Clinical Significance of Coexistence of Hashimoto Thyroiditis and Graves' Disease with Differentiated and Medullary Thyroid Cancer

Authors
Andreas Machens[1], Kerstin Lorenz[1], Frank Weber[2], Henning Dralle[1, 2]

Affiliations
1 Department of Visceral, Vascular and Endocrine Surgery, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
2 Department of General, Visceral and Transplantation Surgery, Section of Endocrine Surgery, University of Duisburg-Essen, Essen, Germany

Key words
Hashimoto's thyroiditis, Graves' disease, autoimmune thyroiditis, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer

received 25.06.2021
revised 20.07.2021
accepted 26.07.2021
published online 13.09.2021

Bibliography
Exp Clin Endocrinol Diabetes 2022; 130: 381–385
DOI 10.1055/a-1562-3455
ISSN 0947-7349

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Andreas Machens, MD
Department of Visceral
Vascular and Endocrine Surgery
Martin Luther University Halle-Wittenberg
Ernst-Grube-Straße 40
D-06097 Halle (Saale)
Germany
Tel.: + 49 345 557 2314, Fax: + 49 345 557 2551
AndreasMachens@aol.com

ABSTRACT

The association of Hashimoto thyroiditis and Graves' disease with papillary, follicular, and medullary thyroid cancer has not been comprehensively investigated until now. This comparative clinicopathological study of consecutive patients thyroidectomized at a surgical referral center aimed to explore interdependencies between chronic autoimmune thyroiditis and thyroid cancer. Altogether, there were 852 (58.4 %) patients with papillary thyroid cancer, 181 (12.4 %) patients with follicular thyroid cancer, and 426 (29.2 %) patients with sporadic medullary thyroid cancer, of whom 75 (5.1%) patients also had Hashimoto thyroiditis and 40 (2.7%) patients also had Graves' disease. Patients with papillary (medians of 42 vs. 48 years; P=0.008) and follicular (medians of 33 vs. 63 years; P = 0.022) thyroid cancer, unlike patients with medullary thyroid cancer (medians of 57.5 vs. 57 years; P = 0.989), were younger at thyroidectomy when they had Hashimoto thyroiditis concomitantly. No such associations were seen with Graves' disease. Primary thyroid cancers tended to be more localized in conjunction with Hashimoto thyroiditis, and less so with Graves' disease, although patterns were not consistent across tumor types. In conclusion, Hashimoto thyroiditis, but not Graves' disease, may be associated with differentiated (papillary and follicular) thyroid cancer but not with medullary thyroid cancer.

Introduction

Certain cancer types are associated with chronic inflammatory diseases whereas others are not; nevertheless, an inflammatory component is present in most human neoplastic lesions [1]. Inflammation can be a double-edged sword, either promoting tumor growth and progression or protecting against tumor development and metastatic spread [2]. For the thyroid gland, an association between Hashimoto thyroiditis and malignant thyroid neoplasms was described as early as 1955 [3]. Hashimoto thyroiditis is characterized by a cellular immune response with lymphatic infiltration of the thyroid gland by T and B cells, as well as by a humoral immune response leading to specific antibody production [4, 5]. The pathology of chronic autoimmune thyroiditis, affecting women more often than men, includes varying degrees of lymphocytic infiltration and fibrosis, with loss (Hashimoto thyroiditis) or without a loss (Graves' disease) of thyroid follicular epithelium.

A large body of evidence has accumulated ever since, indicating a link between autoimmune lymphocytic thyroiditis (Hashimoto thyroiditis) and papillary thyroid cancer. A recent systematic review and meta-analysis estimated the relative risk of Hashimoto thyroiditis among 11155 patients with papillary thyroid cancer at 2.36 ($P<0.001$), and the relative risk of papillary thyroid cancer among 7873 patients with Hashimoto thyroiditis at 1.40 ($P=0.016$) [6]. The linkage between Hashimoto thyroiditis and papillary thyroid cancer is appealing because the concept of chronic inflammation leading to a neoplastic condition is well accepted for other tissues. However, that systematic review and meta-analysis did not find any association between Hashimoto thyroiditis and follicular or medullary thyroid cancer, for which there is a paucity of pertinent studies.

