Review: Thyroid autoimmunity and thyroid cancer – the pathogenic connection: a 2018 update

Running title: Thyroid autoimmunity and cancer

Yuji Nagayama

Department of Molecular Medicine, Atomic Bomb Disease Institute, Nagasaki University, 1-12-4 Sakamoto, Nagasaki, 852-8523 Japan, TEL/FAX: 81+95-819-7173/7175, e-mail: nagayama@nagasaki-u.ac.jp

Key words; papillary thyroid cancer, TSH, benign nodule, bias

Abstract

The association between thyroid cancer and thyroid autoimmunity has long been suggested, but remains to be elucidated for several decades. Here the data on this issue are updated by summarizing relevant papers published between 2012 and early 2018. Although numerous papers demonstrated the significant increase in the prevalence of thyroid autoimmunity (positive intrathyroidal lymphocyte infiltration and/or anti-thyroglobulin/thyroid peroxidase antibodies) in patients with thyroid cancers as compared to those with benign nodules, and also the significant increase in the prevalence of papillary thyroid cancer (PTC) in patients with thyroid autoimmunity as compared to those without, there are some crucial biases that should be taken into account for their interpretation. However, a difference in the incidence of thyroid autoimmunity in patient with PTCs and those with other types of thyroid cancers appears to supports the significant association of two conditions. Thyroid autoimmunity is, at least partly, likely to be elicited against antigens shared by normal and cancerous thyroid tissues, thereby inducing autoimmunity. At the same time, elevated TSH levels (even within the normal reference ranges) which often accompanying Hashimoto's patients are a risk factor for thyroid cancer. However, it is still unclear whether or not the co-existence of thyroid autoimmunity impacts on cancer characteristics and prognosis. This issue needs to be further investigated with large-scale prospective studies.

(I) Introduction

Thyroid cancer and Hashimoto's thyroiditis/chronic thyroiditis are both very common and their prevalence has been increasing worldwide during the last several decades. Association between thyroid cancer, particularly papillary thyroid carcinoma (PTC), and thyroid autoimmunity (intrathyroidal lymphocyte infiltration and/or anti-thyroid antibodies) has long been suggested. The first paper reporting the possible association of these two conditions was published more than 60 years ago [1], and numerous papers were thereafter published to investigate their association.

The data published until 2011 were summarized in several review articles. For example, one performed meta-analysis of 38 eligible studies published between 1957 and 2011 and showed, using >10,000 histologically confirmed thyroid cancer surgical samples, that intrathyroidal lymphocyte infiltration (observed in 23.2% (ranged from 5 to 85) of PTCs) was more frequently observed in PTCs than in other types of thyroid cancers and benign nodules, and PTCs with co-existing lymphocyte infiltration were significantly related to females, multifocal involvement, the absence of extrathyroidal extension, less lymph node metastasis and long recurrence-free survival, confirming the significant association of PTC with pathologically proven Hashimoto's thyroiditis and the favorable clinicopathological characteristics of PTC patients with Hashimoto' thyroiditis as compared to those without thyroiditis [2]. Another study divided the data from 19 articles into two groups - fine needle aspiration cytology (FNAC) group and archival thyroidectomy specimen group, and demonstrated the significant linkage between thyroid cancer and Hashimoto's thyroiditis in the latter, but not the former, groups. Thus the average prevalence rate of PTC in Hashimoto's patients was 1.2% (ranged from 0 to 2.95) in ~18,000 FNA specimens *versus* (*vs.*) 27.6% (ranged from 9.5 to 36.7) in ~10,000 surgical samples [3]. Thus, these results strongly suggest that the higher prevalence of co-occurrence of thyroid cancer and thyroid autoimmunity in the studies with thyroid surgical specimens may be attributed to a bias due to patient selection for thyroidectomy. However, there is also a concern about lower diagnostic accuracy of FNAC than pathological examination of surgical specimens [3]. Indeed, it has been reported that 10 to 30% cytology is actually indeterminate in FNAC [4,5]. The differences in diagnostic criteria, patient backgrounds, etc. also

contributed to these wide variations. Overall, the coexistence of these two conditions ranged from 0 to 85% [2,6,7].

This review summarizes and updates the data on the association of these two conditions reported after the publications of the two review articles mentioned above. Firstly, the association was analyzed by two different ways - (i) incidence of thyroid autoimmunity in patients with thyroid cancer *vs.* those with benign nodules and (ii) incidence of thyroid cancer in patients with thyroid autoimmunity *vs.* those without. The former was further analyzed with two different categories - surgical specimens and FNAC as in the review mentioned above [3]. Then cause-effect relationship between these two conditions and the impacts on their co-occurrence on cancer characteristics was summarized.

The readers can also refer to other recently published reviews [6,8,9].

(II) Association of thyroid autoimmunity with thyroid cancer

In the reports studying the relationship between thyroid autoimmunity and thyroid cancer, the presence of thyroid autoimmunity has been judged by the presence in sera of autoantibodies against thyroid autoantigens [thyroglobulin (Tg) and thyroid peroxidase (TPO)] and/or histopathological evidence of intrathyroidal lymphocyte infiltration. In some studies, only diffuse lymphocyte infiltration was defined as Hashimoto's thyroiditis/chronic thyroiditis, but lymphocyte infiltration just surrounding the malignant tumor was not [10-12], while both were considered as thyroid autoimmunity [13] or the details were not specified in other reports. Although a limited, focal lymphocyte infiltration may just represent the immune response to tumor antigens, the presence of anti-thyroid autoantibodies and/or any type of lymphocyte infiltration was defined as thyroid autoimmunity in this review. This is because immune response to thyroid tumor is a critical issue in this review and also it is difficult to distinguish tumor-associated lymphocyte infiltration from background lymphocytic thyroiditis, irrespective of diffuse or focal [6]. To the best of my knowledge, there is no study comparing the incidence of PTC between patients with diffuse lymphocyte infiltration and those with focal infiltration. Thyroid nodules were, needless to say,

diagnosed pathologically with surgical specimens or with FNAC (as benign or suspicious/malignant in the case of the latter).

(i) Incidence of thyroid autoimmunity in patients with thyroid cancer *vs.* those with benign nodules

In the following sections, the data obtained with surgical samples and FNAC are separately summarized.

