HORMONES 2013, 12(1):46-57

Review

Annual increase in the frequency of papillary thyroid carcinoma as diagnosed by fine-needle aspiration at a cytology unit in Sicily

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ABSTRACT

OBJECTIVE: An increased frequency of papillary thyroid carcinoma (PTC) has been reported in the literature, including studies based on fine-needle aspiration cytology (FNAC). DESIGN: To substantiate our own ascertainment of such an increase, we retrieved all the diagnoses of ultrasound-guided FNAC which was performed on 11,389 patients referred for cytological evaluation of a single or dominant thyroid nodule from 1988 to 2010. FNAC yielded 11,258 adequate specimens. RESULTS: The number of patients with PTC was 200 (age 10-83 yrs) and increased significantly from 1988 to 2010 (r= 0.916, *P<0.001*). Expressing data as percent of FNAC in any given year, PTC and colloid goiter increased, while adenomatous goiter, follicular lesions and anaplastic or medullary thyroid cancer decreased. PTC accounted for 0% of all FNAC diagnoses in 1988 but for 2% in 2010, with a peak of 2.6% in 2006. Of interest, chronic lymphocytic thyroiditis (CLT) also increased, preceding the increase of PTC by 5-6 years. CONCLUSION: We conclude that in the regions on either side of the Strait of Messina (Italy), PTC has become progressively more frequent during the 23-year period between 1988 and 2010 and that this increase lagged behind the increase of CLT.

Key words: Fine-needle aspiration cytology, Papillary thyroid carcinoma, Thyroid cancer

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Received 23-08-12, Accepted 03-12-12

INTRODUCTION

Fine-needle aspiration cytology (FNAC) is the diagnostic modality of choice in the evaluation of thyroid nodules, which in the vast majority of cases are nonneoplastic (benign).[1] FNAC is recommended as the initial diagnostic test for such lesions because of its simplicity and reliability. Even though FNAC cannot differentiate between benign and malignant thyroid nodules in 100% of cases, it helps substantially in selecting patients for surgery. Indeed, FNAC has decreased surgical intervention by 25% and has increased the yield of cancer in surgical specimens from 15% to more than 30%.[2] With reported sensitivity rates exceeding 90%,[1-3] cytological features are particularly accurate in the preoperative detection of papillary thyroid cancer (PTC), which accounts for ≥70% of all thyroid malignancies.[4]

As described in detail under Discussion, there are several FNAC-based studies reporting the frequency of PTC,[5-20] however, with some limitations. None of these studies[5-20] addressed the year-to-year change of PTC over a period of time longer than 15 years, particularly in comparison with other thyroid lesions. We therefore sought to assess the yearly change in the FNAC prevalence of PTC and, for comparison, of other lesions over a wide period of time in patients with thyroid nodules. Accordingly, we quantified the annual frequency of PTC and associated demographic indices (genders and age at presentation).

MATERIALS AND METHODS

All patients who come to our Unit are referred for cytological evaluation of their single or dominant thyroid nodule, all of them confirmed as "cold" nodules when thyroid scintigraphy had been performed. The Cytology Unit of our University Hospital is part of the Department of Oncology and ultrasound-guided FNAC (US-FNAC) of thyroid nodules is performed daily. The thyroid is only one of the organs examined in this Unit, with breast, liver and other abdominal organs also being investigated, both in inpatients and outpatients. The overwhelming majority of thyroid FNAC is performed in outpatients, most of who are referred by endocrinologists. All these patients come from North-Eastern Sicily, with a minority coming from Calabria, which is the region across the Strait of Messina.

