

## RESEARCH ARTICLE

# Association of Papillary Carcinoma of Thyroid and Nonspecific Chronic Lymphocytic Thyroiditis and Its Clinicopathological Effects

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## ABSTRACT

**Introduction:** The most common differentiated malignant thyroid neoplasm is papillary carcinoma. Association of concurrent presence of chronic lymphocytic thyroiditis and its subtypes with differentiated epithelial thyroid carcinoma remains controversial.

**Objective:** To evaluate epidemiological factors of chronic lymphocytic thyroiditis and association between chronic lymphocytic thyroiditis and its subtypes with papillary thyroid carcinoma.

**Materials and methods:** A total of 684 patients who underwent thyroidectomy at Teaching Hospital Kandy, Sri Lanka, for a period of two-and-half years from 2013 January were reviewed. The clinical and pathological characteristics were analyzed. Chronic lymphocytic thyroiditis was diagnosed by histology.

**Results:** Thyroid malignancies were detected in 14.2% of thyroidectomy specimen, of which well-differentiated epithelial thyroid carcinoma was seen in 82%. Chronic lymphocytic thyroiditis was present in 31%, out of which 73.1% were nonspecific chronic lymphocytic thyroiditis and 26.9% were Hashimoto's thyroiditis. Gender, age, and presence of thyroiditis were significantly associated with papillary thyroid carcinoma. Males were more likely to have papillary carcinoma compared with females ( $p = 0.013$ ). Those with nonspecific chronic lymphocytic thyroiditis were more likely to have papillary thyroid carcinoma ( $p = 0.002$ ) compared with those without. With increasing age, proportion of lymphovascular invasion in patients with papillary thyroid carcinoma significantly ( $p = 0.010$ ) decreases. None of the three factors mentioned were significant predictors of tumor focality, capsular or lymphovascular invasion.

**Conclusion:** Presence of nonspecific chronic lymphocytic thyroiditis is associated with papillary thyroid carcinoma at a given age and gender. Influence of nonspecific chronic

lymphocytic thyroiditis on the prognosis of well-differentiated epithelial thyroid carcinoma needs to be investigated further with a larger sample size.

**Keywords:** Age, Gender, Nonspecific chronic lymphocytic thyroiditis, Papillary thyroid carcinoma.

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## INTRODUCTION

Well-differentiated thyroid carcinoma and chronic lymphocytic thyroiditis are commonly encountered conditions in clinical practice. The most common malignant neoplasm of the thyroid is papillary thyroid carcinoma, comprising 70 to 80% of all thyroid cancers. Chronic lymphocytic thyroiditis is one of the most prevalent autoimmune endocrine diseases predominantly affecting females. It is the commonest cause of hypothyroidism in iodine sufficient areas.<sup>1,2</sup> Since Dailey et al<sup>3</sup> first proposed a relationship between Hashimoto's thyroiditis and papillary thyroid carcinoma in 1955, there had been several studies with conflicting conclusions. Some authors concluded that there is a positive correlation between chronic lymphocytic thyroiditis and papillary thyroid carcinoma,<sup>3-9</sup> whereas others did not.<sup>10-14</sup>

Chronic inflammation has been well established as a risk factor for the development of certain malignant tumors. Lymphocytic infiltration is frequently observed in differentiated thyroid carcinoma, suggesting immunological factors might be involved in tumor progression.<sup>15,16</sup> However, with respect to these two entities, their association of cause and effect remains uncertain.