(a) Studies with surgical specimens

Similar to the studies published until 2011 (see above), numerous retrospective studies using surgical specimens reported the higher prevalence of lymphocyte infiltration and/or anti-thyroid autoantibodies (anti-Tg and/or anti-TPO) in patients with PTCs as compared to those with other types of thyroid cancers or benign goiters/nodules [10,11,13-21] (Table 1). The majority of Hashimoto's patients have anti-Tg and/or anti-TPO antibodies, and the minority of healthy subjects have these antibodies without intrathyroidal lymphocyte infiltration. Of interest, the incidence of anti-thyroid antibodies was also higher in thyroid cancers than benign nodules in such sero-positive but non-Hashimoto's patients [14]. Anti-Tg antibodies seem to be better marker than anti-TPO antibodies [15,16]. It is also reported that scattered lymphocyte infiltration is more frequent in benign nodules than PTCs [17].

The similar analyses were done in patients who had thyroid tumors with indeterminate cytology in FNAC which were later confirmed to be cancers by surgery. One paper found the similar results with lymphocyte infiltration as a diagnostic indicator for thyroid autoimmunity [18], and the other did also so with anti-Tg antibodies, but not with lymphocyte infiltration [13].

In contrast, there are some contradictory data; Selek et al. and de Alcantara-Jones et al. [12,22,23] reported no difference in the prevalence of lymphocyte infiltration or anti-thyroid antibodies between thyroid cancer group and benign tumor group.

PTC patients with thyroid autoimmunity were in general younger and occasionally predominant in females, and had smaller tumor sizes and more micro-calcification than those with benign nodules (Table 2). Serum concentrations of TSH were largely higher (even in the normal range) and in some reports T_3 was lower. Other indicatives for the presence of thyroiditis (e.g., hypoechogenicity in ultrasonography) may also be helpful to detect the presence of thyroid autoimmunity.

In these analyses, although the reasons for surgery were not always specified clearly, some papers described the reasons that thyroidectomy was done in general because of suspicion of malignancy for thyroid nodules under diagnostic procedures such as palpation, FNAC and ultrasonography and, in some cases, because of cosmetic reasons or recurrence of Graves' hyperthyroidism [10,15,18]. Selection bias for thyroidectomy is always a critical issue in this type of analysis. It is possible that increased attention to the thyroid gland may facilitate frequent diagnosis of thyroid cancers in Hashimoto's patients [24]. Thus, thyroid nodules may be found at the earlier stage in Hashimoto's patients than non-Hashimoto's patients, because the former group takes often medical follow up for their thyroid autoimmunity/dysfunction. Therefore, if Hashimoto's patients have PTCs more frequently than non-Hashimoto' patients, the prevalence of thyroid autoimmunity may be higher in PTC group than non-PTC group.

This association was only observed in PTC, but not in other types of cancer - follicular thyroid cancer (FTC) or medullary thyroid cancer (MTC) [9,17,25].

(b) Studies with FNAC

Like the studies published until 2011, Castagna et al. [26] reported no difference in the incidence of thyroid autoimmunity (judged by the presence/absence of anti-thyroid antibodies) between thyroid nodules of benign cytology and suspicious/malignant cytology (Table 3). Thus, the presence of thyroid autoimmunity did not affect the diagnostic accuracy. Of interest, in this study, some patients (14.3 %, 358/2,504) with suspicious nodules (Thy4/5), indeterminate nodules (Thy3) or large nodular goiters underwent surgery; the prevalence of cancer at final histology was significantly higher in patients with nodular autoimmune thyroiditis than those with other nodular

diseases (nodular Graves and nodular goiter with/without anti-thyroid antibodies), because the proportion of suspicious nodules was significantly higher in the former than in the latter (60.7% *vs.* 21.5 to 30.0%). However, the significantly higher incidence of thyroid autoimmunity (including both Hashimoto's thyroiditis and Graves' disease) in suspicious/malignant cytology can be calculated in another recent study on FNAC [27]. On an individual basis, Graves' disease and anti-Tg antibodies, not Hashimoto' thyroiditis, are risk factors for suspicious/malignant cytology. The significant difference was also reported in FNAC, in which, however, histologically proven patients were pre-selected for analysis [13]. In both papers, TSH is an independent risk factor for PTC.

Overall, there are only a few papers studied the association between thyroid cancer and thyroid autoimmunity in FNAC specimens since 2012. The results reported by Castagna et al. clearly showed a crucial bias between FNAC and surgery. Surgery is in general performed when thyroid nodules are suspicious for malignancy. Suspicious/malignant cytology was indeed more frequent in patients with nodular autoimmune thyroiditis than those with other nodular diseases [26] and in nodules in patients with Hashimoto' disease/Graves' disease than those without autoimmune thyroid disease (12.8% (25/196) *vs.* 6.9% (23/332)) [27]. On the other hand, the possibility of low sensitivity of FNAC for diagnosis of Hashimoto's thyroiditis and/or thyroid cancer cannot be completely excluded. Especially, follicular and Hurthle cell neoplasms cannot be accurately diagnosed by FNAC [3].

(ii) Incidence of thyroid cancer in patients with thyroid autoimmunity *vs.* those without

Analysis was also done from a different perspective, that is, the incidence of PTC was compared between patients with/without thyroid autoimmunity (Table 4). The significant increases of PTC prevalence were demonstrated in patients with thyroid autoimmunity (judged by the presence of either lymphocyte infiltration or anti-thyroid antibodies) as compared to those without thyroid autoimmunity in all [6,18,28-30] but one [12] of the reports. In most of these studies, when thyroid autoimmunity was diagnosed - prior to or simultaneously with diagnosis of cancer - was unclear.

In one retrospective but longitudinal study conducted by Cho et al. in Taiwan, ~1,500 newly diagnosed Hashimoto's patients (and ~6,000 non-Hashimoto controls) were monitored to determine the incidence of developing cancer, which found 1.7-fold higher for thyroid cancer in Hashimoto's patients than controls (1.58 *vs.* 0.14 per 1,000 person-years). In addition, Hashimoto's patients of older ages were at higher risk of developing thyroid cancers, particularly in the first 3 years after diagnosis of Hashimoto's disease. It is clear that diagnosis of Hashimoto's thyroiditis was made before that of thyroid cancer in this study, indicating a causative role for thyroid autoimmunity in thyroid cancer development [30]. In another study with ~900 Hashimoto' cases operated in Johns Hopkins hospital, the most commonly associated condition was reported to be PTC (followed by medullary thyroid cancers and hürthle cell carcinomas) [31].

The prevalence of PTC was also higher in Graves' disease than non-Graves' thyroid diseases in operated subjects [32-35].