Far fewer data, commonly available case reports or series limited by small sample size, cross-sectional retrospective design and selection bias, have been forthcoming on the association of Graves' disease with differentiated or medullary thyroid cancer. In light of this, the present research aimed to explore interdependencies between chronic autoimmune thyroiditis and thyroid cancer.

Patients and Methods

Study population

This study included all consecutive patients with papillary, follicular, and sporadic medullary thyroid cancer who underwent initial thyroidectomy between November 1994 and April 2021 at the Department of Visceral, Vascular, and Endocrine Surgery in Halle (Saale), a national referral center for thyroid cancer. In order not to confound the association between chronic autoimmune thyroiditis and medullary thyroid cancer, gene carriers with hereditary medullary thyroid cancer were excluded because they are frequently identified on family screening at a younger age.

Informed consent was obtained before each operation, which represented the standard of care in line with the practice guidelines of the German Society of Surgery [7]. Systematic lymph node dissection was carried out on clinical suspicion by ultrasonography, typically on evidence of enlarged nodes, or confirmation of nodal disease during clinical work-up or intraoperatively.

For retrospective analysis of existing data sets from routine patient care, national law and applicable institutional regulations do not require institutional review board approval.

Histopathological examination

The diagnosis of papillary, follicular, and medullary thyroid cancer was based on immunohistochemistry as per the World Health Organization criteria. Primary tumor diameter was determined by direct measurements on the surgical thyroid specimens. All lymph node metastases were diagnosed using the conventional histopathological methodology.

Concomitant Hashimoto thyroiditis was histopathologically diagnosed in the presence of lymphoplasmacytic infiltration with germinative center formation, oxyphilic cell metaplasia, atrophy, and fibrosis of thyroid follicles [8].

Concomitant Graves' disease was defined by a diffusely enlarged thyroid gland, supported by proof of stimulating thyrotropin (thyroid-stimulating hormone [TSH]) receptor serum autoantibodies.

Statistical analysis

For statistical analysis, the software package SPSS® version 25 (IBM, Armonk, New York, USA) was used. Categorical data are given as absolute and relative frequencies and were tested with the two-tailed Fisher's exact test. Continuous data are presented as medians with interquartile ranges. The level of statistical significance (all values were two-tailed) was set at $P<0.05$.

Results

Demographics of the study population

During the study period, 1459 patients with differentiated and medullary thyroid cancer underwent thyroidectomy at the authors' institution, of whom 892 (61.1 %) were female and 567 (38.9 %) were male (▶ **Table 1**).

Altogether, 852 (58.4 %) patients had papillary thyroid cancer, 181 (12.4 %) patients had follicular thyroid cancer, and 426 (29.2 %) patients had medullary thyroid cancer, of whom 75 (5.1%) patients also had Hashimoto thyroiditis and 40 (2.7%) patients also had Graves' disease.

Patients with papillary (medians of 42 vs. 48 years; $P=0.008$) and follicular (medians of 33 vs. 63 years; $P=0.022$) thyroid cancer, unlike patients with medullary thyroid cancer (medians of 57.5 vs. 57 years; $P=0.989$), were younger at thyroidectomy when they had Hashimoto thyroiditis concomitantly. No such association was seen with Graves' disease.

Hashimoto thyroiditis was present significantly more often among female patients with papillary (88 vs. 67 %; $P<0.001$) and medullary (83 vs. 47 %; $P=0.073$) thyroid cancer, whereas this female preponderance was less conspicuous among patients with follicular thyroid cancer (▶ **Table 1**).

In patients with papillary thyroid cancer and concomitant Hashimoto thyroiditis, thyroidectomy was performed twice as often for suspicious nodules than in patients with papillary thyroid cancer and concomitant Graves' disease (35 of 60 patients or 58 % vs. 8 of 32 patients or 25 %; $P=0.004$; data not shown).

In patients with follicular thyroid cancer, thyroidectomy was carried out for suspicious nodules in one-third of patients (1 of 3) each with concomitant Hashimoto thyroiditis and concomitant Graves' disease.

In patients with medullary thyroid cancer, all 12 patients with concomitant Hashimoto thyroiditis, and 4 of 5 patients with concomitant Graves' disease presented with increased basal calcitonin levels > 14 pg/mL suggestive of medullary thyroid cancer (medians of 192 vs. 103 pg/mL, $P=0.446$; data not shown).