Chronic lymphocytic thyroiditis as well as differentiated thyroid carcinoma may be asymptomatic for a long period and diagnosed incidentally on histological examination of thyroidectomy specimen. Most of the thyroid specimens harbored chronic lymphocytic thyroiditis. However, characteristic features of Hashimoto's thyroiditis, such as Hürthle cell changes were not observed

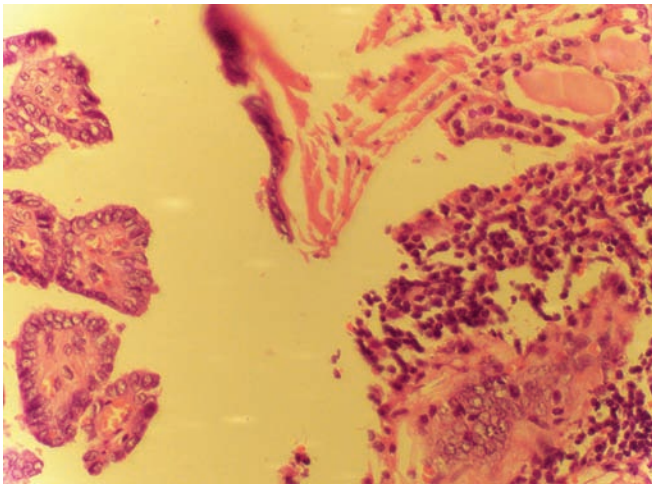
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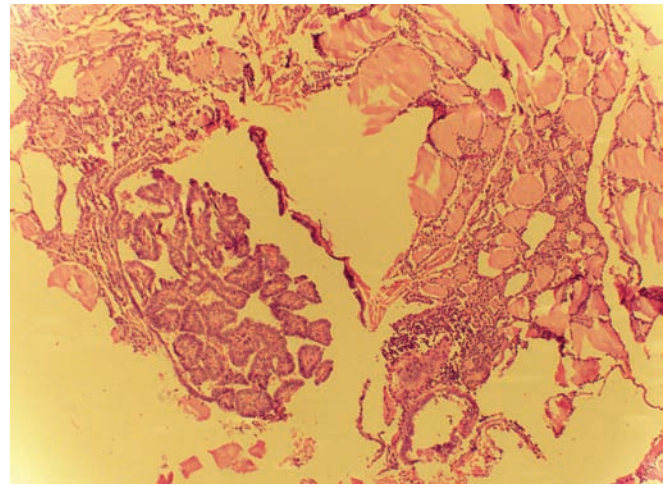
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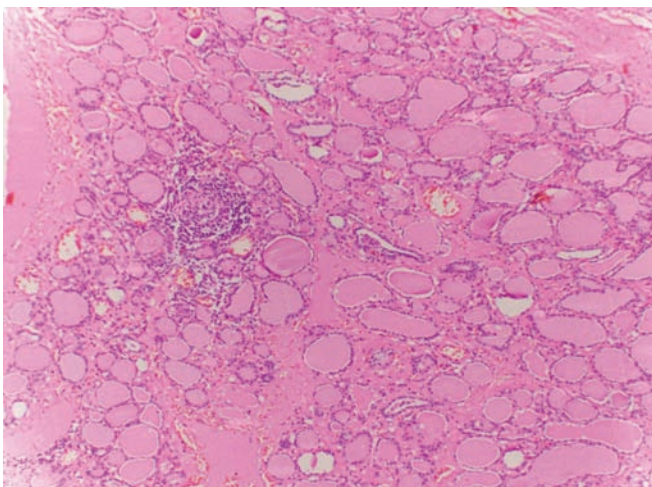
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**Fig. 1:** Papillary carcinoma with chronic nonspecific lymphocytic thyroiditis (×40)



**Fig. 2:** Papillary carcinoma with chronic nonspecific lymphocytic thyroiditis (×10)



**Fig. 3:** Chronic nonspecific lymphocytic thyroiditis

in most of the histological examinations. The lymphocytic infiltrate is focal and lymphoid follicle formation is rare in this form of chronic lymphocytic thyroiditis. It is observed that this form of nonspecific lymphocytic thyroiditis also coexisted with differentiated thyroid carcinoma (Figs 1 to 3). Some authors related this form of thyroiditis to inadvertent use of iodide salt, which had led to the destruction of thyroid gland itself due to chronic inflammatory reaction.<sup>17</sup>

