Endokrynologia Polska
DOI: 10.5603/EP.a2016.0022
Tom/Volume 67; Numer/Number 1/2016
ISSN 0423–104X

Impact of Hashimoto's thyroiditis, TSH levels, and anti-thyroid antibody positivity on differentiated thyroid carcinoma incidence

Wpływ zapalenia tarczycy Hashimoto, stężenia TSH oraz dodatniego wyniku obecności przeciwciał przeciwtarczycowych na występowanie zróżnicowanego raka tarczycy

Filip Gabalec[1*], Libuse Srbova[2*], Marketa Nova[3], Eva Hovorkova[3], Helena Hornychova[3], Iva Jakubikova[1], Ales Ryska[3], Jan Cap[1]
**These authors contributed equally to the work*

[1]University Hospital in Hradec Kralove, 4th Department of Internal Medicine Charles University, Faculty of Medicine in Hradec Kralove, Hradec Kralove, Czech Republi
[2]The Institute of Endocrinology, Department of Clinical Endocrinology, Prague, Czech Republic
[3]The Fingerland Department of Pathology, Charles University, Faculty of Medicine in Hradec Kralove, Hradec Kralove, Czech Republic

Abstract
Introduction: The relationship between Hashimoto's thyroiditis (HT) and thyroid cancer (TC) is controversial. While most surgical studies report a high incidence of malignancy among patients with HT, cytological studies do not. The role of autoantibodies in the incidence of malignancy is unclear.
Material and methods: A single-centre retrospective observational study was conducted in patients evaluated for thyroid nodules by US-guided fine-needle aspiration cytology (FNAC) and, if indicated, by surgery. The levels of thyroid-stimulating hormone (TSH) and anti-thyroid antibodies were measured at the time of FNAC.
Results: Of 4947 patients, 599 (12.1%) were diagnosed with HT. A malignant/suspicious cytological result was found in 14.2% of the patients with HT and in 15.2% of the others. The odds ratio (OR) for malignancy in HT was 0.921 (0.716–1.183, p = 0.51). Of 1603 patients who underwent surgery, differentiated thyroid carcinoma was found in 29.5% of the HT patients and in 15.2% of the others (OR 2.33, 95% confidence interval CI, 1.403–3.854, p < 0,001). Low TSH (< 0.4 mIU/L) decreased the malignancy rate in the entire patient population, both when considering the cytological results and the surgical results. This was not confirmed in the subgroup diagnosed with HT. No relationship was observed between autoantibodies against thyroid peroxidase (ATP) or thyroglobulin (ATG) and malignancy rate.
Conclusions: No association between HT and thyroid cancer was observed cytologically; a positive relationship in histological series was caused by selection bias. Low TSH levels decreased the risk of TC in patients with nodular goitre, but this has not been proven in patients with HT. **(Endokrynol Pol 2016; 67 (1): 48–53)**

Key words: *thyroid cancer; thyroid nodule; biopsy, fine-needle biopsy, thyroiditis*

