



# Cardiometabolic Risks in Patients with Thyroid Cancer

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Thyroid cancer is the most prevalent malignancy in South Korea, with a 5-year survival rate exceeding 100%. As the number of long-term survivors increases, non-cancer-related complications, particularly cardiovascular and metabolic diseases, have emerged as significant contributors to morbidity and mortality. This review aims to summarize current evidence on the association between thyroid cancer and cardiometabolic risk and highlight clinical implications for optimal management.

**Key Words:** Thyroid neoplasms, Cardiovascular diseases, Diabetes mellitus type 2, Dyslipidemias, Thyroxine

## Introduction

Thyroid cancer is one of the most prevalent endocrine malignancies, with a notably high 5-year survival rate. In South Korea, it is the most diagnosed cancer among all malignant diseases, as confirmed by the 2022 national cancer statistics. Although thyroid cancer is the most common malignancy in South Korea, its 5-year relative survival rate exceeds 100%, and as of 2022, approximately 1% of the total Korean population are living with a history of thyroid cancer.<sup>1)</sup> As the population of thyroid cancer survivors grows, attention has shifted toward long-term health risks, particularly non-cancer-related causes of death. Cardiovascular disease (CVD) has emerged as a leading cause of mortality in this population, raising concerns regarding the broader cardiometabolic impact of thyroid cancer and its treatment. This review aims to summarize recent findings on the association between thyroid cancer, CVD, and metabolic disorders, and to provide insights into clinical management strategies.

## Cardiovascular Disease Risk in Thyroid Cancer Survivors

Multiple cohort studies have demonstrated increased risks of ischemic heart disease, stroke, atrial fibrillation, and coronary artery disease in patients with differentiated thyroid cancer (DTC). According to SEER program data, cardiovascular disease accounted for 21.3% of non-cancer-related deaths among thyroid cancer patients, making it the leading cause of non-malignant mortality in this population.<sup>2)</sup> Moreover, the risk of cardiovascular death was found to be 1.59 times higher than that of the general population. In the 2018 Utah Population Database study, thyroid cancer survivors receiving thyroid stimulating hormone (TSH) suppression therapy had an increased risk of cardiovascular disease, with an adjusted hazard ratio (HR) of 1.25 (95% confidence interval [CI], 1.12–1.40). Notably, among those with distant metastasis, the cardiovascular risk was even higher, with an adjusted HR of 1.35 (95% CI, 1.03–1.77), suggesting that both

Received April 15, 2025 / Revised May 9, 2025 / Accepted May 9, 2025

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treatment intensity and cancer stage may contribute to adverse cardiovascular outcomes.<sup>3)</sup> A 2023 meta-analysis evaluating cardiovascular outcomes in thyroid cancer patients also assessed the impact of radioactive iodine (RAI) therapy and found a neutral effect on cardiovascular disease, with a relative risk (RR) of 1.00 (95% CI, 0.87–1.16).<sup>4)</sup> There was no evidence of either beneficial or harmful cardiovascular outcomes across different RAI doses. Therefore, TSH suppression appears to play a key role in the development of both cardiovascular and metabolic disorders in patients with thyroid cancer.

## TSH Suppression and Cardiovascular Disease

Suppressive levothyroxine therapy, aimed at reducing TSH levels to prevent cancer recurrence, has been implicated in elevated heart rate, increased systolic blood pressure, and possible cardiac arrhythmia. A significant study published in 2013 followed 524 DTC patients and found that patients with TSH levels suppressed below 0.02 mIU/L had significantly higher CVD mortality and all-cause mortality compared to matched controls.<sup>5)</sup>

These findings suggest that aggressive TSH suppression may have unintended cardiovascular consequences. A 2019 study using data from the Korean National Health Insurance Service compared to 182,419 thyroid cancer patients with a 1:1 matched control group and found significantly increased risks of coronary heart disease and ischemic heart disease among the thyroid cancer patients. Notably, patients taking levothyroxine doses of 145–169  $\mu$ g/day had a 1.61-fold increased risk of coronary heart disease and a 1.63-fold increased risk of ischemic stroke. For those taking doses of 170  $\mu$ g/day or more, the risks rose to 2.15-fold for both coronary heart disease and ischemic stroke.<sup>6)</sup> In contrast, a 2019 study that compared 3009 patients with differentiated thyroid cancer to 11,303 matched controls in a 1:3 ratio found no significant difference in the risk of ischemic heart disease or stroke.<sup>7)</sup> However, the incidence of atrial fibrillation was significantly higher among thyroid cancer patients.

A 2021 meta-analysis further reported that thyroid cancer patients had a 1.1-fold increased risk of coronary artery disease, and a 1.15-fold increased risk of cerebrovascular disease compared to controls.<sup>8)</sup> However, a more recent meta-analysis published in 2023 found that after adjusting for cardiovascular risk factors, the associations between thyroid cancer and both ischemic heart disease and stroke were no longer statistically significant.<sup>9)</sup> Such inconsistencies may ultimately be attributed to differences in the degree of adjustment for cardiovascular risk factors across individual studies. Therefore, it is important to further investigate the risk of developing metabolic disorders, which are major cardiovascular risk factors, among thyroid cancer patients.