The results of most of the studies do not lead to definitive conclusions. Some evidence suggests that nonspecific focal or multifocal lymphocytic infiltrates may occur more frequently in cases of papillary thyroid carcinoma, possibly indicating that the tumor can exert some degree of influence on the rest of the gland. Some authors have reported that the presence of chronic lymphocytic thyroiditis, especially Hashimoto's thyroiditis in patients with papillary thyroid carcinoma, is associated with a less aggressive clinical presentation and course,<sup>18-20</sup> while other studies have not found a similar

effect.<sup>21,22</sup> The objective of this study was to evaluate the prevalence of an association between chronic lymphocytic thyroiditis and papillary thyroid carcinoma, and to compare clinicopathological characteristics of patients with papillary thyroid carcinoma in association with the presence or absence of chronic lymphocytic thyroiditis in a large institutional series of patients who underwent thyroidectomy.

## MATERIALS AND METHODS

### Patients

The histopathological records of all the patients with goiter who underwent total thyroidectomy irrespective of the underlying indication at Teaching Hospital, Kandy, Sri Lanka, within the period from January 2013 to June 2015 were reviewed. A total of 702 thyroidectomy specimen reports were initially included in the study, out of which, 684 were used in the final analysis after excluding cases with missing data. The following variables were entered into a dedicated database: Age and gender of patient; presence of chronic lymphocytic thyroiditis and its subtype (Hashimoto's thyroiditis or nonspecific chronic lymphocytic thyroiditis); presence of malignancy and its type; in those with malignancy, presence of capsular invasion presence of lymphovascular invasion, multifocality, and tumor size.

### Definitions and Pathology

The diagnosis of chronic lymphocytic thyroiditis and its subtypes was based on histopathological findings. Thyroiditis was divided into Hashimoto's thyroiditis and nonspecific chronic lymphocytic thyroiditis depending on the presence of Hürthle cell changes and dense perifollicular lymphocytic infiltration with reactive lymphoid follicle formation, which is seen in Hashimoto's

thyroiditis and absent or seen in lesser degree in nonspecific chronic lymphocytic thyroiditis.

In this study, tumors were considered multifocal when two or more malignant foci were found in the same gland. Capsular invasion was determined based on evidence of tumor infiltration beyond the capsule of the thyroid gland on microscopic examination. All data were collected by the same researcher and all pathologic reviews were performed by the same consultant pathologist.

### Statistical Analysis and Ethical Aspect

Univariate statistics, such as frequencies, percentages, means, and standard deviations were calculated in describing the data. Multiple logistic regression was used in modeling binary response variables, such as presence of thyroid malignancy, lymphovascular/capsular invasion, and presence of multifocality of the tumor. Multiple linear regression was performed in analyzing the relationship of tumor size with predictor variables. All tests considered a significance level of 5%. The authors guarantee the preservation of data and the confidentiality of the material obtained. Ethical approval was obtained from the Institutional Ethical Review Board.

### RESULTS

Out of the 684 thyroidectomy specimen reports considered within the study period, 611 (89%) were from female patients. Mean age of patients who had undergone thyroidectomy was 48 years (standard deviation [SD] = 12.5). Histopathological reports on the surgically removed thyroid specimens indicated the presence of chronic lymphocytic thyroiditis in 212 (31.0%), out of which 57 (26.9%) had Hashimoto's thyroiditis and 155 (73.1%) had nonspecific chronic lymphocytic thyroiditis without Hurthloid changes. Presence of malignancy was established in 97 (14.2%) cases. The types and frequencies of thyroid malignancies detected are shown in Table 1. There were 43 cases where the thyroid harbored malignancy together with chronic lymphocytic thyroiditis.