Streszczenie
Wstęp: Związek pomiędzy zapaleniem tarczycy Hashimoto (HT) i rakiem tarczycy (TC) jest uważany za kontrowersyjny. Podczas gdy większość badań nad operacjami dokumentuje wysoką częstotliwość występowania guzów wśród pacjentów z HT, badania cytologiczne tego nie potwierdzają. Rola autoprzeciwciał w częstotliwości występowania guzów nie jest do końca jasna.
Materiał i metody: Wśród pacjentów, u których stwierdzono guzki tarczycy przeprowadzono jednoośrodkowe, retrospektywne badanie obserwacyjne poprzez aspiracyjną cytologię cienkoigłową (FNAC) pod kontrolą USG oraz operacyjnie, jeśli takie było wskazanie. Stężenia tyreotropiny (TSH) oraz przeciwciał przeciwtarczycowych zmierzono podczas przeprowadzania FNAC.
Wyniki: Z 4947 pacjentów, u 599 (12,1%) zdiagnozowano HT. Zły/podejrzany wynik cytologii stwierdzono u 14,2% pacjentów z HT oraz u 15,2% innych pacjentów. Iloraz szans (OR) dla guza przy HT wynosił 0,921 (0,716–1,183, p = 0,51). Z 1603 pacjentów, których poddano operacji, zróżnicowanego raka tarczycy wykryto u 29,5% pacjentów z HT i u 15,2% innych pacjentów (OR 2,33; 95% CI; 1,403–3,854, p < 0,001). Niski poziom TSH (< 0,4 mIU/l) obniża wskaźnik występowania guza w całej populacji pacjentów, zarówno gdy bierze się pod uwagę wyniki cytologiczne, jak i operacyjne. Nie zostało to potwierdzone w podgrupie, u której zdiagnozowano HT. Nie zaobserwowano związku pomiędzy autoprzeciwciałami przeciw peroksydazie tarczycowej (ATP) lub tyreoglobulinie (ATG) i wskaźnikiem występowania guzów.
Wnioski: Nie zaobserwowano cytologicznego związku pomiędzy HT i rakiem tarczycy; dodatni związek w seriach histologicznych spowodowany był stronniczością selekcji. Niskie stężenie TSH obniżył ryzyko TC u pacjentów z wolem guzkowym, lecz nie zostało to udowodnione u pacjentów z HT. **(Endokrynol Pol 2016; 67 (1): 48–53)**

Słowa kluczowe: *rak tarczycy; guzek tarczycy; biopsja, biopsja cienkoigłowa, zapalenie tarczycy*

This work was supported by the MH CZ — DRO (UHHK, 00179906), project BBMRI LM2010004, and the programs PRVOUK P37/08 and P37/11.

Filip Gabalec M.D., Ph.D., 4th Department of Internal Medicine — Haematology University Hospital Hradec Kralove, Sokolska 581, 50005 Hradec Kralove,Czech Republic, phone: +420 495 834 676, e-mail: filip.gabalec@fnhk.cz, gabaf@seznam.cz

Introduction

Among endocrine tumours, thyroid cancer (TC) is the most common malignancy. According to the National Oncological Registry of the Czech Republic, the 2011 incidence of malignant thyroid neoplasms was 6.6/100,000 individuals [1]. Papillary thyroid cancer (PTC) is the most frequent TC, representing 70–80% of all TCs. Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease, with an incidence of 30–150 per 100,000 individuals worldwide and striking predominance in females (5–20:1). The relationship between HT and TC has not yet been fully ascertained. According to recent review [2], a significant difference was observed between population-based studies of fine-needle aspiration cytology (FNAC) and thyroidectomy studies. In population-based studies of FNAC from thyroid nodules, no positive correlation was detected between HT and PTC, and the prevalence of PTC in patients with HT was 1.2% with an average risk ratio of 0.69. By contrast, in studies evaluating histology after thyroidectomy, a positive relationship was reported: the prevalence of PTC in patients with HT was 27.56% with an average risk ratio of 1.59 [2]. Unfortunately, the studies evaluated in that review were vulnerable to bias. In a group of patients with HT, the risk of developing TC was 1.68-fold higher than in a control cohort of non-HT patients [3]. In another study, the incidence of PTC was higher only in patients with a nodular form of HT compared to patients with nodular goitre without HT [4]. HT was present in 23.2% of patients with PTC in a recent meta-analysis and was associated with favourable clinicopathological features [5]. Thyroid-stimulating hormone (TSH) levels, starting with the normal range, were positively associated with PTC in patients with HT, who underwent thyroidectomy [6, 7]; however, in another study, the TSH concentration was not different between patients with PTC or benign disease [8]. Thus, the relationship between anti-thyroid antibodies and the incidence of thyroid carcinoma (TC) remains controversial. In several studies, positivity for thyroid peroxidase antibody did not correlate with the malignancy rate [1, 4] while in other studies it showed inverse correlation with malignancy rate [9]. By contrast, anti-thyroglobulin (ATG) antibody positivity was associated with a slightly increased relative risk of thyroid carcinoma [1, 3, 10, 11].