Some critical biases also exist in the above mentioned studies. In the report by Chen et al., because of retrospective nature of this study, it is highly possible that there is a non-negligible bias that Hashimoto' patients took more intense follow-up than control subjects as mentioned above, thereby resulting in earlier finding of thyroid cancer. Also the reasons for thyroidectomy in Hashimoto's patients are not only cancer suspicion but also huge goiter, which likely increases a chance to find occult, subclinical micro-carcinomas.

Similar studies were done in indeterminate cytology patients [5,6,18]. However, the data are inconsistent as shown in Table 5. Thus, the prevalence of PTC was higher in thyroid autoimmunity-negative group in one study [13], lower in other studies [5,18].

(III) Cause-effect relationship

Several possible pathomechanisms for the association of thyroid cancer and thyroid autoimmunity were proposed [8]; (i) immunity is elicited towards pre-existing tumor cells leading to specific autoimmunity (tumor defense-induced autoimmunity), (ii) pre-existing autoimmunity leads to malignancy due to inflammation (inflammation-induced carcinoma), and also (iii) two diseases

co-occur by common causes.

(i) Immunity is elicited towards pre-existing tumor cells leading to specific autoimmunity

Cancers can elicit immune response by secreting several molecules such as cytokines and chemokines, which attract inflammatory/immune cells into tumor sites [6]. Immune system also recognizes tumor antigens, and induces anti-tumor immune response. Therefore, following successful surgical resection of cancer, immune response would theoretically weaken. Several reports show that this is the case [17,36-38]. Among 23 patients in whom TPO antibody titers could be monitored after surgery and radiotherapy, the titers decreased in all patients with an exception who kept high titers and experienced recurrence [17]. Similarly, anti-Tg antibody titers gradually decreased in the majority (84%, 42 out of 50) of thyroid cancer patients who attained remission after treatment and became completely negative [36]. Durante et al. also found that early posttreatment normalization of anti-Tg antibody titers was negatively associated with a persistent/recurrent disease rate [37]. However, these data rather indicate that declines in anti-thyroid antibody titers means complete ablation of the thyroid glands, because decreases of anti-TSH receptor antibodies are well known phenomena in Graves' disease following successful ablation of the thyroid glands by subtotal/total thyroidectomy or radiotherapy [39,40]. However, the fact that rising/de novo appearance of anti-Tg antibodies suggest disease recurrence [41] means induction of anti-Tg antibodies by reaction of immune system to tumor antigens.

Some papers are discussed about this issue from a point of epitope repertoire. Fiore et al. summarized their data on Tg epitopes to anti-Tg antibodies, showing that the epitopes on Tg molecules to anti-Tg antibodies are more diverse in Hashimoto' patients with PTC than those without PTC, which suggests that two different autoimmune mechanisms may be involved in lymphocyte infiltration in PTC; one is typical of AITD and the other is typical of immune reaction to PTC [42]. Lupoli et al. also reported the qualitative difference in Tg epitopes between differentiated thyroid cancers with and without recurrent disease. Thus the former recognizes the immune-dominant Tg epitope clusters (I, III and IV), while the latter non-specific,

non-immune-dominant Tg epitopes [43]. These data clearly demonstrate that generation of autoantibodies in thyroid cancer patients is very likely to be reactive against cancers. Thus, anti-thyroid antibodies may be an indication for a more active immune system [44].

It remains unclear why immune reaction can be elicited against PTC but not other types of thyroid cancers.

(ii) Pre-existing autoimmunity leads to malignancy due to inflammation (inflammation-induced carcinoma).

Thyroid autoimmunity sometimes leads to hypothyroidism with elevated serum TSH. It has long been well known that the risk of thyroid cancer increases with increasing concentrations of serum TSH levels, even within normal ranges [42]. Indeed many papers quoted above reported that both thyroid autoimmunity and TSH are independent risk factors for malignancy in thyroid nodules [10,13-16,18,19,21,22].

Furthermore, the inflammatory response may create a favorable setting for malignant transformation by causing DNA damage through reactive oxygen species formation [3], as well known for the other cancers. However, there is no direct evidence to support this idea in thyroid cancer.

Clear causal relationship is found between Hashimoto' thyroiditis and primary thyroid lymphoma [45,46]. Thus, it is reported that the prevalence of Hashimoto's thyroiditis in patients with primary thyroid lymphoma is almost 100%, lymphoma develops after 3 to 18 year-Hashimoto's history, and the risk of Hashimoto' patients to develop primary thyroid lymphoma is 40 to 80 times greater than that of the general population.

(iii) Two diseases co-occur by common causes.

Benvenga e t al. published the review paper regarding environmental factors such as air pollution and endocrine-disrupting chemicals as a common cause for thyroid autoimmunity and thyroid cancer

[47], but this concept has not yet fully substantiated.

(IV) Is thyroid autoimmunity beneficial for or harmful against thyroid cancer?

Thyroid cancer patients with thyroid autoimmunity were generally younger with female dominance, had smaller tumors, less distant metastasis and favorable TNM stages than those without (Table 6). However, the data on extrathyroidal invasion, lymph node metastasis and prognosis were inconsistent. Some reports showed less extrathyroidal invasion [12,22,29,48-50], but others more [7,19,51] in PTCs with thyroid autoimmunity. Similarly, some less lymph node metastasis [12,29,36,48,51,52], but others more [16,18,28,53,54].

Regarding distant metastasis, Shen et al. reported more cervical lymph node metastasis but less distant metastasis in anti-Tg-antibody positive group [53], suggesting that the positive anti-Tg antibody status could be a risk factor for metastatic cervical lymph nodes but a protective factor for distant metastasis. Jo et al. also concluded that positive anti-Tg antibodies, even without anti-TPO antibodies nor lymphocyte infiltration, are associated with worse primary tumor characteristics (higher rates of lymphatic invasion and lymph node metastasis) but rarely show poor prognosis [54]. They speculated that this might be attributed to more aggressive treatment of these patients.

Jeong et al. and Dvorkin et al. showed better prognosis, but Durante and his colleagues worse prognosis in thyroid cancer patients with thyroid autoimmunity than those without [36,37,49]. Pellegriti et al. and Medas et al. found poorer prognosis in thyroid cancer patients complicated with Graves' disease than those not complicated [34,55]. This is likely due to the presence of thyroid stimulating antibodies, a mimic of thyroid growth stimulator TSH, in Graves's sera. Indeed a higher local lymph node metastasis rate was also noted in one of the latter papers [34]. Incidental micro-PTC patients with Graves' disease are younger than those with euthyroid goiter, suggesting an increased risk for micro-PTC in Graves' patients [56].

