

# Patients with chronic autoimmune thyroiditis are not at higher risk for developing clinically overt thyroid cancer: a 10-year follow-up study

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## Abstract

**Objective:** The association between chronic autoimmune thyroiditis (CAT) and differentiated thyroid cancer (DTC) remains controversial. The incidence of DTC increases when screening procedures are implemented, as typically occurs in CAT patients being routinely submitted to thyroid ultrasound (US). The aim of this study was to longitudinally evaluate the long-term development of DTC in patients with CAT.

**Design and methods:** A retrospective longitudinal cohort study was designed. For the study, 510 patients with chronic autoimmune thyroiditis (CAT) with a 10-year follow-up were enrolled. Patients were divided in two groups according to the presence (CAT+ NOD+;  $n = 115$ ) or absence (CAT+ NOD–;  $n = 395$ ) of co-existent nodules at diagnosis. The main outcome measures were appearance of new thyroid-nodules and development of DTC during follow-up.

**Results:** During a 10-year median follow-up period, new thyroid-nodules were detected in 34/115 (29.5%) patients in the CAT+ NOD+ group and in 41/395 (10.3%) in the CAT+ NOD– group ( $P < 0.001$ ). Logistic regression analysis showed that thyroid-volume at diagnosis and belonging to the CAT+ NOD+ group significantly predicted the appearance of a new thyroid nodule during follow-up, independently of baseline age and sex. Among the 75 patients experiencing the appearance of a new nodule, 27 (39%) met the criteria for fine-needle-aspiration-cytology (FNAC). A benign cytological diagnosis was rendered in all cases.

**Conclusions:** In our series of CAT patients, the appearance of new thyroid-nodules was frequent, but none of them were found to be malignant. The presence of CAT appears to be associated with a negligible risk of developing clinically overt DTC.

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## Introduction

The association between chronic autoimmune thyroiditis (CAT) and differentiated thyroid cancer (DTC), first proposed by Dailey *et al.* in 1955, is a widely debated issue (1). DTCs are frequently diagnosed in the context of CAT and, at histology, display an inflammatory-immune cell infiltration (2, 3). However, it is still a matter of debate whether chronic autoimmune inflammation is responsible for the malignant transformation or cancer-specific inflammatory molecules induce the peri-tumoral immune inflammation. The link between different types of cancer and inflammation has been recognized since more than a century (4, 5), but data regarding thyroid tumors are still controversial. Lots of studies investigated this association, but different approaches have led to discordant findings. A clear association between HT and differentiated thyroid cancer (DTC), mainly papillary, was found in surgical series (6, 7, 8, 9, 10, 11, 12, 13, 14), whereas such an association was not found in cytological studies (15, 16, 17, 18, 19, 20, 21, 22). However, it should be acknowledged that the former studies might carry the risk for selection biases. In addition, Jackson *et al.* recently reported that chronic lymphocytic thyroiditis should be considered a risk factor for incidental thyroid cancer (23).

In a recent review of the literature, which included 11 papers for a total study population of 22 619 subjects, the authors concluded for an overall relative-risk (RR) of 1.36 for PTC in CAT patients (24). Again, discrepant data emerged when comparing cytological as opposed to surgical series. The average prevalence of PTC in CAT patients was 1.20% (RR=0.69) in cytological series (16, 17) and increased up to 27.56% (RR=1.59) in archival thyroidectomy series (6, 12, 14). This discrepancy may be explained by the fact that, because CAT *per se* does not represent an indication for thyroid surgery, retrospective analyses of surgical series introduce a selection bias (17, 24). Indeed, CAT patients undergo thyroidectomy either for the uncommon occurrence of huge Hashimoto's goiters producing compression or, more frequently, for the detection of cytologically suspicious or malignant nodules. The fact that most PTC are slowly growing and asymptomatic malignancies, and that their population incidence increases when screening procedures are implemented, add further arguments favoring a selection bias in surgical series (25, 26). Indeed, patients with CAT are likely to undergo thyroid ultrasound (US) examination both at diagnosis and during the follow-up.

The aim of our study was to longitudinally assess the possible long-term occurrence of DTC in a cohort of CAT patients undergoing regular US follow-up.