The present retrospective study of human clinical specimens investigated FNAC and pathology results to evaluate their association with HT, serum TSH levels, and anti-thyroid antibody positivity.

Material and methods

The results of 6411 FNAC of thyroid nodules performed in 5333 adult patients (14.1% men and 85.9% women) between 1991 and 2014 in the Endocrinology Unit were analysed retrospectively. The study was approved by the Local Ethics Committee. All FNACs were performed under ultrasound (US) guidance. Results were classified as unsatisfactory (non-diagnostic), benign, or malignant/suspicious (undetermined). Unsatisfactory aspirates were excluded from further analysis. The results were classified as unsatisfactory if there were fewer than ten groups of cells, each containing at least ten elements. Nodular goitre with or without regressive changes, granulomatous (de Quervain's) thyroiditis, and chronic lymphocytic inflammation of variable intensity interpreted as either focal lymphocytic thyroiditis or HT were included as benign. The 'malignant/ /suspicious' category included follicular neoplasia, papillary carcinoma, anaplastic carcinoma, medullary carcinoma, lymphoma, and metastatic tumours. These cases were diagnosed either as unequivocally malignant or with varying degrees of certainty. Cases with uncertain cytological findings that could not rule out malignancy were also included in the malignant category. The histopathological examination was performed after surgery (hemithyroidectomy or total thyroidectomy). The histological results were classified as benign (nodular goitre, follicular adenoma, or HT) or malignant (follicular carcinoma, papillary carcinoma, anaplastic carcinoma, medullary carcinoma, lymphoma, or metastatic neoplasms). Anaplastic, medullary and metastatic tumours together with lymphoma were excluded from final analysis. Since it is virtually impossible to identify papillary microcarcinomas by aspiration cytology (these neoplasms were found only by chance in patients operated for suspicious FNAC from another nodule), and since these tumours have a negligible malignant potential, incidentally histologically identified microcarcinomas were also included as benign lesions.

Altogether 823 patients underwent FNAC several times. A patient was considered positive when at least one of the cytological results was classified as suspicious/malignant. The result was repeatedly non-diagnostic in 305 cases. After exclusion of 17 lymphomas, 18 medullary, 13 anaplastic, and 14 metastatic tumours, 4947 patients left for evaluation (Fig. 1).

A comparison of our classification to Bethesda classification, including sensitivity and specificity, was published previously [12]. A total of 1660 patients from 4947 patients with FNAC underwent thyroidectomy. We excluded histological diagnoses of 11 lymphomas, 18 medullary, 13 anaplastic ,and 14 metastatic carcinomas, so that 1603 histological results remained for evaluation. HT was recognised clinically if at least two of three criteria (thyroid antibodies, typical sonographic finding, and/or TSH above normal ranges) were satisfied.

The levels of TSH and anti-thyroid antibodies were detected at the time of FNAC using commercial assays.