US-FNAC was and continues to be requested for the diagnostic work-up of thyroid nodules, independently from thyroid volume. Starting from 1988, the team members (sonographist and cytologists) have been the same and cytological diagnoses have been computer-stored. Of 11,389 FNACs performed under US guidance on 11,389 subjects (9,341 women and 2,048 men, F:M ratio= 4.6:1) with a single or dominant thyroid nodule in the 23-year period between January 01, 1998 and December 31, 2010, FNACs were performed in 11,258 persons. FNACs were considered adequate[21] when a smear contained at least 6 groups each with 10 or more benign, well-preserved cells. Over the years the cytology team was composed of the same operators and used the same methodology. Cells were aspirated from the single or dominant thyroid nodule by the ultrasonographist (C.S.). The sonographist punctured, with a minimum of 5 passes under continuous real-time US guidance, provided by 7.5 or 10 MHz high frequency transducers. FNAC was performed by standard technique, using a 23-gauge needle attached to a 20-ml disposable syringe mounted on Cameco's metal syringe holder. No local anesthesia was employed. Alcohol-fixed and air-dried smears were prepared; one or two slides were utilized for rapid staining (a rapid Papanicolaou method) to make an immediate interpretation of the specimen and a cytological pre-diagnosis. The others specimens were stained by the Papanicolaou and the May-Grumwald-Giemsa methods because experience demonstrated a greater efficiency when the two methods are coupled.

For the purposes of the present study we retrieved all FNAC diagnoses obtained in each of the said 23 years, disregarding the inadequate ones (n=131 or 1.15%). Next, we categorized the diagnoses of adequate FNACs into the following groups: colloid goiter (CG), adenomatous goiter (AG), follicular lesions (FL), Hürthle cell tumors (HCT), PTC, anaplastic thyroid cancer (ATC), medullary thyroid cancer (MTC), others. This last group (n= 767) consisted of benign and malignant lesions. Benign lesions (n=740) represented three types of thyroiditis: chronic lymphocytic thyroiditis (CLT), also known as Hashimoto's thyroiditis (HT, n=700), De Quervain's thyroiditis (n=38) and Riedel's thyroiditis (n=2). The identification of DQT and RT, made

after FNAC evaluation, was based on the following cytopathologic features: DQT was diagnosed based on the presence of numerous multinucleate histiocytes, few mixed inflammatory cells, abundant epitheliod histiocytes and lymphocytes. Giant cells surrounding and engulfing colloid were particularly characteristic. The giant cells in granulomatous thyroiditis were often very large and could be of either Langhans or foreign-body types. Therefore, in contrast to CLT, follicular center (immature) lymphocytes and Hürthle cells were unusual. We have also seen degenerative changes in follicular cells, residual or scanty colloid, very few macrophages and cellular debris (dirty background). Generally, in RT the findings on FNA are non-specific. The aspirate is poorly cellular, scanty or acellular. It may include a few fibroblasts (fibrosis) and a variable rate of inflammatory cells, such as leukocytes, lymphocytes and histiocytes. However, when the lined (wooden) fibrosis permitted the penetration of the needle, the characteristic finding was the presence of fibroblasts, also in tissue fragments. These two cases of RT were thyroidectomized and diagnoses confirmed at histology.

Other malignant lesions (OML, n=27) included lymphomas (n=2), squamous carcinoma (n=2), soft tissue tumors (n=5), melanoma (n= 1) and metastatic lesions (n=17), particularly from the larynx, lungs, kidneys and breasts.

According to the British Thyroid Association,[22] the AACE/AME Task Force on Thyroid Nodules,[23] the Italian Consensus Working Group[24] and the Bethesda system for Thyroid Cytopathology,[21] CG, AG, CLT, DQT and RT are benign lesions, and they are categorized as THY2/TIR 2; FL and HCT are neoplastic/proliferative lesions, and they are categorized as THY3/TIR3; PTC, ATC and MTC are malignant lesions, and they are categorized as THY5/TIR5. Inadequate (or disregarded) FNACs are classified as THY1/TIR1, while FNACs suspicious for malignancy are classified as THY4/TIR4.

Based on our experience with approximately 2,800 cytology and histology paired diagnoses after total/near total thyroidectomy, the following FNAC diagnoses are correct with these rates: 86% (CG), 61% (AG), 98% (PTC), 100% (ATC), 92% (MTC), 92% (CLT); the rate of FL and HTC being malignant (that is, follicular carcinoma or Hürthle cell carcinoma) is 66% and 15%, respectively. In the remaining cases (approximately 8,400), almost all cytological diagnoses were CG, AG and CLT.