Oncological characteristics of the study population

Primary thyroid cancers tended to be more localized in conjunction with Hashimoto thyroiditis, and less so with Graves' disease, although patterns were not consistent across tumor types (▶ **Table 2**).

In patients with Hashimoto thyroiditis (▶ **Table 2**, left column), primary tumors were smaller (medians of 28 vs. 47 mm in follicular thyroid cancer; $P=0.081$; and 8 vs. 14 mm in medullary thyroid cancer; $P=0.035$), exhibiting less often extrathyroid extension (medians of 18 vs. 32 % in papillary thyroid cancer; $P=0.041$) or lymph

▶ **Table 1** Demographics of the study population.

Demographic variables	Thyroid cancer	Hashimoto thyroiditis	*P*	Neither condition *	*P*	Graves' disease
Age at thyroidectomy, in years, median [IQR]	papillary (*n = 852*)	42 [30 ; 52.5] (*n = 60*)	0.008	48 [35 ; 61] (*n = 760*)	0.487	48.5 [31 ; 57.5] (*n = 32*)
	follicular (*n = 181*)	33 [10 ; -] (*n = 3*)	0.022	63 [51 ; 72] (*n = 175*)	0.821	63 [30 ; -] (*n = 3*)
	medullary (*n = 426*)	57.5 [43 ; 67] (*n = 12*)	0.989	57 [46 ; 66] (*n = 409*)	0.974	56 [49 ; 65] (*n = 5*)
Sex, no. of female patients	papillary (*n = 852*)	53 (88) (*n = 60*)	< 0.001	508 (67) (*n = 760*)	0.443	*24 (75)* (*n = 32*)
	follicular (*n = 181*)	2 (67) (*n = 3*)	> 0.999	97 (56) (*n = 175*)	0.257	3 (100) (*n = 3*)
	medullary (*n = 426*)	10 (83) (*n = 12*)	0.073	190 (47) (*n = 409*)	0.065	5 (100) (*n = 5*)

Values in parentheses denote column percentages IQR, interquartile range. * Most patients in this category had thyroid cancer against a background of nodular thyroid disease.

node metastases (medians of 17 vs. 43 % in medullary thyroid cancer; $P = 0.079$).

In patients with Graves' disease (▶ **Table 2**, right column), similar trends were observed towards smaller primary tumors (medians of 4 vs. 14 mm in medullary thyroid cancer; $P = 0.075$) and more infrequently, lymph node metastases (medians of 22 vs. 40 % in papillary thyroid cancer; $P = 0.062$).

Discussion

This is the first clinical investigation to report significantly earlier manifestations of both papillary (medians of 42 vs. 48 years; $P = 0.008$) and follicular (medians of 33 vs. 63 years; $P = 0.022$) thyroid cancer but not medullary thyroid cancer (medians of 57.5 vs. 57 years; $P = 0.989$) with concomitant Hashimoto thyroiditis. In conjunction with Hashimoto thyroiditis, thyroid cancers tended to be more localized although most comparisons were statistically nonsignificant.

In contrast, no significant associations were noted between Graves' disease and papillary, follicular, or medullary thyroid cancer, arguing against a protective role of Graves' disease described elsewhere [9].

These findings showed that Hashimoto thyroiditis may be associated with differentiated (papillary and follicular) thyroid cancer, but not with medullary thyroid cancer.

For this study, medullary thyroid cancer was a valuable reference standard to put the prevalence of Hashimoto thyroiditis and Graves' disease in papillary and follicular thyroid cancer into perspective. Biologically, medullary thyroid cancer derives from the parafollicular C cells, which synthesize and secrete calcitonin. However, Hashimoto thyroiditis, Graves' disease, and papillary and follicular cancers involve the follicular epithelium of the thyroid gland, which produces and secretes thyroxine and triiodothyronine. Conceptually, this difference could have accounted for some of the differences in the coexistence between Hashimoto thyroiditis and Graves' disease on one hand, and papillary, follicular, and medullary thyroid cancer on the other.