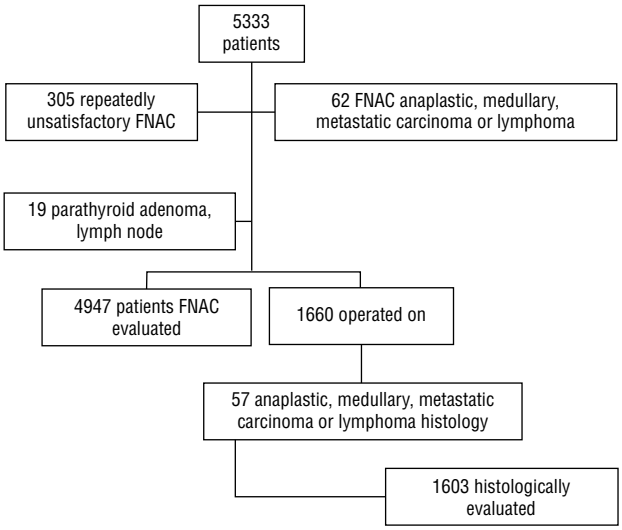

Figure 1. *Study profile*
Rycina 1. *Profil badania*

Table I. *Results of FNAC according to clinical diagnosis. Cases with non-diagnostic FNAC (35 with Hashimoto´s thyroiditis and 270 without), anaplastic, medullary, metastatic carcinomas, and lymphomas were excluded*
Tabela I. *Wyniki FNAC według diagnozy kliniczej. Przypadki z FNAC nie do zdiagnozowania (35 z HT i 270 bez), raka anaplastycznego, raka rdzeniastego i raka z przerzutami oraz chłoniaki zostały wyłączone z badania*

Cytological result	Clinical diagnosis		Altogether
	Hashimoto's thyroiditis	Other	
Thyroiditis	416 (69.5%)	72 (1.6%)	488 (9.9%)
Colloid nodule	98 (16.4%)	3.614 (83.1%)	3.712 (75.0%)
Suspicious	67 (11.2%)	499 (11.5%)	566 (11.4%)
Malignant	18 (3.0%)	163 (3.8%)	181 (3.7%)
Altogether	599	4.348	4.947

Statistics
The odds ratio (OR) for the existence of TC in the presence of HT, ATG, and anti-thyroid peroxidase (ATP) antibody positivity and low TSH (< 0.4 mIU/L) were calculated. The 95% confidence intervals (CI) were determined using online biostatistical software (http://statpages.org/ctab2x2.html). Fisher's exact test and Chi square test were used, and a two-tailed p value ≤ 0.05 was considered statistically significant.

Results

Cytological studies
FNAC results were evaluated in 4947 patients. At the time of FNAC, 599 (12.1%) patients with clinically diagnosed HT (HTpos) had nodules identified by US. Of these, benign results included nodular goitre in 98 (16.4%), HT in 413 (68.9%), and de Quervain's thyroiditis in 3 (0.5%) patients. Malignant/suspicious cytology was observed in 85 of 599 (14.2%) HT patients. In patients without clinical diagnosis of HT (HTneg), benign results included colloid nodules in 3614 (83.1%), HT in 8 (0.2%), granulomatous thyroiditis in 64 (1.7%), and other results (parathyroid gland lesion, lymph node) in 19 (0.4%) patients; the latter cases were excluded from further analysis. Malignant/suspicious FNAC results were present in 662 of 4348 cases (15.2%). The risk of suspicious cytology was not different between HTpos and HTneg patients (OR 0.92, p = 0.51). Data are shown in Table I and II.

Surgical studies
Altogether, histological results of 1603 patients were evaluated. Malignancy was found in 26 of 88 HTpos and in 231 of 1515 HTneg patients. The malignancy rate was 29.5% and 15.2%, respectively. In histological series, the rate of differentiated thyroid carcinoma was higher in HTpos patients than in HTneg patients (OR 2.33). This difference was statistically significant (p < 0.001)

Table II. *OR in this Table evaluates the ratio of malignancy in the presence (HTpos) or absence (HTneg) of clinical diagnosis of Hashimoto's thyroiditis in cytological and histological series*
Tabela II. *Niniejszy OR ocenia wskaźnik występowania guzów w obecności (HTpozytywne) lub nieobecności (HTnegatywne) diagnozy klinicznej zapalenia tarczycy Hashimoto w seriach cytologicznych i histologicznych*

	FNA series		Histology series	
	HTPOS	HTNEG	HTPOS	HTNEG
Benign (n)	514	3686	62	1284
Malignant/susp. (n)	85	662	26	231
Malignancy rate (%)	14.2	15.2	29.5	15.2
OR	0.921		2.331	
95% CI	0.716–1.183		1.403–3.854	
Chi square test	0.507		< 0.001	
Fisher's exact test	0.543		0.001	

