer showed significantly higher rates of hypertension and hypercholesterolemia and a markedly increased prevalence of thyroid disease. These findings suggest that despite having a generally favorable anthropometric profile (lower BMI, waist circumference, and blood pressure), patients with thyroid cancer may harbor specific cardiometabolic alterations that contribute to tumorigenesis. Interestingly, traditional risk factors for cancer, such as obesity, DM, and smoking, were not positively associated with thyroid cancer after PSM. In fact, BMI and DM were either comparable or lower in the thyroid cancer group. This supports previous epidemiological studies that suggest a more complex and perhaps non-linear relationship between obesity and thyroid cancer risk, possibly modulated by hormonal or inflammatory pathways (46). Our multivariate analyses revealed that a history of thyroid disease was the strongest independent predictor of thyroid cancer, highlighting the importance of ongoing surveillance in patients with thyroid-related conditions. Additionally, alcohol consumption emerged as a potential modifiable risk factor; past alcohol consumption was inversely associated with thyroid cancer, whereas current alcohol consumption was positively associated with thyroid cancer. Although causality cannot be inferred, this finding underscores the need for a more nuanced investigation of the role of alcohol in endocrine tumor biology. Notably, beyond the well-known risk factors of family history of thyroid cancer, a history of benign thyroid disease in first-degree relatives has also been identified as a risk factor for thyroid cancer (47). Furthermore, in a study by Feng et al. that analyzed 423 patients with thyroid cancer from the UK Biobank dataset of 264,956 individuals, several factors were associated with thyroid cancer incidence. This study highlighted that a higher polygenic risk score and an unfavorable lifestyle (including lack of moderate-to-vigorous physical activity, obesity, and smoking) were associated with an increased risk of thyroid cancer. In contrast, unhealthy alcohol consumption has been reported to be inversely associated with thyroid cancer risk (48).

Several noteworthy differences emerged when comparing F-TC with S-TC. Patients with F-TC were significantly younger and were more often diagnosed in their 40s, which is consistent with previous reports of earlier onset in familial cases. Despite similar BMI and metabolic syndrome prevalence, patients with F-TC had a higher prevalence of fatty liver and lower AST and ALT levels than patients with S-TC in the national cohort. In multivariate models, fatty liver and past alcohol use were independently associated with F-TC, suggesting that they are potential metabolic and environmental modulators of genetic susceptibility.

Interestingly, in the institutional cohort, patients with F-TC displayed more favorable metabolic profiles than their sporadic counterparts, including lower rates of diabetes and hypertension, and higher hemoglobin levels. These findings may reflect earlier detection due to family awareness, genetic factors conferring different tumor biology, or shared family lifestyle patterns. The inverse association between hypertension and familial thyroid cancer further supports the notion that traditional cardiovascular risk factors may not directly overlap with familial cancer risk.

Lifestyle factors, such as physical activity and diet, did not differ significantly between the F-TC and S-TC groups, suggesting that familial predisposition may outweigh modifiable behaviors in shaping disease development. Nevertheless, higher alcohol consumption among patients with F-TC warrants closer examination, as it may represent a behavioral trait within affected families or contribute to differential cancer biology.

Although this finding suggests a potential metabolic component of familial thyroid cancer, the results are not entirely consistent. Although no specific studies have focused on familial thyroid cancer and its metabolic associations, the relationship between obesity and thyroid cancer incidence has been widely reported in numerous studies. In a review paper, Franchini et al. highlighted that obesity is associated with low-grade chronic inflammation characterized by nonspecific immune system activation, increased inflammatory factors, and the production of various cytokines and adipokines. These elements may directly or indirectly stimulate cell proliferation and promote tumorigenesis in various tissues including the thyroid gland. Therefore, a healthy diet rich in fruits and vegetables and regular physical activity may be crucial for reducing the risk of thyroid cancer. The influence of lifestyle factors on thyroid cancer incidence warrants further investigation in future research (49). Kwon et al. reported that obesity was associated with an increased risk of incident thyroid cancer in metabolically healthy (MH) and metabolically unhealthy (MUH) men, indicating that excessive adiposity is an independent risk factor for thyroid cancer. Conversely, women with