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables as percentages. Differences between means were assessed by the ANOVA test, while the percentages of categorical variables (cytological diagnoses) based on classes of years were evaluated by the χ^2 test. To test for linear trend of change of a given index over time, Pearson's correlation coefficient was calculated between the index and the 23 calendar years. Regardless of the test, a P value of <0.05 was considered statistically significant, while a P value between 0.05 and 0.10 was considered borderline significant. Statistical analysis was performed using Kyplot v2.0 beta 13 version.

RESULTS

All data are summarized in Tables 1-3 and illustrated in Figures 1-3. As shown in Figure 1, the number of adequate FNACs increased linearly ($r= 0.956$, *$P<0.001$*). The highest increase between two subsequent years occurred between 1998 and 1999 (+75%), the smallest between 2005 and 2006 as well as between 2006 and 2007 (+3% both).

Dividing patients into year groups of equal duration, also in order to maximize numbers for scantily represented diagnoses, the chi square test showed, with respect to number of total FNACs, that: the distribution of CG and CLT was significantly increased ($P<0.001$), the distribution of PTC was borderline increased ($P= 0.075$), the distribution of HCT and MTC remained unchanged ($P= 0.59$ and 0.22, respectively), the distribution of AG, FL, ATC, suspicious for malignancy and OML was significantly decreased (*$P<0.001$*) (Table 1). On a percent basis, CG and CLT were the only categories that increased significantly over time, at a linear rate (*$P<0.001$*) (Table 2). In contrast, PTC increased borderline significantly ($P= 0.062$) (Table 2), while AG, FL, ATC and OML decreased significantly (Table 2), and MTC decreased nearly significantly ($P= 0.080$) (Table 2).

In Figure 3, all lesions whose number augmented

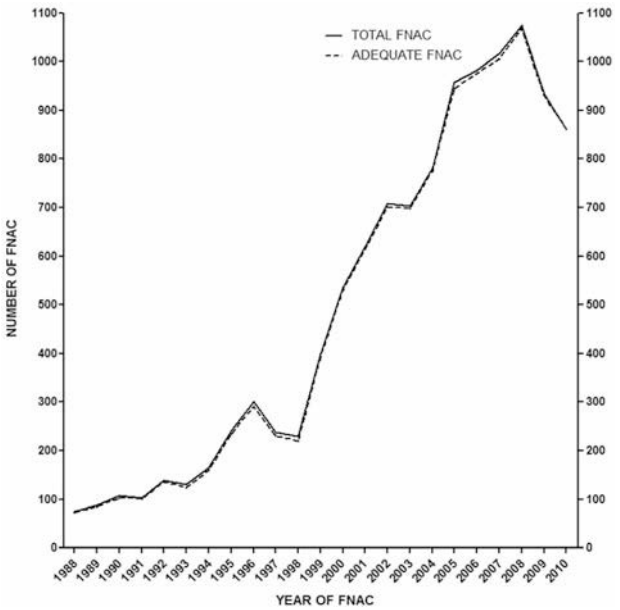

Figure 1. Yearly number of total FNACs (continuous line) and adequate FNACs (discontinuous line) performed at our cytological unit over the study period (1988-2010). The number of total FNACs increased from 75 (year 1988; adequate, n=73) to 1,075 (2008; adequate, n=1,069, a 15-fold change) and decreased in 2009 and 2010. The two curves overlap because there were only 131 inadequate specimens out of a total of 11,389 FNACs (1.2%) performed in 11,389 persons.

over time are represented on the same scale in terms of fold-increase. From this Figure, one can appreciate comparatively the time it took for any such lesion to increase by a given factor, for instance to double. Differences among lesions are evident in the new millennium, while they start becoming appreciable from the late 90's. It took 13 years for both PTC and CG to increase by 10-fold (year 2001); thereafter, it took only three years for PTC to double again (22-fold over the initial number), whereas CG did not double yet in the following six years. CLT was the only other lesion that "grew" faster than PTC (see below under the heading "Non PTC lesions").

PTC

Demographics of the 200 cases of PTC (158 women, 42 men; age 10 to 83 years) are summarized in Table 3. Consistently, men were at least 2 years younger than women, a not statistically significant difference, except in the last 3 years when men were half a year older. Moreover, males were progressively more represented over the 23-yr period.