The data implying a protective effect of anti-TPO antibodies on thyroid cancer progression are reported; progression to TNM stage 4 only in patients with thyroid cancers and no anti-TPO antibodies (4/67, 6%) [17], and a higher relative risk for thyroid cancers in Hashimoto's patients

with low-negative anti-TPO antibodies as compared to those with positive TPO antibodies [57]. Anti-TPO antibodies may exert their anti-cancer effect by complement-mediated cell death and/or antibody-dependent cell-mediated cytotoxicity [13].

Whether infiltrative lymphocytes are beneficial (anti-tumorigenic or protective) or harmful (pro-tumorigenic) in thyroid cancer patients may depend on their phenotypes. The presence of lymphocyte infiltration, such as T cells, B cells, macrophages, Th17 cells, NK cells, $CD83^+$ mature and activated dendritic cells (DCs) is related with a better prognosis in patients with differentiated thyroid cancer, while infiltration of programmed death-1^+ T cells, $CD25^+$ regulatory T cells [58], plasmacytoid DCs [59] and double-negative T cells [60] and macrophages with M2 phenotype [61] seem to be a marker for poor prognosis. $CD25^+$ regulatory T cells are well known to negatively regulate immune response and their frequency increases with PTC aggressiveness, and conversion of naïve T cells to regulatory T cells is facilitated by plasmacytoid DCs [8]. Thus, it can be mentioned that immune response plays a protective role in some patients, but, promotes cancer development and progression in other patients, explaining the inconsistent data on the influence of thyroid autoimmunity on cancer characteristics and progression.

Relationship between Hashimoto's disease and RET-PTC chromosome translocation in PTC has long been discussed [6,62]. PTC with $BRAF^{V600E}$, another important driver mutation in PTC, has been well known to be more aggressive than PTC without the mutation [63,64]. In contrast to RET-PTC which is frequently associated with Hashimoto's thyroiditis, several studies show that the presence of $BRAF^{V600E}$ is negatively associated with lymphocyte infiltration, and is protective for aggressiveness of PTC [62,65-67].

(V) Discussion

Here this review summarized papers studied the relationship between thyroid autoimmunity and thyroid cancer, especially PTC, published between 2012 and early 2018. The association between these two conditions, analyzed in two different ways - (i) the prevalence of thyroid autoimmunity in thyroid cancer *vs.* benign nodules and (ii) the prevalence of thyroid cancer in patients with thyroid

autoimmunity *vs.* those without, summarized in the sections (II) and (III), was largely significant when analyzed with surgical specimens, but not always so with FNAC samples. There are numerous biases that should be taken into account when interpret all these data. Main biases include, on the one hand, selection of patients for thyroidectomy in surgical specimens and, on the other hand, lower diagnostic accuracy of FNAC. However, the significance in an increase of the prevalence of thyroid autoimmunity in PTC as compared to other types of thyroid cancer is likely meaningful. Resnde de Paiva et al. recently published a systematic review regarding the association between thyroid cancer and Hashimoto's thyroiditis with 36 studies published between 1955 and 2016 [9]. Although the data obtained with surgery and FNAC were mixed up, they found the statistically significant association between two conditions in PTC, not in FTC or MTC. There seems to be no, or if any only a little, bias for selection of patients for thyroidectomy of PTC or other types of thyroid cancer. From these data, I would first like to conclude that the association between thyroid autoimmunity and PTC appears to be significant.

Given the significant association between thyroid autoimmunity and thyroid cancer, rising/appearance of anti-thyroid antibodies after cancer recurrence and differences in epitope repertoire of anti-Tg antibodies between Hashimoto's patients and PTC patients support "tumor defense-induced autoimmunity" theory (see the section (IV)). In contrast, although elevated serum TSH levels (even within the normal reference ranges) which are often observed in Hashimoto's patients are a well-known risk factor for thyroid cancer, no definitive data exist to support "inflammation-induced carcinoma" theory. Thus, the second conclusion is that immune response is likely elicited towards tumor antigens in PTC patients, which are shared with normal thyroid tissues thereby inducing specific thyroid autoimmunity. An exception may be primary thyroid lymphoma, which has an intimate cause-effect relationship with Hashimoto' disease.

The data summarized in the section (V) indicate that thyroid autoimmunity does not appear to substantially affect the characteristics and prognosis of thyroid cancer, or its effect may be dependent on types of lymphocytes infiltrated into the thyroid gland. Although the data are so variable, the presence of thyroid autoimmunity tends to confer favorable characteristics such as smaller tumors, less distant metastasis and lower TNM stages, but not less extrathyroidal invasion or lymph node

metastasis, or better prognosis, to PTCs. To draw a definitive conclusion about the impact of the co-existence of thyroid autoimmunity on cancer characteristics and prognosis, the prospective and long-term follow-up studies with a large number of normal subjects and Hashimoto' patients are definitely necessary.