MUH obesity but not MH obesity, were found to have an increased risk of thyroid cancer, indicating that obesity with accompanying metabolic abnormalities may affect the risk of thyroid cancer in women (46). Collectively, these findings reinforce the importance of metabolic health in the development of thyroid cancer. Based on this perspective, it is reasonable to consider the potential role of diet as a contributing factor in thyroid carcinogenesis. Notably, iodine imbalance is a well-established risk factor for thyroid cancer, highlighting the potential interplay between dietary intake and thyroid cancer risk. Although the overall nutritional analysis based on the KoGES data in this study did not show significant differences between the groups, the results suggest the need for more in-depth investigations, specifically focusing on dietary patterns and nutritional components. Future research incorporating comprehensive dietary assessments may provide further insights into modifiable dietary risk factors and clarify the role of nutrition in the development and progression of thyroid cancer.

Through a large-scale cohort study of KoGES and institutional cohorts, we aimed to identify factors influencing familial aggregation of thyroid cancer. However, given the complexity of cancer development and the multiple hereditary and environmental factors, we could not derive a unified conclusion or highly significant result. The intricate interplay among genetic predisposition, metabolic factors, environmental influences, and lifestyle components suggests that the development of thyroid cancer is multifactorial and cannot be solely attributed to familial inheritance. Despite these limitations, this study provides valuable insights into the potential contributing factors and highlights the need for further investigation using more refined methodologies. Future research should focus on more comprehensive genetic analyses, interactions between metabolic and environmental factors, and long-term follow-up studies to better understand the hereditary mechanisms of thyroid cancer. Expanding cohort sizes, incorporating multi-omics approaches, and integrating family-based genetic screening may enhance the accuracy of risk assessments and contribute to personalized prevention strategies. Continuous efforts in this field are essential to elucidate the complex nature of thyroid cancer and its familial components.

This study has several limitations that (1) In case of institutional data analysis, sociodemographic, lifestyle, and health-related variables available in the KoGES database could not be obtained, which limited the ability to fully compare and integrate the findings between the institutional data and the KoGES cohort. (2) For the population-based cohort analysis: a). Although the data collection period (2004 to 2016) included the early 2000s, when the incidence of thyroid cancer in Korea began to

rise rapidly, the relatively small number of individuals diagnosed with thyroid cancer within the cohort may have served as an important limiting factor influencing study outcomes. b). The pathological classifications of differentiated and medullary thyroid cancers are not clearly defined in the available data. Although medullary thyroid cancer is extremely rare in Korea, there remains a possibility that some cases may have been included in the cohort. c). The response rates for the variables used in the comparative analysis varied across data items, which may have introduced bias into the analysis.

5. CONCLUSION

With an increasing incidence of NMTC, the proportion of FNMTC cases has also increased. FNMTC exhibits aggressive clinical characteristics and is a significant risk factor for disease recurrence. Factors associated with the occurrence of thyroid cancer and family history of thyroid cancer, as identified through large-scale cohort and institutional analyses, did not show consistent results. Due to the complex interplay among genetic predisposition, metabolic factors, and environmental influences, it is difficult to identify a single risk factor for familial thyroid cancer. In the future, personalized prognostic assessments and management strategies will be necessary for patients with a family history of thyroid cancer.

REFERENCES

1. Miranda-Filho A, Lortet-Tieulent J, Bray F, Cao B, Franceschi S, Vaccarella S, et al. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. Lancet Diabetes Endocrinol. 2021;9(4):225-34. Epub 2021/03/05. doi: 10.1016/s2213-8587(21)00027-9. PubMed PMID: 33662333.

2. Park D, Lee J-H, Back K, Park KS, Chung YS. Changes in the Trend of Thyroid Cancer Epidemiology According to South Korean Nationwide Database, 1999–2020. J Endocr Surg. 2024;24(2):31-8.

3. Pizzato M, Li M, Vignat J, Laversanne M, Singh D, La Vecchia C, et al. The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020. The Lancet Diabetes & Endocrinology. 2022;10(4):264-72.