## Patients and methods

The outpatients' Data Base of the Unit of Endocrinology of ICS Maugeri (Pavia, Italy) was searched for patients who received a diagnosis of CAT between 1997 and 2014. Pavia, located in Northern Italy, is an area of mild iodine deficiency. Inclusion criteria were: (1) a diagnosis of CAT, as assessed by positive tests for circulating thyroglobulin (TgAb) and/or thyroid peroxidase (TPOAb) antibodies, and/or a hypoechoic pattern of the gland at US; (2) the availability of a thyroid US at diagnosis; (3) a benign cytology in patients initially presenting an associated thyroid nodule (NOD); and (4) a minimal follow-up period of 5 years, with a yearly thyroid US scan performed by the same operator.

The final study cohort included 510 patients (476 females and 34 males). In detail, 297 (58.2%) patients showed positive tests for both TgAb and TPOAb; 134 (26.3%) patients had only TPO Ab; 44 (8.6%) had only Tg Ab; and 35 (6.9%) patients had negative tests for both Ab and based upon a diffuse hypoechoic pattern of the thyroid at ultrasound were diagnosed with serum negative autoimmune thyroiditis (27, 28). Their median (range) age was 49 (19–82 years).

Patients were further subdivided in two groups according to the presence or absence of co-existent nodule/s at diagnosis. Group 1 (CAT+, NOD+) and group 2 (CAT+, NOD–) included 115 and 395 patients, respectively.

The median (range) follow-up period was 10 (5–17) years. The development of new thyroid nodule/s and/or significant modifications in pre-existent nodules were registered throughout the follow-up.

All patients signed an informed consent concerning the future use of their clinical-pathological data for research purposes. This study was approved by the Ethical Committee of ICS Maugeri, Pavia (Protocol N. 2403 CE).

## Thyroid ultrasound

Thyroid US evaluation was performed using a real-time US device equipped with a linear transducer operating at 7.5 MHz. All thyroid US scans were performed by the same experienced operator. Thyroid nodules were examined for the following US features: nature (i.e. solid, cystic, or mixed); echogenicity (i.e. hyperechoic, isoechoic, or hypoechoic compared with normal thyroid parenchyma and with neck muscles); size and

homogeneity (i.e. homogeneous or inhomogeneous); microcalcifications (hyperechoic spots of at least 2 mm without acoustic shadowing); regular or irregular margins; halo sign (i.e. presence or absence of an hypoechoic rim); and pattern of color-flow Doppler. The mentioned characteristics were summarized according to the EU-TIRADS classification system (29). Thyroid volume was estimated by the elliptical shape volume formula (length  $\times$  width  $\times$  depth  $\times$  0.479). Lateral neck lymph nodes were routinely examined.

### Fine needle-aspiration cytology (FNAC)

FNAC was performed in all newly developing nodules when they were larger than 1 cm in maximum diameter or, irrespective of their size, when they showed suspicious features at US. FNAC was performed under US guidance by a skilled endocrinologist using a 23-gauge needle attached to a 2.5-mL syringe. Cytological samples were classified into six classes: THY1 (nondiagnostic), THY2 (benign), THY3 (Atypia of undetermined significance or follicular lesion of undetermined significance), THY4 (follicular neoplasm or suspicious for a follicular neoplasm), THY5 (suspicious for malignancy), and THY6 (malignant), according to the Bethesda classification (30). None of the lymph node was found to require FNAC.

### Statistical analysis

Statistical analysis was performed using the SPSS Software (SPSS, Inc.). Between-groups comparisons were performed using the Student's *t*-test for unpaired data and the Mann–Whitney *U*-test according to a normal or a non-parametric distribution. Within-group comparisons

were performed using the Student's *t*-test for paired data and the Wilcoxon's test according to a normal or a non-parametric distribution. Frequencies among groups were compared using the  $\chi^2$ -test with Fisher's correction when appropriate. To test the effects of different variables independent of a covariate, multivariate logistic regression analysis was used and partial correlation coefficients were computed. The multivariate model was constructed by entering the occurrence of a new nodule as a dependent variable, while age, gender, thyroid volume at baseline and the Group (CAT+ NOD+ and CAT+ NOD–) were entered as covariates.

Kaplan–Meier estimates were used to generate an overall survival curve for new nodules occurrence and differences among CAT+ NOD+ and CAT+ NOD– groups were assessed by log-rank test. A *P* value of <0.05 was considered statistically significant. Results are expressed as mean  $\pm$  s.d., unless otherwise stated.