References

1. Dailey ME, Lindsay S, Skahen R. Relation of thyroid neoplasms to Hashimoto disease of the thyroid gland. AMA archives of surgery 1955; 70: 291-297
2. Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. European journal of endocrinology 2013; 168: 343-349
3. Jankovic B, Le KT, Hershman JM. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? The Journal of clinical endocrinology and metabolism 2013; 98: 474-482
4. Keutgen XM, Filicori F, Fahey TJ, 3rd. Molecular diagnosis for indeterminate thyroid nodules on fine needle aspiration: advances and limitations. Expert review of molecular diagnostics 2013; 13: 613-623
5. Karatzas T, Vasileiadis I, Zapanti E, Charitoudis G, Karakostas E, Boutzios G. Thyroglobulin antibodies as a potential predictive marker of papillary thyroid carcinoma in patients with indeterminate cytology. American journal of surgery 2016; 212: 946-952
6. Boi F, Pani F, Mariotti S. Thyroid Autoimmunity and Thyroid Cancer: Review Focused on Cytological Studies. European thyroid journal 2017; 6: 178-186
7. Iliadou PK, Effraimidis G, Konstantinos M, Grigorios P, Mitsakis P, Patakiouta F, Pazaitou-Panayiotou K. Chronic lymphocytic thyroiditis is associated with invasive characteristics of differentiated thyroid carcinoma in children and adolescents. European journal of endocrinology 2015; 173: 827-833
8. Ehlers M, Schott M. Hashimoto's thyroiditis and papillary thyroid cancer: are they immunologically linked? Trends in endocrinology and metabolism: TEM 2014; 25: 656-664
9. Resende de Paiva C, Gronhoj C, Feldt-Rasmussen U, von Buchwald C. Association between Hashimoto's Thyroiditis and Thyroid Cancer in 64,628 Patients. Frontiers in oncology 2017; 7: 53
10. Ye ZQ, Gu DN, Hu HY, Zhou YL, Hu XQ, Zhang XH. Hashimoto's thyroiditis, microcalcification and raised thyrotropin levels within normal range are associated with thyroid cancer. World journal of surgical oncology 2013; 11: 56
11. Zhang Y, Ma XP, Deng FS, Liu ZR, Wei HQ, Wang XH, Chen H. The effect of chronic lymphocytic thyroiditis on patients with thyroid cancer. World journal of surgical oncology 2014; 12: 277
12. Giagourta I, Evangelopoulou C, Papaioannou G, Kassi G, Zapanti E, Prokopiou M, Papapostolou K, Karga H. Autoimmune thyroiditis in benign and malignant thyroid nodules: 16-year results. Head & neck 2014; 36: 531-535
13. Boi F, Minerba L, Lai ML, Marziani B, Figus B, Spanu F, Borghero A, Mariotti S. Both thyroid autoimmunity and increased serum TSH are independent risk factors for malignancy in patients with thyroid nodules. Journal of endocrinological investigation 2013; 36: 313-320
14. Lun Y, Wu X, Xia Q, Han Y, Zhang X, Liu Z, Wang F, Duan Z, Xin S, Zhang J. Hashimoto's thyroiditis as a risk factor of papillary thyroid cancer may improve cancer prognosis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2013; 148: 396-402
15. Azizi G, Keller JM, Lewis M, Piper K, Puett D, Rivenbark KM, Malchoff CD. Association of Hashimoto's thyroiditis with thyroid cancer. Endocrine-related cancer 2014; 21: 845-852
16. Wu X, Lun Y, Jiang H, Gang Q, Xin S, Duan Z, Zhang J. Coexistence of thyroglobulin antibodies and thyroid peroxidase antibodies correlates with elevated thyroid-stimulating hormone level and advanced tumor stage of papillary thyroid cancer. Endocrine 2014; 46: 554-560

17. Veit F, Graf D, Momberger S, Helmich-Kapp B, Ruschenburg I, Peters A, Kussmann J, Saeger W, Schmidt KW, Toetsch M, Nestler K, Mann K. Papillary Thyroid Cancer and Coexisting Autoimmune Thyroiditis. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2017; 49: 869-872
18. Vasileiadis I, Boutzios G, Charitoudis G, Koukoulioti E, Karatzas T. Thyroglobulin antibodies could be a potential predictive marker for papillary thyroid carcinoma. Annals of surgical oncology 2014; 21: 2725-2732
19. Qin J, Yu Z, Guan H, Shi L, Liu Y, Zhao N, Shan Z, Han C, Li Y, Teng W. High Thyroglobulin Antibody Levels Increase the Risk of Differentiated Thyroid Carcinoma. Disease markers 2015; 2015: 648670
20. Campos LA, Picado SM, Guimaraes AV, Ribeiro DA, Dedivitis RA. Thyroid papillary carcinoma associated to Hashimoto's thyroiditis. Brazilian journal of otorhinolaryngology 2012; 78: 77-80
21. Cho YA, Kong SY, Shin A, Lee J, Lee EK, Lee YJ, Kim J. Biomarkers of thyroid function and autoimmunity for predicting high-risk groups of thyroid cancer: a nested case-control study. BMC cancer 2014; 14: 873
22. Selek A, Cetinarslan B, Tarkun I, Canturk Z, Ustuner B, Akyay Z. Thyroid autoimmunity: is really associated with papillary thyroid carcinoma? European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2017; 274: 1677-1681
23. de Alcantara-Jones DM, de Alcantara-Nunes TF, Rocha Bde O, de Oliveira RD, Santana AC, de Alcantara FT, de Faria TM, da Silva IC, Araujo LM. Is there any association between Hashimoto's thyroiditis and thyroid cancer? A retrospective data analysis. Radiologia brasileira 2015; 48: 148-153
24. Hacihamdioglu B, Ocal G, Berberoglu M, Savas Erdeve S, Camtosun E, Kocaay P, Fitoz S, Ceyhan K, Dindar H, Yagmurlu A, Kir M, Unal E, Siklar Z. The evaluation of thyroid carcinoma in childhood and concomitance of autoimmune thyroid disorders. Journal of pediatric endocrinology & metabolism : JPEM 2014; 27: 901-908
25. Zayed AA, Ali MK, Jaber OI, Suleiman MJ, Ashhab AA, Al Shweiat WM, Momani MS, Shomaf M, AbuRuz SM. Is Hashimoto's thyroiditis a risk factor for medullary thyroid carcinoma? Our experience and a literature review. Endocrine 2015; 48: 629-636
26. Castagna MG, Belardini V, Memmo S, Maino F, Di Santo A, Toti P, Carli AF, Caruso G, Pacini F. Nodules in autoimmune thyroiditis are associated with increased risk of thyroid cancer in surgical series but not in cytological series: evidence for selection bias. The Journal of clinical endocrinology and metabolism 2014; 99: 3193-3198
27. Hadjisavva IS, Dina R, Talias MA, Economides PA. Prevalence of Cancer in Patients with Thyroid Nodules in the Island of Cyprus: Predictive Value of Ultrasound Features and Thyroid Autoimmune Status. European thyroid journal 2015; 4: 123-128
28. Konturek A, Barczynski M, Wierzchowski W, Stopa M, Nowak W. Coexistence of papillary thyroid cancer with Hashimoto thyroiditis. Langenbeck's archives of surgery 2013; 398: 389-394
29. Zhang Y, Dai J, Wu T, Yang N, Yin Z. The study of the coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma. Journal of cancer research and clinical oncology 2014; 140: 1021-1026
30. Chen YK, Lin CL, Cheng FT, Sung FC, Kao CH. Cancer risk in patients with Hashimoto's thyroiditis: a nationwide cohort study. British journal of cancer 2013; 109: 2496-2501
31. Caturegli P, De Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. Thyroid : official journal of the American Thyroid Association 2013; 23: 142-150