4. Araque DVP, Bleyer A, Brito JP. Thyroid cancer in adolescents and young adults. Future Oncology. 2017;13(14):1253-61. doi: 10.2217/fon-2017-0024.

5. Korea Central Cancer Registry, National Cancer Center. Annual report of cancer statistics in Korea in 2021, Ministry of Health and Welfare, 2023.

6. Current Status of Cancer Prevalence [Internet]. National Cancer Information Center.

7. Chen DW, Lang BHH, McLeod DSA, Newbold K, Haymart MR. Thyroid cancer. Lancet. 2023;401(10387):1531-44. Epub 2023/04/07. doi: 10.1016/s0140-6736(23)00020-x. PubMed PMID: 37023783.

8. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"--screening and overdiagnosis. N Engl J Med. 2014;371(19):1765-7. Epub 2014/11/06. doi: 10.1056/NEJMp1409841. PubMed PMID: 25372084.

9. Haymart MR, Banerjee M, Reyes-Gastelum D, Caoili E, Norton EC. Thyroid Ultrasound and the Increase in Diagnosis of Low-Risk Thyroid Cancer. J Clin Endocrinol Metab. 2019;104(3):785-92. Epub 2018/10/18. doi: 10.1210/jc.2018-01933. PubMed PMID: 30329071; PubMed Central PMCID: PMCPMC6456891.

10. Shakhtarin VV, Tsyb AF, Stepanenko VF, Orlov MY, Kopecky KJ, Davis S. Iodine deficiency, radiation dose, and the risk of thyroid cancer among children and adolescents in the Bryansk region of Russia following the Chernobyl power station accident. Int J Epidemiol. 2003;32(4):584-91. Epub 2003/08/13. doi: 10.1093/ije/dyg205. PubMed PMID: 12913034.

11. Kitahara CM, Platz EA, Freeman LE, Hsing AW, Linet MS, Park Y, et al. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. Cancer Epidemiol Biomarkers Prev. 2011;20(3):464-72. Epub 2011/01/27. doi: 10.1158/1055-9965.Epi-10-1220. PubMed PMID: 21266520; PubMed Central PMCID: PMCPMC3079276.

12. Lee J, Lee CR, Ku CR, Kang SW, Jeong JJ, Shin DY, et al. Association Between Obesity and BRAFV600E Mutation Status in Patients with Papillary Thyroid Cancer. Ann Surg Oncol. 2015;22 Suppl 3:S683-90. Epub 2015/07/29. doi: 10.1245/s10434-015-4765-z. PubMed PMID: 26215201.

13. Son H, Lee H, Kang K, Lee I. The risk of thyroid cancer and obesity: A nationwide population-based study using the Korea National Health Insurance Corporation cohort database. Surg Oncol. 2018;27(2):166-71. Epub 2018/06/26. doi: 10.1016/j.suronc.2018.03.001. PubMed PMID: 29937167.

14. Yoon JH, Choi W, Park JY, Hong AR, Kim HK, Kang HC. Active Surveillance for Low-Risk Papillary Thyroid Carcinoma as an Acceptable Management Option with Additional Benefits: A Comprehensive Systematic Review. Endocrinol Metab (Seoul). 2024;39(1):152-63. Epub 2024/02/29. doi: 10.3803/EnM.2023.1794. PubMed PMID: 38417830; PubMed Central PMCID: PMCPMC10901657.

15. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133. Epub 2015/10/16. doi: 10.1089/thy.2015.0020. PubMed PMID: 26462967; PubMed Central PMCID: PMCPMC4739132.

16. Cho SJ, Suh CH, Baek JH, Chung SR, Choi YJ, Chung KW, et al. Active Surveillance for Small Papillary Thyroid Cancer: A Systematic Review and Meta-Analysis. Thyroid. 2019;29(10):1399-408. Epub 2019/08/02. doi: 10.1089/thy.2019.0159. PubMed PMID: 31368412.