Patients with Hashimoto thyroiditis often develop hypothyroidism with an elevation of TSH levels in the course of their disease, due to the destruction of thyroid follicles by the autoimmune process. Although the role of TSH was not an objective of the present study, TSH is believed to play an important role in the etiology of thyroid cancer. In a systematic review and meta-analysis [10], higher serum TSH concentrations were associated with moderately higher odds of developing thyroid cancer even at normal and subnormal TSH levels. Studies controlling for autoimmunity reported markedly attenuated odds ratios for the TSH-thyroid cancer relationship [10]. Despite the presence of lymphocytic infiltration, such follicular destruction is absent in Graves' disease, a condition characterized by hyperthyroidism with a decline in TSH levels due to stimulating thyrotropin receptor autoantibodies.

The present work has strengths and limitations. A key asset was the controlled clinical environment of a tertiary surgical center with standardized histopathologic examination of thyroid specimens, creating straightforward case definitions of autoimmune disease and thyroid cancer. People with Hashimoto thyroiditis, in general, may be younger than patients with papillary and follicular thyroid cancer alone. Thus, it could not be completely ruled out that patients with either form of cancer and concomitant Hashimoto thyroiditis may have been younger just because of this possibility. However, patients with concomitant Hashimoto disease were operated more often in this study for suspicious thyroid nodules than patients with Graves' disease (58 vs. 25 %; $P = 0.004$; data not shown) and had larger primary tumor diameters (medians of 14 mm for concomitant Hashimoto's disease vs. 7 mm for concomitant Graves' disease; ▶ **Table 2**).

To study the complete tumor spectrum, incidental and nonincidental thyroid cancers were retained irrespective of surgical indication and evaluated together. Because clinical work-up in health care can vary a great deal, in particular regarding the use of fine-needle aspiration cytology, the same thyroid tumor can be incidental in one setting, and nonincidental in another setting, depending on the circumstances of the case. By implication, there is always some form of selection in clinical research which cannot be avoided altogether, whatever the study design.

▶ **Table 2** Oncological characteristics of the study population.

Oncologic variables	Thyroid cancer type	Hashimoto thyroiditis	*P*	Neither condition *	*P*	Graves' disease
Largest primary tumor diameter, in mm, median [IQR]	papillary (*n = 825*)	14 [5 ; 19] (*n = 59*)	0.695	10 [4 ; 22] (*n = 734*)	0.348	7 [4 ; 15] (*n = 32*)
	follicular (*n = 164*)	28 [11 ; -] (*n = 3*)	0.081	47 [26 ; 65] (*n = 159*)	0.254	28 [20 ; -] (*n = 2*)
	medullary (*n = 412*)	8 [5 ; 13] (*n = 12*)	0.035	14 [7 ; 25] (*n = 395*)	0.075	4 [2 ; 17.5] (*n = 5*)
Extrathyroid extension, no. of patients	papillary (*n = 852*)	11 (18) (*n = 60*)	0.041	240 (32) (*n = 760*)	0.846	9 (28) (*n = 32*)
	follicular (*n = 178*)	0 (*n = 3*)	0.269	72 (42) (*n = 172*)	> 0.999	1 (33) (*n = 3*)
	medullary (*n = 425*)	0 (*n = 12*)	0.136	84 (21) (*n = 408*)	> 0.999	1 (20) (*n = 5*)
Tumor multifocality, no. of patients	papillary (*n = 852*)	14 (23) (*n = 60*)	0.217	129 (17) (*n = 760*)	0.473	7 (22) (*n = 32*)
	follicular (*n = 181*)	0 (*n = 3*)	> 0.999	2 (1) (*n = 175*)	> 0.999	0 (*n = 3*)
	medullary (*n = 426*)	0 (*n = 12*)	> 0.999	28 (7) (*n = 409*)	> 0.999	0 (*n = 5*)
Lymph node metastases, no. of patients	papillary (*n = 852*)	24 (40) (*n = 60*)	> 0.999	301 (40) (*n = 760*)	0.062	7 (22) (*n = 32*)
	follicular (*n = 181*)	0 (*n = 3*)	> 0.999	32 (18) (*n = 175*)	0.462	1 (33) (*n = 3*)
	medullary (*n = 426*)	2 (17) (*n = 12*)	0.079	177 (43) (*n = 409*)	0.396	1 (20) (*n = 5*)

Values in parentheses denote column percentages IQR, interquartile range. * Most patients in this category had thyroid cancer against a background of nodular thyroid disease.