TSH levels
The level of TSH measured at the time of FNAC was available in 2268 patients. The malignancy rate was calculated based on the TSH level, which was either low (< 0.4 mIU/L) or higher (≥ 0.4 mIU/L) (Table III). Low TSH was associated with a low probability of dif-

Table III. *OR in this Table evaluates the ratio of malignancy in patients with TSH < 0.4 as compared to the group of patients TSH > 0.4 in 2268 patients in whom TSH level was measured at the time of FNAC*

Tabela III. *Niniejszy OR ocenia wskaźnik występowania guzów wśród pacjentów ze stężeniem TSH < 0,4 w porównaniu z grupą pacjentów ze stężeniem TSH > 0,4 w grupie 2268 pacjentów, u których stężenie TSH badano w czasie przeprowadzania FNAC*

	FNAC series		Histology series	
	TSH < 0.4	TSH ≥ 0.4	TSH < 0.4	TSH ≥ 0.4
Benign (n)	608	1385	173	294
Malignant/susp. (n)	66	209	21	71
Malignancy rate (%)	9.8	13.1	10.8	19.5
OR	0.719		0.503	
95% CI	0.531–0.973		0.288–0.871	
Chi square test	0.027		0.009	
Fisher's exact test	0.029		0.008	

ferentiated thyroid carcinoma both cytologically (OR, 0.719, p = 0.027) and histologically in surgical specimens (OR 0.503, p = 0.009).

For HTpos patients the OR for malignancy in case of low TSH was 0.8, both in the cytological and histological studies, and the difference did not reach statistical significance (p = 0.704 and p = 0.835, respectively). Interpretation is difficult since the number of such cases was low. For HTneg patients, the malignancy rate was lower in case of low TSH 10.9% *vs.* 22.6% (OR 0.417, 95% CI 0.237–0.727, p = 0.001) in histological series and 9.6 *vs.* 16.7 (OR 0.529, 95% CI 0.386–0.722, p < 0.001) in cytological series.

Antibody positivity

The association of the FNAC results and surgical specimen histology with the presence of ATP and ATG autoantibodies is summarised in Table IV. The malignancy rate showed no correlation with the autoimmune status.

Discussion

The relationship between HT and thyroid carcinoma was proposed for the first time by Dailey in 1955 [13]. His work was based on surgical pathology data; however, in 1985, Holm et al. [14] published results from a 22-year study of patients with HT, in which only 2 of 829 patients developed TC. Many subsequent studies were published with controversial results. Among surgical studies, some demonstrated an association between HT [15–20] and TC, whereas others did not [21, 22]. In a systematic review published by Jankovic et al. [2], surgical studies showed a high incidence of PTC in HT. The average rate in eight retrospective thyroidectomy studies was 27.56%.

Recently, in a large series of 8524 patients who underwent surgery, Zhang also observed a significantly higher incidence of PTC in HTpos (29.4%) than in HTneg (19.4%) patients [23]. We also found a significantly higher incidence of TC in HTpos patients in our histological data. The prevalence was 29.5% for all differentiated TC. By contrast, several surgical studies reported that thyroid nodules are not more likely to be malignant in patients with HT than in patients without HT [22, 24]. Unfortunately, since the decision for surgery is mostly based on suspicious cytology results, any demonstration of association between HT and PTC in surgical studies is strongly affected by a serious selection bias [2, 25]. The retrospective character of studies is another disadvantage. Differences in results between

Table IV. *OR in this Table evaluates the ratio of malignancy according to the positivity of ATP (> 50 mIU/L) and ATG (> 300 mIU/L) in FNAC and histology series*

Tabela IV. *Niniejszy OR ocenia wskaźnik występowania guzów według podwyższonych stężeń ATP (> 50 mIU/l) i ATG (> 300 mIU/l) we FNAC i seriach histologicznych*

	FNAC series				Histology series			
	ATP+	ATP–	ATG+	ATG–	ATP+	ATP–	ATG+	ATG–
Benign (n)	513	1096	269	1340	85	300	44	346
Malignant/susp. (n)	84	197	44	225	17	66	8	75
Malignancy rate (%)	14.2	14.4	14.1	14.4	16.7	18.0	15.4	17.8
OR	0.987		0.978		0.888		0.839	
95% CI	0.74–1.32		0.74–1.32		0.47–1.65		0.35–1.95	
Chi square test	0.926		0.926		0.691		0.664	
Fisher's exact test	0.944		0.944		0.772		0.847	

individual studies may be caused, at least in part, by differences in the histopathological evaluation of the extent of lymphocytic infiltration in the tissue [24].