17. Mai PL, Garceau AO, Graubard BI, Dunn M, McNeel TS, Gonsalves L, et al. Confirmation of Family Cancer History Reported in a Population-Based Survey. JNCI: Journal of the National Cancer Institute. 2011;103(10):788-97. doi: 10.1093/jnci/djr114.

18. Capezzone M, Robenshtok E, Cantara S, Castagna MG. Familial non-medullary thyroid cancer: a critical review. J Endocrinol Invest. 2021;44(5):943-50. Epub 2020/10/08. doi:

10.1007/s40618-020-01435-x. PubMed PMID: 33025555; PubMed Central PMCID: PMCPMC8049908.

19. Frank C, Fallah M, Sundquist J, Hemminki A, Hemminki K. Population Landscape of Familial Cancer. Scientific Reports. 2015;5(1):12891. doi: 10.1038/srep12891.

20. Moses W, Weng J, Kebebew E. Prevalence, clinicopathologic features, and somatic genetic mutation profile in familial versus sporadic nonmedullary thyroid cancer. Thyroid. 2011;21(4):367-71. Epub 2010/12/31. doi: 10.1089/thy.2010.0256. PubMed PMID: 21190444; PubMed Central PMCID: PMCPMC3070337.

21. Lamartina L, Grani G, Durante C, Filetti S, Cooper DS. Screening for differentiated thyroid cancer in selected populations. Lancet Diabetes Endocrinol. 2020;8(1):81-8. Epub 2019/10/09. doi: 10.1016/s2213-8587(19)30324-9. PubMed PMID: 31591051.

22. Vriens MR, Suh I, Moses W, Kebebew E. Clinical features and genetic predisposition to hereditary nonmedullary thyroid cancer. Thyroid. 2009;19(12):1343-9. Epub 2009/12/17. doi: 10.1089/thy.2009.1607. PubMed PMID: 20001717.

23. Robinson DW, Orr TG. Carcinoma of the thyroid and other diseases of the thyroid in identical twins. AMA Arch Surg. 1955;70(6):923-8. Epub 1955/06/01. doi: 10.1001/archsurg.1955.01270120131015. PubMed PMID: 14375516.

24. Ammar SA, Alobuia WM, Kebebew E. An update on familial nonmedullary thyroid cancer. Endocrine. 2020;68(3):502-7. Epub 2020/03/13. doi: 10.1007/s12020-020-02250-3. PubMed PMID: 32162184.

25. Charkes ND. On the prevalence of familial nonmedullary thyroid cancer in multiply affected kindreds. Thyroid. 2006;16(2):181-6. Epub 2006/04/15. doi: 10.1089/thy.2006.16.181. PubMed PMID: 16613533.

26. Klubo-Gwiezdzinska J, Yang L, Merkel R, Patel D, Nilubol N, Merino MJ, et al. Results of Screening in Familial Non-Medullary Thyroid Cancer. Thyroid. 2017;27(8):1017-24. Epub 2017/06/29. doi: 10.1089/thy.2016.0668. PubMed PMID: 28657510; PubMed Central PMCID: PMCPMC5564020.

27. Majdalani P, Yoel U, Nasasra T, Fraenkel M, Haim A, Loewenthal N, et al. Novel Susceptibility Genes Drive Familial Non-Medullary Thyroid Cancer in a Large Consanguineous Kindred. Int J Mol Sci. 2023;24(9). Epub 2023/05/13. doi: 10.3390/ijms24098233. PubMed PMID: 37175943; PubMed Central PMCID: PMCPMC10179265.

28. Srivastava A, Giangiobbe S, Skopelitou D, Miao B, Paramasivam N, Diquigiovanni C, et al. Whole Genome Sequencing Prioritizes CHEK2, EWSR1, and TIAM1 as Possible Predisposition Genes for Familial Non-Medullary Thyroid Cancer. Front Endocrinol (Lausanne). 2021;12:600682. Epub 2021/03/12. doi: 10.3389/fendo.2021.600682. PubMed PMID: 33692755; PubMed Central PMCID: PMCPMC7937922.