Of the specimens with malignancy, 49.5% showed lymphovascular invasion and 51.6% had capsular inva-

**Table 2:** Logistic regression analysis output for presence of papillary carcinoma of thyroid

Model terms	Estimate (beta)	Significance (p)	Odds ratio	95% CI for odds ratio	
				Lower	Upper
Gender (male) <sup>a</sup>	0.957	0.013	2.603	1.227	5.523
Age	-0.044	<0.001	0.957	0.934	0.981
Thyroiditis <sup>b</sup>		0.007			
Thyroiditis (Hashimoto)	-0.143	0.822	0.867	0.251	2.993
Thyroiditis (nonspecific)	0.939	0.002	2.557	1.397	4.680
Constant (intercept)	-0.892	0.102			

<sup>a</sup>The variable Gender has two levels, with females taken as the reference category; <sup>b</sup>The variable Thyroiditis has three levels with "No thyroiditis" taken as the reference category, with the other two being Hashimoto's and nonspecific lymphocytic thyroiditis

sion. Multifocal tumors constituted 28.7% of the malignancies. The size of tumors ranged from 3 to 120 cm, with a mean of 28.3 cm (SD = 26.6).

To study the association of papillary thyroid carcinoma with chronic lymphocytic thyroiditis, logistic regression analysis was performed. Presence of malignancy was modeled using the dependent variables: Type of thyroiditis (categories being: No thyroiditis, Hashimoto's thyroiditis, and nonspecific chronic lymphocytic thyroiditis), age, and gender. The analyses were also done separately for papillary thyroid carcinoma.

When analyzing the 54 cases of papillary carcinoma, all three factors considered were significant predictors of presence or absence of papillary carcinoma (Table 2).

Gender was significant at  $p = 0.013$ . Males were more likely to have papillary carcinoma in our population compared with females. The odds ratio was 2.603 [95% confidence interval (CI) = 1.227–5.523], which means that males had 2.6 times the odds of developing papillary carcinoma compared with females when age and thyroiditis type were kept fixed.

With increasing age, the proportion with papillary carcinoma significantly ( $p < 0.001$ ) decreased. The odds ratio was 0.957 (95% CI = 0.934–0.981), which means with each year of increase in age, the odds of developing papillary carcinoma decreases by 4.3%, for a given gender and thyroiditis type.

Those with nonspecific lymphocytic thyroiditis were more likely to have papillary carcinoma of the thyroid ( $p = 0.002$ ) than those without thyroiditis. Odds ratio for this was 2.557 (95% CI = 1.397–4.680). Those with nonspecific lymphocytic thyroiditis are therefore, 2.5 times more likely to have papillary carcinoma than those without thyroiditis, at a given age and gender.

Having Hashimoto's thyroiditis was not found to be associated with papillary carcinoma in this series

**Table 1:** Frequency of different types of thyroid malignancies documented in the histopathological reports

Thyroid malignancy type	Frequency (%)
Papillary	54 (55.7%)
Follicular	26 (26.8%)
Medullary	8 (8.2%)
Lymphoma	4 (4.1%)
Other	5 (5.2%)
Total	97 (100.0%)

**Table 3:** Logistic regression analysis output for presence of lymphovascular invasion in papillary carcinoma of thyroid

Model terms	Estimate (beta)	Significance (p)	Odds ratio	95% CI for odds ratio	
				Lower	Upper
Gender (male) <sup>a</sup>	0.779	0.318	2.180	0.472	10.072
Age	-0.091	0.010	0.913	0.852	0.979
Thyroiditis <sup>b</sup>		0.707			
Thyroiditis (Hashimoto)	1.263	0.405	3.535	0.182	68.823
Thyroiditis (nonspecific)	0.101	0.879	1.106	0.302	4.044
Constant (intercept)	2.679	0.052			

<sup>a</sup>The variable Gender has two levels, with females taken as the reference category; <sup>b</sup>The variable Thyroiditis has three levels with "No thyroiditis" taken as the reference category, with the other two being Hashimoto's and nonspecific lymphocytic thyroiditis

**Table 5:** Logistic regression analysis output for presence of multifocality in papillary carcinoma of thyroid

Model terms	Estimate (beta)	Significance (p)	Odds ratio	95% CI for odds ratio	
				Lower	Upper
Gender (male) <sup>a</sup>	-0.127	0.868	0.881	0.196	3.958
Age	-0.047	0.104	0.954	0.901	1.010
Thyroiditis <sup>b</sup>		0.417			
Thyroiditis (Hashimoto)	1.407	0.303	4.085	0.280	59.621
Thyroiditis (nonspecific)	0.638	0.306	1.893	0.557	6.430
Constant (intercept)	0.913	0.446			

<sup>a</sup>The variable Gender has two levels, with females taken as the reference category; <sup>b</sup>The variable Thyroiditis has three levels, with "No thyroiditis" taken as the reference category, with the other two being Hashimoto's and nonspecific lymphocytic thyroiditis

(compared with not having thyroiditis or having non-specific lymphocytic thyroiditis).