Controversial results were also reported in population-based studies of thyroid nodules by FNAC. Some studies reported an association between HT and TC [4, 6, 8], whereas others did not [25–31]. Possible sources of bias in Boi's [6] and Fiore's [4, 28] studies were discussed previously [25]. In a systematic review of cytological studies, [2] no positive correlation was observed between HT and PTC, and the prevalence of PTC in patients with HT was 1.2% with an average risk ratio of 0.69 [2]. Similar results were published recently in a large cytological series of 2504 consecutive patients, in which the prevalence of results suggestive or indicative of malignancy was not different between the groups studied [25]. Similarly to Castagna et al., [25] we analysed cytology and surgical specimen histology results in the same group of patients. Sample size is one of the strengths of our study. Our analysis of FNAC in 5314 patients showed no difference in risk of TC between patients with HT and patients without HT. Incidental microcarcinomas (less than 10 mm) were considered benign in histological series. There were 7 microcarcinomas with clinical diagnosis of Hashimoto thyroiditis and 33 in other diagnoses. We recalculated statistics considering them as malignant histology and the result did not change considerably.

High levels of TSH are associated with increased risk of TC [8, 10, 25, 28, 32, 33]. This was well-demonstrated in a review by McLeod et al.; [34] however, studies evaluating thyroid autoimmunity reported a lower OR for TC than other studies. In our study, we divided the population according to TSH level using a threshold of 0.4 mIU/L. In contrast to previous studies, we did not find any statistically significant difference in the incidence of malignant/suspicious FNAC result or histologically proven carcinoma between HT patients with normal TSH and HT patients with low TSH. This finding was published previously, [1] but in our series the number of histologically verified patients with HT was small. Among patients with nodular goitre, but not among patients with HT, the malignancy rate of TC was lower in patients with low TSH than in patients with normal TSH.

The relationship between thyroid autoantibodies and malignancy is controversial. Boelaert et al. [10] did not find any relationship between ATP antibody positivity and cancer risk after correction for TSH level. These results were also confirmed by others [4]. By contrast, in the study by Boi et al., positivity for autoantibodies (the authors did not specify whether thyroglobulin or thyroid peroxidase was assessed) was associated with increased probability of Bethesda IV category FNAC in patients under 53 years of age (OR, 2.29). Wong et al. [35] found that in patients with a previous benign FNAC result, malignant neoplasms confirmed by histology were more frequent in the presence than in the absence of thyroid antibodies (OR, 2.16). Similarly, in the study by Paparodis et al., [9] in patients with HT who were either euthyroid or treated with a high thyroxine dose, high ATP levels were significantly associated with a decreased incidence of TC.

As to ATG autoantibody levels, Kim et al. [8] first reported an association between ATG positivity and TC (OR, 1.61), and this finding was confirmed by subsequent studies; however, a lack of association was reported too.[35] In our series, we were not able to demonstrate any association between ATG or ATP antibody levels and cancer risk.

In conclusion, we confirmed, in a large patient population, no association between HT and TC based on cytology results. We also confirmed the fact that studies based on surgical specimens are strongly affected by selection bias. Low TSH levels are associated with a decreased risk of TC in patients with nodular goitre without HT; however, this could not be proven in patients with HT in this series. In addition, the ATG and ATP autoantibody status had no impact on cancer risk.