### Results

Table 1 shows demographic data and thyroid US features in CAT+ NOD+ and in CAT+ NOD– groups. Patients in the two subgroups had a similar gender ratio, but those in the CAT+ NOD+ group were older and had a larger thyroid gland at diagnosis. The two groups were characterized by similar frequencies of patients displaying both Tg Ab and TPO Ab, TPO Ab alone, Tg Ab alone and negative tests for Tg Ab and TPO Ab in the presence of a diffuse hypoechoic pattern of the thyroid parenchyma at US. Compared to the CAT+ NOD+ group, the CAT+ NOD– one comprised a higher percentage of patients who were on LT4 replacement therapy when they entered the study or who were started on LT4 replacement therapy just at the beginning of the follow-up. In the CAT+ NOD– group

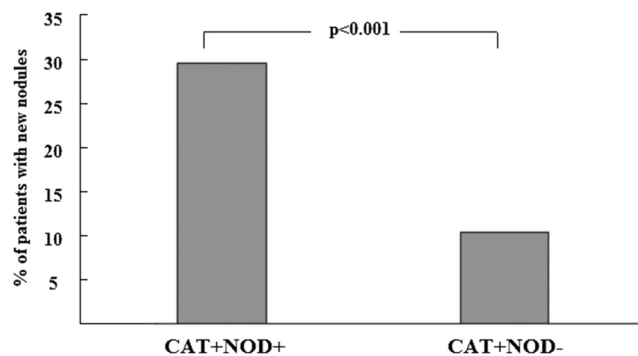
**Table 1** Demographic data, thyroid function and thyroid autoantibody status and US features in the CAT+ NOD+ and CAT+ NOD– groups.

	CAT+, NOD+ (n = 115)	CAT+, NOD– (n = 395)	P value
M/F	7/108	27/368	0.486
Age (years; median (range))	52 (21–81)	48 (19–82)	<0.001
Thyroid volume (mL; median (range))	13 (4–64)	10 (2–70)	<0.001
Serum TSH (median, 5th–95th centiles)			
At study entry	2.4 (0.6–11.37)	4.38 (10.73–38.0)	<0.001
At last evaluation	1.76 (0.50–5.72)	2.14 (0.60–6.57)	<0.05
Thyroid antibody status			0.586
TgAb+/TPOAb+	62 (53.9%)	235 (59.5%)	
TgAb+/TPOAb–	13 (11.3%)	31 (7.8%)	
TgAb–/TPOAb+	31 (27.0%)	103 (26.1%)	
TgAb–/TPOAb–	9 (7.9%)	26 (6.6%)	

143/395 (36.2%) patients were receiving LT4 when they entered the study, the correspondent figure in the CAT+ NOD+ group was 29/115 (25.2%);  $P < 0.05$ . The median serum level of TSH at study entry was higher in the CAT+ NOD- as compared to CAT+ NOD+ (4.38 vs 2.14  $\mu\text{U/mL}$ ;  $P < 0.001$ ) group. At the last evaluation, the difference was less evident although still significant (2.4 vs 1.76  $\mu\text{U/mL}$ ;  $P < 0.05$ ). Similarly, 154/252 (61.1%) patients in the CAT+ NOD- group and 31/86 (36.0%) in the CAT+ NOD+ one ( $P < 0.001$ ) were started on LT4 when recruited. The overall median and range follow-up time was 10 years (5–17) in the whole cohort, without significant differences between the two subgroups (11 (5–16) years for CAT+ NOD+ vs 10 (5–17) years for CAT+ NOD-;  $P = 0.083$ ).

Throughout the follow-up period, the US appearance of new thyroid nodules was detected in 75 out of 510 (14.7%) patients of the whole cohort. When patients' subgroups were analyzed separately, findings differed in that 34 out of 115 (29.5%) patients in the CAT+ NOD+ subgroup developed new nodules as compared with a significantly lower frequency in the CAT+ NOD- subgroup: 41 out of 395 (10.3%) patients ( $P < 0.001$ ) (Fig. 1). The median and range time for new nodules appearance was 4 (1–13) years. As shown in Fig. 2, life time survival analysis for new nodule development confirmed a significant difference between the two subgroups, with a higher risk for new nodule development in the CAT+ NOD+ subgroup (Kaplan–Meier Log Rank 24.441,  $P < 0.001$ ).