32. Boutzios G, Vasileiadis I, Zapanti E, Charitoudis G, Karakostas E, Ieromonachou P, Karatzas T. Higher incidence of tall cell variant of papillary thyroid carcinoma in Graves' Disease. Thyroid : official journal of the American Thyroid Association 2014; 24: 347-354
33. Pazaitou-Panayiotou K, Michalakis K, Paschke R. Thyroid cancer in patients with hyperthyroidism. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2012; 44: 255-262
34. Medas F, Erdas E, Canu GL, Longheu A, Pisano G, Tuveri M, Calo PG. Does hyperthyroidism worsen prognosis of thyroid carcinoma? A retrospective analysis on 2820 consecutive thyroidectomies. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale 2018; 47: 6
35. Yeh NC, Chou CW, Weng SF, Yang CY, Yen FC, Lee SY, Wang JJ, Tien KJ. Hyperthyroidism and thyroid cancer risk: a population-based cohort study. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2013; 121: 402-406
36. Dvorkin S, Robenshtok E, Hirsch D, Strenov Y, Shimon I, Benbassat CA. Differentiated thyroid cancer is associated with less aggressive disease and better outcome in patients with coexisting Hashimotos thyroiditis. The Journal of clinical endocrinology and metabolism 2013; 98: 2409-2414
37. Durante C, Tognini S, Montesano T, Orlandi F, Torlontano M, Puxeddu E, Attard M, Costante G, Tumino S, Meringolo D, Bruno R, Trulli F, Toteda M, Redler A, Ronga G, Filetti S, Monzani F. Clinical aggressiveness and long-term outcome in patients with papillary thyroid cancer and circulating anti-thyroglobulin autoantibodies. Thyroid : official journal of the American Thyroid Association 2014; 24: 1139-1145
38. Li TJ, Lin YS, Liang J, Li F. Time to disappearance of thyroglobulin antibodies and influencing factors in patients with papillary thyroid carcinoma. Zhongguo yi xue ke xue yuan xue bao Acta Academiae Medicinae Sinicae 2012; 34: 258-261
39. Yoshioka W, Miyauchi A, Ito M, Kudo T, Tamai H, Nishihara E, Kihara M, Miya A, Amino N. Kinetic analyses of changes in serum TSH receptor antibody values after total thyroidectomy in patients with Graves' disease. Endocrine journal 2016; 63: 179-185
40. Takamura Y, Nakano K, Uruno T, Ito Y, Miya A, Kobayashi K, Yokozawa T, Matsuzuka F, Kuma K, Miyauchi A. Changes in serum TSH receptor antibody (TRAb) values in patients with Graves' disease after total or subtotal thyroidectomy. Endocrine journal 2003; 50: 595-601
41. Spencer C, Fatemi S. Thyroglobulin antibody (TgAb) methods - Strengths, pitfalls and clinical utility for monitoring TgAb-positive patients with differentiated thyroid cancer. Best practice & research Clinical endocrinology & metabolism 2013; 27: 701-712
42. Fiore E, Latrofa F, Vitti P. Iodine, thyroid autoimmunity and cancer. European thyroid journal 2015; 4: 26-35
43. Lupoli GA, Okosieme OE, Evans C, Clark PM, Pickett AJ, Premawardhana LD, Lupoli G, Lazarus JH. Prognostic significance of thyroglobulin antibody epitopes in differentiated thyroid cancer. The Journal of clinical endocrinology and metabolism 2015; 100: 100-108
44. Frohlich E, Wahl R. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. Frontiers in immunology 2017; 8: 521
45. Teixeira Mendes LS, Wotherspoon A. Marginal zone lymphoma: Associated autoimmunity and auto-immune disorders. Best practice & research Clinical haematology 2017; 30: 65-76
46. Mizokami T, Hamada K, Maruta T, Higashi K, Yamashita H, Noguchi Y, Noguchi H, Tajiri J. Development of Primary Thyroid Lymphoma during an Ultrasonographic Follow-up of Hashimoto's Thyroiditis: A Report of 9 Cases. Internal medicine (Tokyo, Japan) 2016; 55: 943-948
47. Benvenga S, Antonelli A, Vita R. Thyroid nodules and thyroid autoimmunity in the

context of environmental pollution. Reviews in endocrine & metabolic disorders 2015; 16: 319-340
48. Yoon YH, Kim HJ, Lee JW, Kim JM, Koo BS. The clinicopathologic differences in papillary thyroid carcinoma with or without co-existing chronic lymphocytic thyroiditis. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2012; 269: 1013-1017
49. Jeong JS, Kim HK, Lee CR, Park S, Park JH, Kang SW, Jeong JJ, Nam KH, Chung WY, Park CS. Coexistence of chronic lymphocytic thyroiditis with papillary thyroid carcinoma: clinical manifestation and prognostic outcome. Journal of Korean medical science 2012; 27: 883-889
50. Girardi FM, Barra MB, Zettler CG. Papillary thyroid carcinoma: does the association with Hashimoto's thyroiditis affect the clinicopathological characteristics of the disease? Brazilian journal of otorhinolaryngology 2015; 81: 283-287
51. Zhu F, Shen YB, Li FQ, Fang Y, Hu L, Wu YJ. The Effects of Hashimoto Thyroiditis on Lymph Node Metastases in Unifocal and Multifocal Papillary Thyroid Carcinoma: A Retrospective Chinese Cohort Study. Medicine 2016; 95: e2674
52. Ieni A, Vita R, Magliolo E, Santarpia M, Di Bari F, Benvenga S, Tuccari G. One-third of an Archivial Series of Papillary Thyroid Cancer (Years 2007-2015) Has Coexistent Chronic Lymphocytic Thyroiditis, Which Is Associated with a More Favorable Tumor-Node-Metastasis Staging. Frontiers in endocrinology 2017; 8: 337
53. Shen CT, Zhang XY, Qiu ZL, Sun ZK, Wei WJ, Song HJ, Luo QY. Thyroid autoimmune antibodies in patients with papillary thyroid carcinoma: a double-edged sword? Endocrine 2017; 58: 176-183
54. Jo K, Kim MH, Ha J, Lim Y, Lee S, Bae JS, Jung CK, Kang MI, Cha BY, Lim DJ. Prognostic value of preoperative anti-thyroglobulin antibody in differentiated thyroid cancer. Clinical endocrinology 2017; 87: 292-299
55. Pellegriti G, Mannarino C, Russo M, Terranova R, Marturano I, Vigneri R, Belfiore A. Increased mortality in patients with differentiated thyroid cancer associated with Graves' disease. The Journal of clinical endocrinology and metabolism 2013; 98: 1014-1021
56. Ergin AB, Saralaya S, Olansky L. Incidental papillary thyroid carcinoma: clinical characteristics and prognostic factors among patients with Graves' disease and euthyroid goiter, Cleveland Clinic experience. American journal of otolaryngology 2014; 35: 784-790
57. Paparodis R, Imam S, Todorova-Koteva K, Staii A, Jaume JC. Hashimoto's thyroiditis pathology and risk for thyroid cancer. Thyroid : official journal of the American Thyroid Association 2014; 24: 1107-1114
58. Yu H, Huang X, Liu X, Jin H, Zhang G, Zhang Q, Yu J. Regulatory T cells and plasmacytoid dendritic cells contribute to the immune escape of papillary thyroid cancer coexisting with multinodular non-toxic goiter. Endocrine 2013; 44: 172-181
59. Lewinski A, Sliwka PW, Stasiolek M. Dendritic cells in autoimmune disorders and cancer of the thyroid. Folia histochemica et cytobiologica 2014; 52: 18-28
60. Imam S, Paparodis R, Sharma D, Jaume JC. Lymphocytic profiling in thyroid cancer provides clues for failure of tumor immunity. Endocrine-related cancer 2014; 21: 505-516
61. Fang W, Ye L, Shen L, Cai J, Huang F, Wei Q, Fei X, Chen X, Guan H, Wang W, Li X, Ning G. Tumor-associated macrophages promote the metastatic potential of thyroid papillary cancer by releasing CXCL8. Carcinogenesis 2014; 35: 1780-1787
62. Zeng RC, Jin LP, Chen ED, Dong SY, Cai YF, Huang GL, Li Q, Jin C, Zhang XH, Wang OC. Potential relationship between Hashimoto's thyroiditis and BRAF(V600E) mutation status in papillary thyroid cancer. Head & neck 2016; 38 Suppl 1: E1019-1025
63. Xing M, Clark D, Guan H, Ji M, Dackiw A, Carson KA, Kim M, Tufaro A, Ladenson P,