29. Miasaki FY, Fuziwara CS, Carvalho GA, Kimura ET. Genetic Mutations and Variants in the Susceptibility of Familial Non-Medullary Thyroid Cancer. Genes (Basel). 2020;11(11). Epub 2020/11/22. doi: 10.3390/genes11111364. PubMed PMID: 33218058; PubMed Central PMCID: PMCPMC7698903.

30. Lee CR, Park S, Kang SW, Lee J, Jeong JJ, Nam KH, et al. Is familial papillary thyroid microcarcinoma more aggressive than sporadic form? Ann Surg Treat Res. 2017;92(3):129-35. Epub 2017/03/16. doi: 10.4174/astr.2017.92.3.129. PubMed PMID: 28289666; PubMed Central PMCID: PMCPMC5344802.

31. Zhou YM, Luo H, Gou JX, Zhao WJ, Dai WY, Zhu J, et al. Second generation of familial nonmedullary thyroid carcinoma: A meta-analysis on the clinicopathologic features and prognosis. Eur J Surg Oncol. 2017;43(12):2248-56. Epub 2017/09/25. doi: 10.1016/j.ejso.2017.09.005. PubMed PMID: 28942234.

32. Wang X, Cheng W, Li J, Su A, Wei T, Liu F, et al. Endocrine tumours: familial nonmedullary thyroid carcinoma is a more aggressive disease: a systematic review and meta-analysis. Eur J Endocrinol. 2015;172(6):R253-62. Epub 2015/02/01. doi: 10.1530/eje-14-0960. PubMed PMID: 25637073.

33. Park YJ, Ahn HY, Choi HS, Kim KW, Park DJ, Cho BY. The long-term outcomes of the second generation of familial nonmedullary thyroid carcinoma are more aggressive than sporadic cases. Thyroid. 2012;22(4):356-62. Epub 2012/01/28. doi: 10.1089/thy.2011.0163. PubMed PMID: 22280228; PubMed Central PMCID: PMCPMC3315159.

34. Cao J, Chen C, Chen C, Wang QL, Ge MH. Clinicopathological features and prognosis of familial papillary thyroid carcinoma--a large-scale, matched, case-control study. Clin Endocrinol (Oxf). 2016;84(4):598-606. Epub 2015/07/21. doi: 10.1111/cen.12859. PubMed PMID: 26191611.

35. Muallem Kalmovich L, Jabarin B, Koren S, Or K, Marcus E, Tkacheva I, et al. Is Familial Nonmedullary Thyroid Cancer A More Aggressive Type of Thyroid Cancer? Laryngoscope. 2021;131(2):E677-E81. Epub 2020/08/08. doi: 10.1002/lary.28989. PubMed PMID: 32761812.

36. Lee YM, Jeon MJ, Kim WW, Chung KW, Baek JH, Shong YK, et al. Comparison Between Familial and Sporadic Non-medullary Thyroid Carcinoma: A Retrospective Individual Risk Factor-Matched Cohort Study. Ann Surg Oncol. 2021;28(3):1722-30. Epub 2020/08/18. doi: 10.1245/s10434-020-09025-0. PubMed PMID: 32803550.

37. Jiwang L, Zhendong L, Shuchun L, Bo H, Yanguo L. Clinicopathologic characteristics of familial versus sporadic papillary thyroid carcinoma. Acta Otorhinolaryngol Ital. 2015;35(4):234-42. Epub 2016/01/30. PubMed PMID: 26824209; PubMed Central PMCID: PMCPMC4731882.

38. Capezzone M, Fralassi N, Secchi C, Cantara S, Brilli L, Pilli T, et al. Long-Term Clinical Outcome in Familial and Sporadic Papillary Thyroid Carcinoma. European Thyroid Journal. 2020;9(4):213-20. doi: 10.1159/000506955.

39. Lee YM, Yoon JH, Yi O, Sung TY, Chung KW, Kim WB, et al. Familial history of non-medullary thyroid cancer is an independent prognostic factor for tumor recurrence in younger patients with conventional papillary thyroid carcinoma. J Surg Oncol. 2014;109(2):168-73. Epub 2013/10/18. doi: 10.1002/jso.23447. PubMed PMID: 24132694.