Twenty-seven out of 75 (36%) patients experiencing the appearance of a new nodule met the US criteria for performing a FNAC. In 23 of them (85% of cases), FNAC was performed due to the detection of a  $>1$  cm in maximum diameter nodule, whereas in four patients (15%) the indication for FNAC derived from suspicious US features. No difference in the rate of nodules requiring

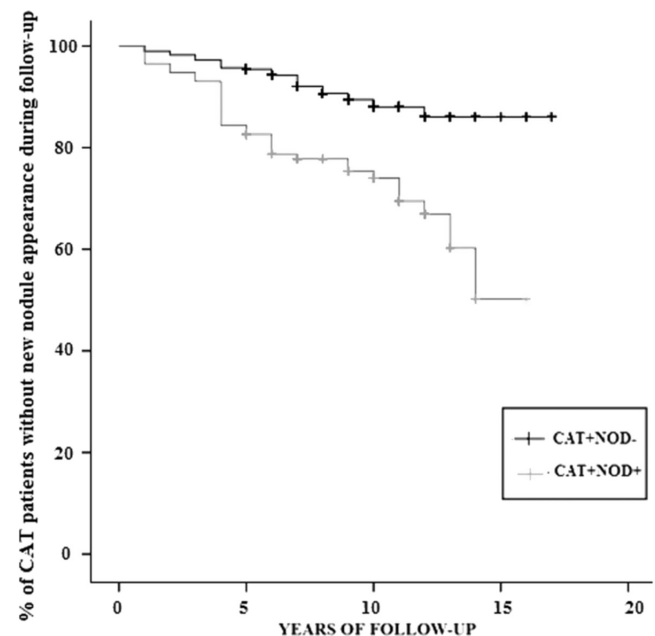


**Figure 1**

Percentage of patients who developed new nodules during the follow-up.

FNAC was observed in the two subgroups of patients (14 out of 34 patients in the CAT+ NOD+ and 13 out of 41 patients in the CAT+ NOD-;  $P = 0.472$ ). A benign cytology was observed in all the 27 patients who underwent FNAC (Table 2). The ultrasound characteristics at the end of the follow-up of both nodules requiring or not requiring FNAC are shown in Table 2. We also compared the median follow-up time calculated from the first ultrasound detection of a new nodule and the end of the follow-up in the two subgroups of nodules (6 (0–11) years vs 3.5 (0–11) years, respectively;  $P = 0.051$ ). Although statistical significance was not reached, nodules requiring FNAC showed a trend for a longer follow-up time. Table 1 summarizes the ultrasound features at the end of the follow-up of nodules requiring or not requiring FNAC.

The different rate of new nodule appearance between the two subgroups prompted further investigation. A multiple binary logistic regression model was constructed entering the appearance of new nodules (yes/no) as dependent variable and age, sex, thyroid volume at diagnosis, subgroup of patients (CAT+ NOD+/CAT+ NOD-), and number of nodules at first US as covariates. As shown in Table 3, multiple regression analysis confirmed that patients in the CAT+ NOD+ subgroup carried a significantly higher risk for developing new thyroid



**Figure 2**

Survival analysis for the development of new nodules in the CAT+ NOD+ and CAT+ NOD- subgroups. (Kaplan–Meier Log Rank 24.441,  $P < 0.001$ ).

**Table 2** Appearance of new nodules in CAT+ NOD+ and CAT+ NOD– groups and corresponding ultrasound and FNAC results.

	CAT+, NOD+ (n = 115)	CAT+, NOD– (n = 395)	P value
Follow-up time (years; (median and range))	11 (5–16)	10 (5–17)	0.083
Patients developing neo nodules (n(%))	34/115 (29.5%)	41/395 (10.3%)	<0.001
Nodules not requiring FNAC (%)	20/34 (58.8%)	28/41 (68.3%)	0.472
Maximum diameter (mm)	7.5 ± 1.6	6.6 ± 2.0	0.108
EUTIRADS			0.297
3	13/20 (65.0%)	22/28 (78.6%)	
4	7/20 (35.0%)	6/28 (21.4%)	
Nodules requiring FNAC (%)	14/34 (41.2%)	13/41 (31.7%)	0.472
Maximum diameter (mm)	13.2 ± 3.7	12.8 ± 4.3	0.831
EUTIRADS			0.989
3	9/14 (64.3%)	8/13 (51.5%)	
4	3/14 (21.4%)	3/13 (23.1%)	
5	2/14 (14.3%)	2/13 (15.4%)	
Benign cytology	14/14 (100%)	13/13 (100%)	0.989

nodules throughout the follow-up, independently of age and sex. Thyroid volume at diagnosis also independently predicted the risk of developing new nodules.