Zeiger M, Tufano R. BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009; 27: 2977-2982

64. Xing M, Alzahrani AS, Carson KA, Viola D, Elisei R, Bendlova B, Yip L, Mian C, Vianello F, Tuttle RM, Robenshtok E, Fagin JA, Puxeddu E, Fugazzola L, Czarniecka A, Jarzab B, O'Neill CJ, Sywak MS, Lam AK, Riesco-Eizaguirre G, Santisteban P, Nakayama H, Tufano RP, Pai SI, Zeiger MA, Westra WH, Clark DP, Clifton-Bligh R, Sidransky D, Ladenson PW, Sykorova V. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. Jama 2013; 309: 1493-1501
65. Marotta V, Guerra A, Zatelli MC, Uberti ED, Di Stasi V, Faggiano A, Colao A, Vitale M. BRAF mutation positive papillary thyroid carcinoma is less advanced when Hashimoto's thyroiditis lymphocytic infiltration is present. Clinical endocrinology 2013; 79: 733-738
66. Kim SJ, Myong JP, Jee HG, Chai YJ, Choi JY, Min HS, Lee KE, Youn YK. Combined effect of Hashimoto's thyroiditis and BRAF(V600E) mutation status on aggressiveness in papillary thyroid cancer. Head & neck 2016; 38: 95-101
67. Kim SK, Woo JW, Lee JH, Park I, Choe JH, Kim JH, Kim JS. Chronic lymphocytic thyroiditis and BRAF V600E in papillary thyroid carcinoma. Endocrine-related cancer 2016; 23: 27-34

Table 1. Comparison of the prevalence of thyroid autoimmunity between PTCs and benign nodules in surgical specimens.

First author, ref#	Prevalence of thyroid autoimmunity [a] [%, (#patients / #samples)]		p
	in PTCs	in benign nodules	
Campos [20]	26.8 (11/41)	6.6 (13/198)	0.0058
Ye [10]	18.4 (188/1,024)	6.4 (66/1,028)	<0.001
Boi [13]	40.0 (38/95) [b]	26.0 (25/96) [b]	0.04
	2.9 (1/35)	36.5 (19/52)	<0.001
Lun [14]	18.8 (127/676)	7.2 (129/1,802)	<0.01
	27.2 (140/514) [c]	15.4 (232/1,510) [c]	
	15.4 (79/513) [d]	8.1 (122/1,507) [d]	
Zhang [11]	40.7 (44/144)	12.7 (64/503)	<0.001
Giagouta [12]	32.0 (441/1380)	29.1 (240/824)	*0.61* [i]
Azizi [15]	20.6 (48/233) [e]	10.2 (182/1,790) [e]	<0.0001
	31.3 (73/233) [f]	26.7 (478/1,790) [f]	*0.13*
Wu [16]	16.2 (87/537) [e]	10.4 (166/1,595) [e]	0.000
	5.2 (28/537) [f]	3.4 (54/1,595) [f]	*0.06*
Vasileiadis [18]	33.2 (129/389)	26.2 (117/447)	0.027
	32.4 (11/34) [b]	24.2 (22/91) [b]	*0.356*
	38.2 (13/34) [b,e]	19.8 (18/91) [b,e]	0.033
Cho [21]	70.1 (180/257) [f]	25.3 (65/257) [f]	<0.001
Qin [19]	23.6 (56/237) [e]	12.6 (177/1,401) [e]	<0.001
	12.7 (30/237) [f]	7.6 (106/1,401) [f]	0.009
de Alcantara-Jones [23]	27.3 (9/33)	31.3 (5/16)	*0.8*
Veit [17]	47.8 (32/67)	3.0 (3/100) [g]	<0.001
		27.0 (27/100) [h]	<0.01
	34.0 (23/67) [f]	5.0 (3/60) [f]	<0.001
Selek [22]	29.8 (172/577)	30.7 (90/293)	*0.34*
	17.0 (98/577) [e]	14.0 (41/293) [e]	*0.31*
	25.1 (145/577) [f]	28.3 (83/293) [f]	*0.36*

a, judged by histology of the surgical specimens, if not specified.
b, the tumors with indeterminate cytology were selected. Pathological diagnosis was done following surgery.
c and d, judged by anti-Tg antibodies and anti-TPO antibodies, respectively, after removing patients with histologically proven Hashimoto's thyroiditis.
e and f, judged by anti-Tg antibodies and anti-TPO antibodies, respectively.
g, in focal to diffuse dense lymphocyte infiltration with germinal centers.
h, in focal to diffuse dense lymphocyte infiltration with germinal centers and also scant scattered lymphocyte infiltration.
i, $p>0.05$ is depicted in italic.

Table 2. Comparison of clinical and biochemical markers for PTCs *vs.* benign nodules in surgical specimens.