40. Liu M, Park S. A causal relationship between alcohol intake and type 2 diabetes mellitus: A two-sample Mendelian randomization study. Nutr Metab Cardiovasc Dis. 2022;32(12):2865-76. Epub 2022/10/03. doi: 10.1016/j.numecd.2022.08.013. PubMed PMID: 36184363.

41. Hemminki K, Sundquist K, Sundquist J, Försti A, Hemminki A, Li X. Familial Risks and Proportions Describing Population Landscape of Familial Cancer. Cancers (Basel). 2021;13(17). Epub 2021/09/11. doi: 10.3390/cancers13174385. PubMed PMID: 34503195; PubMed Central PMCID: PMCPMC8430802.

42. Barrea L, Gallo M, Ruggeri RM, Giacinto PD, Sesti F, Prinzi N, et al. Nutritional status and follicular-derived thyroid cancer: An update. Critical Reviews in Food Science and Nutrition. 2021;61(1):25-59. doi: 10.1080/10408398.2020.1714542.

43. Ito Y, Kakudo K, Hirokawa M, Fukushima M, Yabuta T, Tomoda C, et al. Biological behavior and prognosis of familial papillary thyroid carcinoma. Surgery. 2009;145(1):100-5. Epub 2008/12/17. doi: 10.1016/j.surg.2008.08.004. PubMed PMID: 19081481.

44. Pinto AE, Silva GL, Henrique R, Menezes FD, Teixeira MR, Leite V, et al. Familial vs sporadic papillary thyroid carcinoma: a matched-case comparative study showing similar clinical/prognostic behaviour. Eur J Endocrinol. 2014;170(2):321-7. Epub 2013/11/26. doi: 10.1530/eje-13-0865. PubMed PMID: 24272198.

45. Mazeh H, Benavidez J, Poehls JL, Youngwirth L, Chen H, Sippel RS. In patients with thyroid cancer of follicular cell origin, a family history of nonmedullary thyroid cancer in one first-degree relative is associated with more aggressive disease. Thyroid. 2012;22(1):3-8. Epub 2011/12/06. doi: 10.1089/thy.2011.0192. PubMed PMID: 22136209.

46. Kwon H, Chang Y, Cho A, Ahn J, Park SE, Park CY, et al. Metabolic Obesity Phenotypes and Thyroid Cancer Risk: A Cohort Study. Thyroid. 2019;29(3):349-58. Epub 2019/01/17. doi: 10.1089/thy.2018.0327. PubMed PMID: 30648486.

47. Parad MT, Fararouei M, Mirahmadizadeh AR, Afrashteh S. Thyroid cancer and its associated factors: A population-based case-control study. Int J Cancer. 2021;149(3):514-21. Epub 2021/02/27. doi: 10.1002/ijc.33537. PubMed PMID: 33634859.

48. Feng X, Wang F, Yang W, Zheng Y, Liu C, Huang L, et al. Association Between Genetic Risk, Adherence to Healthy Lifestyle Behavior, and Thyroid Cancer Risk. JAMA Netw Open. 2022;5(12):e2246311. Epub 2022/12/13. doi: 10.1001/jamanetworkopen.2022.46311. PubMed PMID: 36508215; PubMed Central PMCID: PMCPMC9856466.

49. Franchini F, Palatucci G, Colao A, Ungaro P, Macchia PE, Nettore IC. Obesity and Thyroid Cancer Risk: An Update. Int J Environ Res Public Health. 2022;19(3). Epub 2022/02/16. doi: 10.3390/ijerph19031116. PubMed PMID: 35162142; PubMed Central PMCID: PMCPMC8834607.