Only age was found to be a significant predictor for lymphovascular invasion in papillary carcinoma of the thyroid (Table 3). With increasing age, the proportion of those with lymphovascular invasion in papillary carcinoma significantly decreased ( $p = 0.010$ ). The odds ratio was 0.913 (95% CI = 0.852–0.979), meaning with each year of increase in age, the odds of developing papillary carcinoma decreases by 8.7%.

None of the factors were significant predictors of capsular invasion in papillary carcinoma of thyroid according to the logistic regression analysis performed (Table 4).

Focality in papillary carcinoma of thyroid was also not predicted by any of the factors considered (Table 5).

When analyzing the relationship of tumor size with gender, age, and thyroiditis, multiple linear regression was used. According to the results, age was the only variable

**Table 4:** Logistic regression analysis output for presence of capsular invasion in papillary carcinoma of thyroid

Model terms	Estimate (beta)	Significance (p)	Odds ratio	95% CI for odds ratio	
				Lower	Upper
Gender (male) <sup>a</sup>	-0.061	0.935	0.941	0.218	4.062
Age	-0.039	0.168	0.962	0.910	1.016
Thyroiditis <sup>b</sup>		0.897			
Thyroiditis (Hashimoto)	-0.235	0.863	0.790	0.055	11.429
Thyroiditis (nonspecific)	0.242	0.693	1.274	0.382	4.243
Constant (intercept)	0.753	0.520	2.123		

<sup>a</sup>The variable Gender has two levels, with females taken as the reference category; <sup>b</sup>The variable Thyroiditis has three levels with "No thyroiditis" taken as the reference category, with the other two being Hashimoto's and nonspecific lymphocytic thyroiditis

**Table 6:** Multiple linear regression analysis output for tumor size in papillary carcinoma of thyroid

Model terms	Estimate (beta)	Standard error	Significance (p)
Gender <sup>a</sup>	-11.062	7.234	0.133
Age	0.653	0.256	0.014
Hashimoto <sup>b</sup>	21.477	12.921	0.103
Nonspecific <sup>b</sup>	3.193	5.977	0.596
Constant (intercept)	10.968	15.438	0.481

<sup>a</sup>The variable Gender was taken as a dummy variable, with males coded 1 and females coded 0; <sup>b</sup>The variables Hashimoto's and nonspecific lymphocytic thyroiditis were taken as dummy variables, with presence coded 1 and absence coded 0

out of the three that became significant (Table 6). Therefore, the presence (or absence) of Hashimoto's thyroiditis and nonspecific lymphocytic thyroiditis was not found to be significant factors in predicting size of thyroid tumors. Tumor size was shown to increase with advancing age.

**DISCUSSION**

Papillary thyroid carcinoma is the commonest malignancy in the thyroid gland. Many factors had been studied to find out the causal relationship or as predictors of papillary thyroid carcinoma. In this study sample, presence of nonspecific lymphocytic thyroiditis, age, and gender were significant predictors of presence or absence of papillary thyroid carcinoma.

**Nonspecific Chronic Lymphocytic Thyroiditis associated with Increased Incidence of Papillary Thyroid Carcinoma**

The association between thyroid lymphoma and papillary thyroid carcinoma with chronic lymphocytic thyroiditis is well established in some parts of the world. But influence of chronic lymphocytic thyroiditis on thyroid



malignancy in our country is needed to be studied. Although they represent spectrum of manifestations of chronic lymphocytic thyroiditis, various subtypes of thyroid lymphocytic infiltrate exist. Exact correlation and prognostic influences of these subtypes on differentiated thyroid carcinoma need to be assessed separately.