References

1. Dušek L, Mužík J, Kubásek M et al. Epidemiology of Malignant Tumours in the Czech Republic [online]. Masaryk University, Czech Republic. edn Version 7.0 2007, 2005.
2. Jankovic B, Le KT, Hershman JM. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? J Clin Endocrinol Metab 2013; 98: 474–482. doi: 10.1210/jc.2012-2978
3. Chen YK, Lin CL, Cheng FT et al. Cancer risk in patients with Hashimoto's thyroiditis: a nationwide cohort study. Br J Cancer 2013; 109: 2496–2501. doi: 10.1038/bjc.2013.597
4. Fiore E, Rago T, Latrofa F et al. Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. Endocr Relat Cancer 2011; 18: 429–437. doi: 10.1530/ERC-11-00210.1530/ERC-11-0028
5. Lee JH, Kim Y, Choi JW et al. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol 2013; 168: 343–349. doi: 10.1530/EJE-12-0903
6. Boi F, Lai ML, Marziani B et al. High prevalence of suspicious cytology in thyroid nodules associated with positive thyroid autoantibodies. Eur J Endocrinol 2005; 153: 637–642. doi: 10.1530/eje.1.02020
7. Ye ZQ, Gu DN, Hu HY et al. Hashimoto's thyroiditis, microcalcification and raised thyrotropin levels within normal range are associated with thyroid cancer. World J Surg Oncol 2013; 11: 56. doi: 10.1186/1477-7819-11-56
8. Kim KW, Park YJ, Kim EH et al. Elevated risk of papillary thyroid cancer in Korean patients with Hashimoto's thyroiditis. Head Neck 2011; 33: 691–695. doi: 10.1002/hed.21518
9. Paparodis R, Imam S, Todorova-Koteva K et al. Hashimoto's thyroiditis pathology and risk for thyroid cancer. Thyroid 2014; 24: 1107–1114. doi: 10.1089/thy.2013.0588
10. Boelaert K, Horacek J, Holder RL et al. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 2006; 91: 4295–4301. doi: 10.1210/jc.2006-0527
11. Fiore E, Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. J Clin Endocrinol Metab 2012; 97: 1134–1145. doi: 10.1210/jc.2011-2735
12. Cap J, Ryska A, Rehorkova P et al. Sensitivity and specificity of the fine needle aspiration biopsy of the thyroid: clinical point of view. Clin Endocrinol (Oxf) 1999; 51: 509–515. doi: 10.1046/j.1365-2265.1999.00847.x