	Age	Sex	T3/T4	TSH	Lymphocyte infiltration	TgAb	TPOAb	Others
Ye [10]	younger	M<F	→ [a]	↑ [b]	↑	↑	↑	micro-calcification ↑
Boi [13]	younger	N.A.[d]	N.A.	↑	N.A.	↑	↑	
Lun [14]	younger	→	↑ [c] (fT_3)	↑	↑	↑	↑	
Azizi [15]	younger	→	N.A.	↑	N.A.	↑	→	
Wu [16]	younger	→	↓ (fT_3)	↑	N.A.	↑	→	
Vasileiadis [18]	→	→	N.A.	↑	↑	↑	N.A.	tumor sizes ↓
Qin [19]	younger	→	N.A.	↑	N.A.	↑	↑	tumor sizes ↓
Selek [22]	younger	M<F	N.A.	N.A.	→	→	→	

a, b and c, no change, an increase and a decrease, respectively.
d, not assessed.

Table 3. Comparison of the prevalence of thyroid autoimmunity between benign and suspicious/malignant cytology.

First author, ref#	Prevalence of thyroid autoimmunity [%, (#patients / #samples)]		p
	Suspicious/malignant cytology	Benign cytology	
Boi [13]	49.2 (93/189) [a]	30.0 (560/1,864) [a]	<0.001
Castagna [26]	10.7 (13/121) [b]	13.0 (279/2,148) [b]	*0.57* [e]
	15.7 (19/121) [c]	16.9 (363/2,148) [c]	*0.80*
Hadjisavva [27]	52.1 (25/48) [d]	35.6 (162/455) [d]	0.025

a, b and c, judged by lymphocyte infiltration, anti-Tg antibodies and anti-TPO antibodies, respectively.
d, judged by combination of history, clinical and ultrasonographic examination and anti-thyroid antibodies.
e, p>0.05 is depicted in italic.

Table 4. Comparison of the prevalence of PTCs between patients with/without thyroid autoimmunity.

First author (ref#)	Prevalence of PTC [%, (#patients / #samples)]		p
Lymphocyte infiltration/ anti-thyroid antibodies	+	-	
Boi [13]	60.3 (38/63) [a]	44.5 (57/128) [a]	0.04
	66.0 (66/100) [b]	52.7 (106/201) [b]	0.03
Konturek [28]	23.5 (106/452) [a]	7.5 (530/7,093) [a]	<0.001
Zhang [29]	29.4 (247/839) [a]	19.4 (1,488/7,685) [a]	<0.05
Giagouta [12]	64.8 (441/681)	939/1523	*0.16* [d]
Chen [30]	1.58 [c], 0.9 (14/1,521) [a]	0.14 [c], 0.08 (5/6,084) [a]	<0.001
Vasileiadis [18]	57. 9 (128/221) [b]	42.3 (261/615) [b]	<0.001
Graves' disease	+	-	
Boutzios [32]	33.7 (61/181)	5.7 (509/9,007)	0.01
Medas [34]	20.6 (87/423)	34.3 (822/1,576)	<0.01
Yeh [35]	1.23 (210/17,033)	1.02 (347/34,066)	<0.05

a and b, judged by lymphocyte infiltration and anti-thyroid antibodies, respectively.
c, the incidence rates (per 1,000 person-years)
d, p>0.05 is depicted in italic.

Table 5. Comparison of the prevalence of PTC in indeterminate cytology with/without thyroid autoimmunity.

First author, ref#	Prevalence of PTC [%, (#patients / #samples)]		p
	thyroid autoimmunity-positive	thyroid autoimmunity-negative	
Boi [13]	5.0 (1/20) [a]	50.7 (34/67) [a]	<0.001
Vasileiadis [18]	33.3 (13/31) [a]	25.0 (23/92) [a]	*0.36* [c]
	40.6 (13/31) [b]	22.3 (21/94) [b]	0.033
Karatzas [5]	49.2 (30/61) [a]	23.7 (31/133) [a]	<0.001

a and b, thyroid autoimmunity positivity/negativity was judged by lymphocyte infiltration and anti-Tg antibodies, respectively.
c, p>0.05 is depicted in italic.

Table 6. Analysis of characteristics for PTCs co-occurrent with thyroid autoimmunity vs. PTCs without thyroid autoimmunity.

	markers	age	sex (male)	tumor size	invasion	lymph node metastasis	distant metastasis	TNM	prognosis
Thyroid autoimmunity (lymphocyte infiltration and/or positive anti-thyroid antibodies)									
Yoon [48]	LI [a]	younger	↓	↓	↓	↓	N.A.	N.A.	N.A.
Jeong [49]	LI	younger	↓	↓	↓	→	N.A.	→	↑
Ye [10]	LI	→	↓	→	→	→	→	→	N.A.
Lun [14]	ATAb [b]	younger	↓	↓	N.A.	→	N.A.	↓	N.A.
Zhang [11]	LI	→	↓	→	N.A.	→	N.A.	→	N.A.
Wu [16]	ATAb	→	↓	↑	N.A.	↑	N.A.	N.A.	N.A.
Vasileiadis [18]	LI	→	→	→	→	↑	N.A.	N.A.	N.A.
Giagouta [12]	LI	younger	→	↓	↓	↓	↓	↓	N.A.
Durante [37]	TgAb	→	→	↓	↑	→	→	N.A.	↓
Qin [19]	TPOAb	younger	→	→	→	→	N.A.	→	N.A.
	TgAb	→	↓	→	↑	→	N.A.	→	N.A.
Konturek [28]	TPOAb	N.A.	N.A.	↓	N.A.	↑	N.A.	N.A.	N.A.
Dvorkin [36]	LI or ATAb	→	↓	↓	→	↓	→	N.A.	↑
Zhang [29]	LI	younger	↓	↓	↓	↓ (lateral LN)	N.A.	↓	N.A.
Hacihamdioglu [24]	LI or ATAb	older	↓	↓	→	→	→	N.A.	→

Iliadou [7]	LI	→	→	→	↑	→	→		→
Girardi [50]	LI	→	↓	↓	→	→	→	↓	N.A.
Zhu [51]	LI	→	↓	→	↑	↓ (central LN)	N.A.	N.A.	N.A.
Shen [53]	ATAb	younger	↓	→	N.A.	↑	↓	→	N.A.
Ieni [52]	LI	younger	↓	↓	N.A.	↓	N.A.	↓	N.A.
Selek [22]	LI, ATAb	→	↓	↓	↓	→	↓	↓	N.A.
Jo [54]	TgAb		→	↓	→	→	↑	N.A.	N.A.
Graves' disease									
Pellegriti [55]	TH [c], ^{131}I-uptake	→	→	→	N.A.	→	→	→	↓
Medas [34]	TH	→	→	→	→	↑	N.A.	N.D.	↓

a, lymphcote infiltration.
b, anti-thyroid antibodies.
c, thyroid hormones.