Lymphocytic thyroiditis is believed to be a disease with a range of histological features. At one end of the spectrum is Hashimoto's thyroiditis in which the thyroid tissue is affected secondary to immune-mediated insult, showing destruction and replacement of thyroid tissue by an infiltrate of reactive lymphocytes forming lymphoid follicles with active germinal centers and follicular epithelium of remaining follicles showing diffuse oxyphilia.

The World Health Organization (WHO) in 1993 recommended iodization of edible salt to prevent iodine deficiency. After introduction of iodization program, the number of thyroiditis patients recorded in the countries that used iodide salt appeared to increase. In Australia, there was a 50% increase in thyroiditis. The animal studies reviewed that iodine in excess can destroy thyroid tissue, leading to different form of thyroiditis.<sup>23</sup> Same WHO program was implemented in 1993 in Sri Lanka just after the WHO recommendations. Many studies done in Sri Lanka after initiation of the iodization program highlighted the use of unacceptable amount of iodine in different salt preparations.<sup>17</sup> It was observed that most of these patients had higher prevalence of antithyroid peroxidase antibodies in contrast to the prevalence of antithyroglobulin antibodies. However, this study is still in the preliminary stages.<sup>24</sup>

After the year 2000, Sri Lankan pathologists throughout the country had noticed increased numbers of patients with thyroiditis who presented with diffuse enlargement of thyroid gland with nonspecific chronic inflammation of the thyroid leading to chronic lymphocytic thyroiditis. Characteristically, these thyroids did not show Hurthloid changes seen in Hashimoto's thyroiditis and the lymphoid cell infiltrate was not as destructive as in Hashimoto's thyroiditis. Some of these patients with nonspecific chronic lymphocytic thyroiditis presented with well-differentiated thyroid malignancies. Some patients had two types of well-differentiated thyroid carcinomas (papillary and follicular) in the same thyroid.<sup>25</sup> However, it is needed to study this entity of thyroiditis in greater detail with clinicopathological and serological correlation.

Most studies have used Hashimoto's thyroiditis and nonspecific chronic lymphocytic thyroiditis interchangeably in order to assess association of thyroiditis with thyroid malignancy. In different studies, the incidence of thyroid cancer developing against the background of chronic lymphocytic thyroiditis has been reported to be between 0.5 and 23%.<sup>26-29</sup> Certain authors believe that there is a positive correlation between Hashimoto's

thyroiditis (a subtype of chronic lymphocytic thyroiditis) and papillary thyroid carcinoma.<sup>3-9</sup> Singh et al<sup>5</sup> and Replinger et al<sup>8</sup> reported that the prevalence of thyroid cancer was significantly higher in patients with Hashimoto's thyroiditis compared with those without thyroiditis. In the present study, nonspecific chronic lymphocytic thyroiditis, a subtype of lymphocytic thyroiditis with similar histopathological features, was compared with existence and influence on differentiated thyroid carcinoma, and the results revealed nonspecific chronic lymphocytic thyroiditis was a significant predictor of presence of papillary thyroid carcinoma. Those with nonspecific chronic lymphocytic thyroiditis were 2.5 times more likely to have papillary thyroid carcinoma than those without thyroiditis, at a given age and gender.