13. Dailey ME, Lindsay S, Skahen R. Relation of thyroid neoplasms to Hashimoto disease of the thyroid gland. AMA Arch Surg 1955; 70: 291–297. doi: 10.1001/archsurg.1955.01270080137023
14. Holm LE, Blomgren H, Lowhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med 1985; 312: 601–604. doi: 10.1056/NEJM198503073121001
15. Cipolla C, Sandonato L, Graceffa G et al. Hashimoto thyroiditis coexistent with papillary thyroid carcinoma. Am Surg 2005; 71: 874–878. doi: NA
16. Dvorkin S, Robenshtok E, Hirsch D et al. Differentiated thyroid cancer is associated with less aggressive disease and better outcome in patients with coexisting Hashimotos thyroiditis. J Clin Endocrinol Metab 2013; 98: 2409–2414. doi: 10.1210/jc.2013-1309
17. Eisenberg BL, Hensley SD. Thyroid cancer with coexistent Hashimoto's thyroiditis. Clinical assessment and management. Arch Surg 1989; 124: 1045–1047. doi: 10.1001/archsurg.1989.01410090055012
18. Ott RA, McCall AR, McHenry C et al. The incidence of thyroid carcinoma in Hashimoto's thyroiditis. Am Surg 1987; 53: 442–445.
19. Repplinger D, Bargren A, Zhang YW et al. Is Hashimoto's thyroiditis a risk factor for papillary thyroid cancer? J Surg Res 2008; 150: 49–52. doi: 10.1016/j.jss.2007.09.020
20. Buyukasik O, Hasdemir AO, Yalcin E et al. The association between thyroid malignancy and chronic lymphocytic thyroiditis: should it alter the surgical approach? Endokrynol Pol 2011; 62: 303–308.
21. Rago T, Di Coscio G, Ugolini C et al. Clinical features of thyroid autoimmunity are associated with thyroiditis on histology and are not predictive of malignancy in 570 patients with indeterminate nodules on cytology who had a thyroidectomy. Clin Endocrinol (Oxf) 2007; 67: 363–369. doi: 10.1111/j.1365-2265.2007.02892.x
22. Mazokopakis EE, Tzortzinis AA, Dalieraki-Ott EI et al. Coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma. A retrospective study. Hormones (Athens) 2010; 9: 312–317.
23. Zhang Y, Dai J, Wu T et al. The study of the coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma. J Cancer Res Clin Oncol 2014; 140: 1021–1026. doi: 10.1007/s00432-014-1629-z
24. Giagourta I, Evangelopoulou C, Papaioannou G et al. Autoimmune thyroiditis in benign and malignant thyroid nodules: 16-year results. Head Neck 2014; 36: 531–535. doi: 10.1002/hed.23331
25. Castagna MG, Belardini V, Memmo S et al. Nodules in autoimmune thyroiditis are associated with increased risk of thyroid cancer in surgical series but not in cytological series: evidence for selection bias. J Clin Endocrinol Metab 2014; 99: 3193–3198. doi: 10.1210/jc.2014-1302
26. Anil C, Goksel S, Gursoy A. Hashimoto's thyroiditis is not associated with increased risk of thyroid cancer in patients with thyroid nodules: a single-center prospective study. Thyroid 2010; 20: 601–606. doi: 10.1089/thy.2009.0450
27. Erdogan M, Erdem N, Cetinkalp S et al. Demographic, clinical, laboratory, ultrasonographic, and cytological features of patients with Hashimoto's thyroiditis: results of a university hospital of 769 patients in Turkey. Endocrine 2009; 36: 486–490. doi: 10.1007/s12020-009-9258-z
28. Fiore E, Rago T, Provenzale MA et al. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. Endocr Relat Cancer 2009; 16: 1251–1260. doi: 10.1677/ERC-09-0036
29. Grani G, Calvanese A, Carbotta G et al. Thyroid autoimmunity and risk of malignancy in thyroid nodules submitted to fine-needle aspiration cytology. Head Neck 2015; 37: 260–264. doi: 10.1002/hed.23587
30. Matesa-Anic D, Matesa N, Dabelic N et al. Coexistence of papillary carcinoma and Hashimoto's thyroiditis. Acta Clin Croat 2009; 48: 9–12.
31. de Alcantara-Jones DM, de Alcantara-Nunes TF, Rocha Bde O et al. Is there any association between Hashimoto's thyroiditis and thyroid cancer? A retrospective data analysis. Radiol Bras 2015; 48: 148–153. doi: 10.1590/0100-3984.2014.0072
32. Fiore E, Rago T, Provenzale MA et al. L-thyroxine-treated patients with nodular goiter have lower serum TSH and lower frequency of papillary thyroid cancer: results of a cross-sectional study on 27 914 patients. Endocr Relat Cancer 2010; 17: 231–239. doi: 10.1677/ERC-09-0251
33. Haymart MR, Glinberg SL, Liu J et al. Higher serum TSH in thyroid cancer patients occurs independent of age and correlates with extrathyroidal extension. Clin Endocrinol (Oxf) 2009; 71: 434–439. doi: 10.1111/j.1365-2265.2008.03489.x
34. McLeod DS, Watters KF, Carpenter AD et al. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. J Clin Endocrinol Metab 2012; 97: 2682–2692. doi: 10.1210/jc.2012-1083
35. Wong SL, Grodski S, Yeung MJ et al. Anti-thyroid antibodies as a predictor of thyroid cancer. ANZ J Surg 2013. doi: 10.1111/ans.12453