## Discussion

The findings of the present study, performed in a large cohort of patients with CAT followed by US for a median time of 10.0 years, can be summarized as follows: (1) The appearance of new thyroid nodules is not a rare event being found in 14.7% patients with CAT; (2) new nodules appeared at significantly higher rate in CAT patients with thyroid nodules at diagnosis compared with those having a nodule-free CAT (29.5% vs 10.3%, respectively); (3) all newly appeared thyroid nodules were benign at FNAC analysis; and (4) multivariate analysis identified thyroid volume and presence or absence of nodule/s at diagnosis as significantly related covariates for new-nodule development.

The main result of our study was that, during a 10-year follow-up observation, CAT did not represent a risk factor for the development of clinically overt DTC. This finding argues against the hypothesis that CAT is pathogenetically involved in the development of DTC. Rather, new thyroid nodules more frequently

appeared in patients having a larger thyroid gland and thyroid nodules at diagnosis. This observation suggests that environmental and genetic factors involved in the development of nodular goiter play a major role in the appearance of new nodules even in patients with CAT (31, 32). The present study was performed in an area of mild iodine deficiency and it should be remembered that iodine intake status, which was not assessed in our series of patients, is indeed a major factor driving development of thyroid nodularity as reported by epidemiological studies (33). Previous studies highlighted the role of higher serum levels of TSH as a risk factor for DTC development (34) being nodular autonomy a protective factor (35, 36). Furthermore, it was reported that Tg Ab but not TPO Ab would be associated with increased frequency of DTC (9, 37). However, since, in the present study, no case of DTC was observed throughout the follow-up, neither the role of serum TSH levels nor that of specific thyroid circulating antibody could be addressed. It should be noted that the limited number of nodules eligible for FNAB in our series could represent a limitation of this study.

The results of the present study are in agreement with previous studies. In 1985, Holm *et al.* (38) evaluated the incidence of DTC in 829 patients with CAT and in 829 age- and sex-matched patients with colloid goiter who

**Table 3** Logistic regression analysis for assessing the risk of new nodule development.

	P value	Exp(B)	95% CI fo Exp(B)	
			Lower	Upper
Age (years)	0.532	0.994	0.975	1.013
Gender (M/F)	0.674	0.797	0.276	2.298
Thyroid volume (mL)	<b>0.028</b>	1.030	1.003	1.057
Group (CATNOD–/CATNOD+)	<b>&lt;0.001</b>	3.337	1.942	5.734

enlisted in the Swedish cancer register from 1959 to 1981. The incidence of DTC was similar in patients with CAT compared with those having a colloid goiter (two cases in each group). The main limitation of this early study is that no ultrasound evaluation was available; thus, small non-palpable thyroid cancers could have been missed. In a more recent multicenter retrospective study, Radetti *et al.* (22) assessed the role of CAT on the development of thyroid nodules and DTC in a pediatric population of 904 children and adolescents. During a median (range) ultrasound follow-up of 4.5 (1.2–12.8) years, 10 DTC cases were recorded making an overall rate of 0.87%. However, DTC was detected in three patients at CAT diagnosis and in five patients by submitting to FNAC nodules which were already present at CAT presentation. In two patients only there was enough evidence for the development of DTC during the follow-up, thus making a 0.2% rate. Based on our and previous data, it appears that, when evaluating the risk for DTC in patients with CAT, a great discrepancy exists between cross-sectional, mainly surgical, studies, which consistently report an association, and longitudinal investigations, which fail to support this relationship. Thus, it is conceivable to believe that routine thyroid ultrasound examination of CAT patients is responsible for the high prevalence of DTC in cross sectional studies.

Taken together, the reported data support the hypothesis that patients with CAT are not characterized by an increased occurrence of clinically overt DTC, even in the long-term. Consistent with this statement is the study by Dvorkin *et al.* (15) who reported that, at diagnosis, CAT-associated DTCs are small in size and have a low rate of nodal involvement. These peculiarities suggest an earlier diagnosis and indirectly support the concept that CAT patients represent a more ultrasound screened population (15).

In conclusion, although histology remains the gold standard for diagnosing DTC, based on the results of the present study, CAT appears to be associated with a negligible risk of developing clinically overt DTC.

#### Declaration of interest

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

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