Prognosis of thyroid cancers is affected by multiple clinicopathological factors, such as gender, age, tumor size, multifocality, capsular invasion, lymphovascular invasion, lymph node metastasis, and distant metastasis.<sup>30-32</sup> However, the influence of coexisting nonspecific chronic lymphocytic thyroiditis on the behavior of thyroid carcinoma is still debatable. Although majority of studies showed a protective effect of associated chronic lymphocytic thyroiditis, some studies reported a worse prognosis, while others pointed that it does not affect its prognosis.<sup>33-35</sup> Kashima et al<sup>18</sup> reported a mortality and disease-free interval of 5 and 85% after 10 years among the patients without associated thyroiditis, compared with 0.7 and 95% among cases with associated thyroiditis respectively. While lymphocytic infiltration is considered as an aggressive feature in breast and renal cell neoplasms, it is considered as a favorable prognostic indicator in hepatocellular carcinoma, melanoma, and transitional tumors of the bladder. But association of lymphocytic infiltration in different patterns with thyroid malignancy, especially with differentiated thyroid carcinoma, is yet to be evaluated. Although immune cell infiltration among some malignant tumors has prognostic benefit, presence of nonspecific chronic lymphocytic thyroiditis was not a significant predictor of focality, lymphovascular and capsular invasion in papillary thyroid carcinoma, indicating that presence of nonspecific chronic lymphocytic thyroiditis does not change the morbidity in patients with papillary thyroid malignancy in this sample. Malignancies in patients with chronic lymphocytic thyroiditis were not always multifocal, even though thyroiditis diffusely affects the gland.

#### **With increasing Age, the Proportion with Papillary Thyroid Carcinoma significantly Decreases**

Although papillary thyroid carcinomas are common in middle age, some studies reported that with time, age distribution had changed in patients with papillary

thyroid carcinoma. When the number of new papillary thyroid carcinoma cases was compared over the last 20 years, the age group with the most new cases shifted from patients aged 25 to 34 years to patients aged 45 to 54 years. Although all age groups had an increase in new papillary thyroid carcinoma cases, the largest increase occurred in patients aged 45 to 54 years, with a 10-fold increase over the past 20 years.<sup>32</sup> But in our sample, the proportion of papillary thyroid carcinoma significantly decreased with increasing age.

### **With increasing Age, Proportion of Lymphovascular Invasion in Patients with Papillary Carcinoma significantly Decreases**

Thyroid cancer is unique among malignancies because age is an important prognostic indicator in the majority of staging systems. Multiple population-based studies, including the National Cancer Database report on 53,856 cases of thyroid cancer over a 10-year period and the Surveillance, Epidemiology, and End Results study on 15,698 thyroid cancer cases over an 18-year period, have found that age is an important independent prognostic indicator for well-differentiated thyroid cancer.<sup>36,37</sup> Increase of mortality rate starts from the age 40 to 45 years.<sup>38</sup> With the same degree of cancer involvement, patients aged <45 years have a distinctly different prognosis than those aged >45 years. Using the tumor–node–metastasis staging system for well-differentiated thyroid carcinoma, patients aged <45 years can have extensive distant metastases and, at maximum, have stage II disease, whereas if aged >45 years, tumor size, extrathyroidal extension, lymph node involvement, and distant metastases contribute to the classification of stage I–IV disease.<sup>39</sup> But age was not a significant predictor of focality or capsular invasion in papillary thyroid carcinoma according to the logistic regression analysis of these data. With increasing age, proportion of lymphovascular invasion in patients with papillary thyroid carcinoma significantly decreases.

### **Out of all Patients who underwent Thyroidectomy, Males were more Likely to have Papillary Thyroid Carcinoma compared with Females**

Papillary thyroid carcinoma mainly affects women, with a female-to-male ratio of 5:1 in Korea compared with 2.5:1 in the UK. But in this sample of patients with goiters who underwent thyroidectomy, male patients carried a high risk to be malignant than the females with similar conditions.

### **CONCLUSION**

There is a significant association between nonspecific chronic lymphocytic thyroiditis and papillary thyroid

carcinoma. Incidence of nonspecific chronic lymphocytic thyroiditis was significant and may contribute to the increased incidence of papillary thyroid carcinoma. Patients with chronic lymphocytic thyroiditis, especially nonspecific chronic lymphocytic thyroiditis, should be appraised more carefully to exclude any coexisting malignancy, especially in the presence of other risk factors, such as male gender and young patients. Causes for increased incidence of nonspecific chronic lymphocytic thyroiditis, papillary thyroid carcinoma, and the influences of nonspecific chronic lymphocytic thyroiditis on the prognosis of the thyroid carcinoma with 5-year survival should still need to be investigated with a larger sample size.

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