Abstract in Korean

가족성 갑상선암 : 기관의 임상 결과 및 인구기반 코호트 분석을 통한 연구

서론 : 최근 전 세계적으로 갑상선암의 발생률이 급격히 증가하고 있으며, 갑상선암의 가족력과의 관계에 대한 연구가 활발히 이루어지고 있다. 본 연구는 비수질성 갑상선암(non-medullary thyroid cancer, NMTC) 환자를 대상으로 가족성 비수질성 갑상선암(familial non-medullary thyroid cancer, FNMTC)의 유병률, 임상적 특징, 장기 예후를 분석하는 것을 목적으로 한다. 또한, 한국 유전체 역학조사(Korean Genome and Epidemiology Study, KoGES) 데이터를 활용하여 가족성 갑상선암과 관련된 사회인구학적 및 임상적 요인을 분석함으로써 가족성 갑상선암의 위험 요인을 탐색하고자 하였다.

방법 : 본 연구에서는 42,743명의 NMTC 환자 중 가족력이 없는 경우를 산발성 비수질성갑상선암으로(SNMTC),3,829명(8.2%)을 가족성비수질성갑상선암으로(FNMTC)로 분류하였다. 진단 및 수술 당시의 임상병리학적 특징을 비교하고, 추적 관찰이 가능한 환자에서 예후를 분석하였다. 또한, KoGES 데이터베이스에 등록된 172,479명 중 갑상선암을 진단받은 941명을 대상으로, 암의 과거력이 없는 대조군과의 사회인구학적 및 생활습관 요인을 비교하였으며, 갑상선암 환자 내에서도 가족력 여부에 따라 분석을 수행하였다. 또한 기관 기반 갑상선암 환자 11,143명중 885명(7.9%)은 F-TC, 10,258명(92.1%)은 S-TC로 분류하여, 두 그룹간의 임상적 특성을 비교하였다.

결과: 전체 NMTC 환자 중 8.2%(n = 3,829)가 가족력을 보였으며, FNMTC는 여성에서 더 흔하고 산발성에 비해 더 젊은 연령에서 발생하는 경향을 보였다. FNMTC는 양측성 종양(23.5% vs. 17.5%, $p < 0.001$), 다발성 병변(39.0% vs. 30.5%, $p < 0.001$), 중심부 림프절 전이(41.5% vs. 38.8%, $p = 0.001$)가 유의하게 많았고, 종양

크기는 더 작았음에도($p < 0.001$) 임상병리학적으로 더 공격적인 특징을 보였다. 재발률은 두 그룹 간 차이가 없었지만(1.9% vs. 2.3%, $p = 0.1$), 전체 생존율은 FNMTC에서 유의하게 높았다(99.6% vs. 98.6%, $p < 0.001$). 다변량 Cox 회귀 분석에서 가족력, 피막외 침범, 림프절 전이, 종양 크기가 재발의 독립적인 위험인자로 확인되었다. 위험군에 따른 생존 분석에서는 중고위험군에서만 가족력이 무병생존율에 유의한 영향을 미쳤다($HR = 1.65$, $p < 0.001$).

국가 코호트 분석에서는 갑상선암 환자군이 암 병력이 없는 군에 비해 갑상선 질환 병력과 현재 음주가 유의하게 관련이 있는 인자로 나타났으며, 가족성 갑상선암과 관련이 있는 인자로는 지방간 및 과거 음주력이 나왔다. 기관 코호트 분석에서 가족성 갑상선암 환자환자에서 고혈압이 음성 예측인자($OR = 0.667$, $p = 0.040$)로 나타났다.

결론 : NMTC 환자는 일부 공격적인 임상적 특성을 보이며, 질병 재발의 중요한 위험 요인으로 작용할 수 있다. 대규모 코호트 분석 및 기관 분석을 통한 갑상선암의 발생 및 갑상선암의 가족력과 관련있는 인자는 일관된 결과를 보이지는 않았으며, 유전적 소인과 대사 요인, 환경 요인의 복합적 작용으로 인해 갑상선암의 가족력에 대한 단일한 위험 요인을 도출하기는 어려웠다. 추후 가족력이 있는 갑상선암 환자에 대한 맞춤형 예후 평가 및 관리 전략이 필요하겠다.

핵심되는 말 : 비수질성 갑상선암, 갑상선암, 가족력, 재발, 유병률, 예후