## TSH Suppression and Metabolic Disorders

TSH suppression has also been associated with an increased risk of hypertension. Levothyroxine doses that suppress TSH may elevate sympathetic activity, contributing to higher systolic and diastolic blood pressure.<sup>10)</sup> A 2018 study utilizing data from the Utah Population Database reported that thyroid cancer survivors undergoing TSH suppression therapy had a 1.22-fold increased risk of developing hypertension compared to those not receiving suppression therapy.<sup>3)</sup> TSH suppression also appears to influence various metabolic parameters. Several studies have noted that patients receiving high-dose levothyroxine exhibit elevated fasting glucose, insulin resistance, and a heightened risk of developing type 2 diabetes mellitus. In particular, a study involving 36,377 thyroid cancer patients and matched controls showed that the risk of diabetes mellitus was significantly elevated.<sup>11)</sup> Notably, patients taking less than 101  $\mu$ g/day of levothyroxine had a 1.5-fold increased risk of diabetes mellitus, while those taking 150  $\mu$ g/day or more had a 1.39-fold increased risk, indicating that both lower and higher levothyroxine doses may influence glucose metabolism.<sup>11)</sup> Additionally, a 2024 study using the Korean National Health Insurance Service–National Sample Cohort compared 2649 patients with differ-

entiated thyroid cancer to a 1:3 matched control group and found that the risk of developing type 2 diabetes mellitus was 1.22 times higher, while the risk of dyslipidemia was 1.36 times higher in thyroid cancer patients.<sup>12)</sup> Interestingly, when levothyroxine dosage exceeded 2.63  $\mu\text{g/kg/day}$ , the risks of type 2 diabetes mellitus and hypertension increased by 1.45-fold and 1.52-fold, respectively. In contrast, for dyslipidemia, the risk was significantly lower—0.68-fold—among patients receiving doses between 2.14 and 2.62  $\mu\text{g/kg/day}$ .<sup>12)</sup> Furthermore, a 2019 study focusing on female thyroid cancer patients found that when the reference range for postoperative TSH was set at 0.03–0.3 mIU/L, those with TSH levels of 0.3–2 mIU/L had a 2.76-fold increased risk of having low-density lipoprotein (LDL)-cholesterol levels  $\geq 160$  mg/dL, while those with TSH levels of 2–5 mIU/L had a 4.17-fold increased risk.<sup>13)</sup>

## Risk of Thyroid Cancer in Type 2 Diabetes Mellitus or Metabolic Disease

While thyroid cancer patients are prone to developing metabolic disorders such as diabetes mellitus and dyslipidemia, accumulating evidence also indicates that individuals with pre-existing diabetes mellitus and metabolic syndrome may have an elevated risk of developing thyroid cancer.

A 2022 meta-analysis confirmed that the risk of thyroid cancer in patients with type 2 diabetes mellitus was 1.34 times higher overall, with significantly elevated risks in both men (1.32-fold) and women (1.37-fold).<sup>14)</sup> Epidemiological evidence from large-scale studies of Shanghai cohort suggests that individuals with type 2 diabetes mellitus, especially those with early-onset type 2 diabetes mellitus and higher BMI, have a higher standardized incidence ratio (SIR) for thyroid cancer.<sup>15)</sup> Among individuals under 50 years of age with a BMI of  $\geq 30$  kg/m<sup>2</sup>, the standardized incidence ratio (SIR) for thyroid cancer increased by 3.91-fold.<sup>15)</sup> In a Korean National Health Insurance dataset with an average follow-up of 7.2 years, individuals with metabolic syndrome had a 1.15-fold in-

creased risk of developing thyroid cancer. Notably, among obese men, the risk rose to 1.58-fold.<sup>16)</sup> These findings suggest that metabolic disturbances may contribute to increased thyroid cancer risk.

## Summary and Conclusion

Given the growing evidence linking thyroid cancer and cardiometabolic disease, clinicians must take a balanced approach in managing TSH levels, especially in low-risk patients where aggressive suppression may not be necessary. Long-term follow-up should include screening and management of type 2 diabetes mellitus, hypertension, and dyslipidemia. It is also important to consider that a substantial proportion of thyroid cancer patients already have pre-existing diabetes and other metabolic disorders, which may complicate their long-term management.

As survival rates in thyroid cancer improve, the focus must expand beyond cancer recurrence to encompass the broader health risks faced by survivors. Cardiovascular and metabolic disorders represent significant threats to long-term survival and quality of life. Careful attention to TSH management, coupled with proactive screening and prevention strategies for cardiometabolic conditions, will be key to optimizing outcomes in this growing patient population. Further prospective studies are warranted to evaluate whether effective management of cardiometabolic conditions among thyroid cancer survivors can lead to improved long-term survival outcomes.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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