Association between Hashimoto Thyroiditis and Mortality in Differentiated Thyroid Cancer

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Background/Aims: Many studies have shown that Hashimoto's thyroiditis (HT) acts as a protective factor in differentiated thyroid carcinoma (DTC), but little is known about its effects on mortality. Therefore, this study was performed to reveal the prognosis of HT on mortality in patients with DTC.

Methods: This study included two types of research results: retrospective cohort study using The National Epidemiologic Survey of Thyroid cancer (NEST) in Korea and meta-analysis study with the NEST data and 8 selected studies. Multiple Cox regression analysis was performed to assess the hazard ratios for all-cause and thyroid cancer-related mortality. A regression-based causal mediation analysis was conducted to investigate the direct and indirect effect of HT on DTC-specific mortality through advanced clinicopathologic status of DTC. A meta-analysis was performed with the eight included studies and NEST analysis results.

Results: Of the 4,398 patients with DTC in NEST, 341 patients (7.8%) died during the median follow-up period of 180 months (interquartile range: 148-187 months). Of these, 91 deaths (2.1%) were related to DTC. In Cox regression analysis after adjusting for age and sex, patients with HT showed a significantly lower risk of all-cause death (HR, 0.71; 95% CI, 0.52-0.96) and DTC-related death (HR, 0.33; 95% CI, 0.14-0.77). In the mediation analysis, HT indirectly decreased the risk of DTC-specific mortality through a low risk of advanced DTC and directly decreased the risk of DTC-specific mortality. The meta-analysis showed that patients with HT showed a lower risk of all-cause mortality (RR, 0.24; 95% CI, 0.13 to 0.47) and thyroid cancer-specific mortality (RR, 0.22; 95% CI, 0.13 to 0.38) in comparison with patients without HT.

Conclusions: This study showed that DTC co-presenting with HT is associated with a low risk of advanced DTC and presents a low risk for all-cause and DTC specific death.

Fig. 1. Kaplan-Meier plot of cumulative mortality for all-cause and thyroid cancer specific death according to Hashimoto thyroiditis

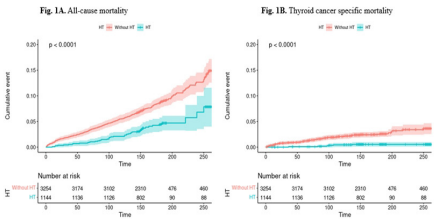
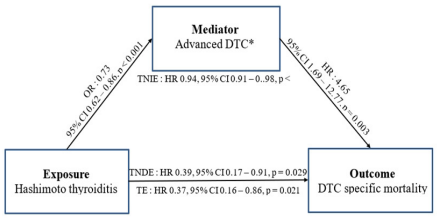


Figure 2. Mediation analysis for Hashimoto thyroiditis and differentiated thyroid cancer specific mortality



TNIE, total natural indirect effect; TNDE, total natural direct effect; TE, total effect according to Hashimoto thyroiditis
Adjusted with age and sex
* Defined as patients with T3-4, lymph node metastasis, or distant metastasis.

Table 1. NEST: The Baseline Characteristics According To Coexistence of Hashimoto's Thyroiditis In Patients Differentiated Thyroid Cancer

	Without HT (N=3254)	With HT (N=1144)	p
Age	46.2 ± 12.6	44.8 ± 11.3	0.001
Sex			
Men	621 (19.1%)	70 (6.1%)	< 0.001
Women	2633 (80.9%)	1074 (93.9%)	
Tumor size (mm)	14.1 ± 12.0	11.2±8.6	<0.001
T stage			< 0.001
T1	1281 (42.8%)	558 (50.3%)	
T2	163 (5.4%)	40 (3.6%)	
T3	1441 (48.1%)	492 (44.4%)	
T4	109 (3.6%)	19 (1.7%)	
Extrathyroidal extension	1509 (50.1%)	503 (45.1%)	0.005
Lymph node metastasis	1228 (49.7%)	395 (39.3%)	< 0.001
Distant metastasis	20 (0.7%)	0 (0.0%)	0.014
Stage (AJCC 6th ed.)			
Age < 45years			0.467
Stage I	1413 (99.7%)	538 (100%)	
Stage II	4 (0.3%)	0	
Age ≥ 45years			0.001
Stage I	1730 (28.4%)	690 (34.5%)	
Stage II	24 (2.1%)	5 (1.1%)	
Stage III	533 (47.7%)	227 (51.5%)	
Stage IV	243 (21.8%)	57 (12.9%)	
All-cause mortality	293 (9.0%)	48 (4.2%)	< 0.001
TC related mortality	85 (2.6%)	6 (0.5%)	< 0.001

HT, Hashimoto's thyroiditis; TC, Thyroid cancer

Figure 3 Schema of the search strategy

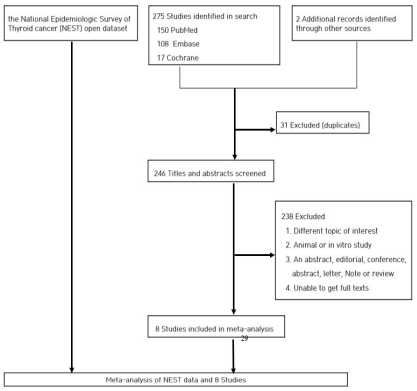


Figure 4. Risk ratio of Hashimoto thyroiditis for mortality

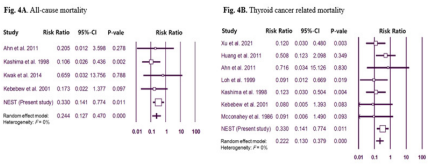


Table 2. Association between Hashimoto's thyroiditis and clinicopathologic characteristics of thyroid cancer

	Adjusted OR (95% CI)	P-value
T 3-4	0.82 (0.71-0.94)	0.005
Extrathyroidal extension	0.83 (0.73-0.96)	0.011
Lymph node metastasis	0.68 (0.58-0.79)	<0.001
TNM stage III-IV	0.83 (0.66-1.05)	0.125

OR, odds ratio of differentiated thyroid cancer patients' group with Hashimoto's thyroiditis (HT) compared to group without HT

Adjusted with age and sex

Table 3. Association between Hashimoto's thyroiditis and mortality

	Adjusted HR (95%CI)	P-value
Total dataset		
All-cause mortality	0.71 (0.52-0.96)	0.028
TC-mortality	0.33 (0.14-0.77)	0.01
PSM dataset*		
All-cause mortality	0.60 (0.42-0.86)	0.005
TC-mortality	0.21 (0.09-0.50)	<0.001

HR, Hazard ratio of differentiated thyroid cancer patients' group with Hashimoto's thyroiditis (HT) compared to group without HT

Adjusted with age and sex

* Propensity score matching with age and sex