Because patients with suspicious nodules are preferentially referred for thyroidectomy in Germany, a previously iodine-deficient country [11], the present study may have been enriched with thyroid cancer patients, some of whom exhibited advanced disease.

Although patients referred for thyroidectomy had thyroid autoantibodies measured at the referring institutions over the years, these outside assays were not sufficiently standardized to allow for further analysis. Compared with other studies, the strong focus of the authors' institution on thyroid cancer surgery may explain the lower prevalence of papillary thyroid cancer among Hashimoto thyroiditis and Graves' disease patients (7.0 vs. 19.6–30 %, and 3.8 vs. 6.1–10.3 %) [9]. Alternatively, because the diagnosis of Hashimoto thyroiditis was largely histology-driven, milder forms of this condition may have gone unaccounted for. Enrichment of the study with more clear-cut cases of advanced disease may have augmented the effect size of some associations, which may not equally extend to primary care facilities.

Including patients with benign conditions who underwent total thyroidectomy would have broadened the study base further, probably at the cost of introducing more heterogeneity into the present investigation, which would have made controlling for confounding harder.

As in all cross-sectional studies, it was not possible to determine whether Hashimoto thyroiditis preceded papillary and follicular thyroid cancer; whether both conditions occurred simultaneously; or whether papillary and follicular thyroid cancer may have induced Hashimoto thyroiditis. This rendered it difficult to decide whether patients developed Hashimoto thyroiditis prior to their cancer.

Using stringent clinical criteria, prospective studies would have to recruit, and follow up on prohibitively large numbers of patients over extended periods of time to confirm a modest, though biologically plausible tissue-specific sequence from Hashimoto thyroiditis to differentiated thyroid cancer. Defining dose-response relationships and putting the severity of Hashimoto thyroiditis in proportion to the frequency of differentiated thyroid cancer are challenging in a population-based study because patients with Hashimoto thyroiditis frequently receive thyroxin supplementation to normalize otherwise increased TSH levels.

Conclusion

Hashimoto thyroiditis, but not Graves' disease, may be associated with differentiated (papillary and follicular) thyroid cancer but not with medullary thyroid cancer.

Conflicts of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this research.

References

[1] Guarino V, Castellone MD, Avilla E et al. Thyroid cancer and inflammation. Mol Cell Endocrinol 2010; 321: 94–102

[2] Ehlers M, Kuebart A, Hautzel H et al. Epitope-specific antitumor immunity suppresses tumor spread in papillary thyroid cancer. J Clin Endocrinol Metab 2017; 102: 2154–2161

[3] Dailey ME, Lindsay S, Skahen R. Relation of thyroid neoplasms to Hashimoto disease of the thyroid gland. AMA Arch Surg 1955; 70: 291–297

[4] 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

[5] Ehlers M, Schott M. Hashimoto's thyroiditis and papillary thyroid cancer: are they immunologically linked? Trends Endocrinol Metab 2014; 25: 656–664

[6] Resende de Paiva C, Grønhøj C, Feldt-Rasmussen U et al. Association between Hashimoto's thyroiditis and thyroid cancer in 64 628 patients. Front Oncol 2017; 7: 53

[7] Dralle H, Musholt TJ, Schabram J et al. German Association of Endocrine Surgeons practice guideline for the surgical management of malignant thyroid tumors. Langenbecks Arch Surg 2013; 398: 347–375

[8] Mizukami Y, Michigishi T, Kawato M et al. Chronic thyroiditis: thyroid function and histologic correlations in 601 cases. Hum Pathol 1992; 23: 980–988

[9] Paparodis RD, Karvounis E, Bantouna D et al. Incidentally discovered papillary thyroid microcarcinomas are more frequently found in patients with chronic lymphocytic thyroiditis than with multinodular goiter or Graves' disease. Thyroid 2020; 30: 531–535

[10] 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

[11] Völzke H, Lüdemann J, Robinson DM et al. The prevalence of undiagnosed thyroid disorders in a previously iodine-deficient area. Thyroid 2003; 13: 803–810