There were no cases of PTC in 1988, but there were 26 in 2006 and 17 in 2010 (Figure 2). As mentioned above, distribution of PTC as a function of calendar years was trendwise significant in the years 1988-2010 (P= 0.075) (Table 1), but it became significant considering distribution in the four 5-year periods between 1988 and 2007 (χ^2= 8.2, *P= 0.040*). Indeed, the number of PTC doubled in 1993-1997 compared to 1988-1992, and tripled in 1998-2002 compared to 1993-1997 and in 2003-2007 compared to 1998-2002 (Table 1). During 2000-2004, the number of both total FNAC and total adequate FNAC increased by only 1.4-fold (537 to 781, and 530 to 775) and at a significantly linear pace.

Non PTC lesions

Not unexpectedly, CG was the leading lesion, which was at least 39 times more represented than PTC (Table 1), with the lowest number (51) in 1988 and the highest number (901, an 18-fold increase) in 2008. Concerning the 27 malignant lesions categorized as "Others", there were none in the years 1988, 1993, 1995, 1998, 1999, 2001 and 2004; in each of the remaining years, we observed 1 to 3 such lesions [data not shown].

As shown in Figure 3, CLT was the only lesion that "grew" faster than PTC, starting already in the mid-90's. It took 6 to 8 years for CLT to increase by 10-fold, and by the year 1999 CLT had doubled again (19-fold increase over the initial value in 1988). One year later, CLT continued to double (35-fold increase over the initial value), and doubled again after another 4 years (66-fold over the initial value). The 2007 value (90-fold increase over the initial value) is double with respect to the value in 2002 (44-fold increase over the initial value). Comparing the CLT curve with the PTC curve, it is evident that PTC lags behind CLT by 5-6 years (Figure 3). In addition, it is striking that both CLT and PTC had two peaks in around the same years. The implication of this parallelism between CLT and PTC is the still controversial issue that CLT might be a precancerous lesion, in that CLT would favor the appearance of PTC.

Table 1. Fine-needle aspiration cytology (FNAC) diagnoses in 11,389 single or dominant thyroid nodules from 11,389 persons during the years 1988-2010 and 5-year-classes thereof (except the last three years)[a]

	1988-2010	1988-1992	1993-1997	1998-2002	2003-2007	2008-2010	Statistics
Total FNAC (total adequate FNAC)	11,389 (11,258)	510 (498)	1,076 (1,040)	2,494 (2,459)	4,440 (4,400)	2,869 (2,861)	
Significantly increased							
Colloid goiter (CG)	n=9,136 80.2% (81.2%)	n=303 59.4% (60.8%)	n=816 75.8% (78.5%)	n=2,033 81.5% (82.7%)	n=3,598 81.0% (81.8%)	n=2,386 83.2% (83.4%)	**P<0.001**
Others (chronic lymphocytic thyroiditis, CLT)	n=700 6.1% (6.2%)	n=6 1.2% (1.2%)	n=25 2.3% (2.4%)	n=148 5.9% (6.0%)	n=311 7% (7.1%)	n=210 7.3% (7.3%)	**P<0.001**
Borderline increased							
Papillary thyroid cancer (PTC)	n=200 1.8% (1.8%)	n=7 1.4% (1.4%)	n=13 1.2% (1.2%)	n=32 1.3% (1.3%)	n=92 2.1% (2.1%)	n=56 2% (2%)	P=***0.075***
Unchanged							
Hürthle cell tumors (HCT)	n=32 0.28% (0.28%)	n=2 0.4% (0.4%)	n=1 0.09% (0.10%)	n=6 0.2% (0.2%)	n=12 0.3% (0.3%)	n=11 0.4% (0.4%)	P=0.590
Medullary thyroid cancer (MTC)	n=12 0.11% (0.11%)	n=2 0.4% (0.4%)	n=2 0.2% (0.2%)	n=1 0.04% (0.04%)	n=4 0.09% (0.09%)	n=3 0.1% (0.1%)	P=0.220
Significantly decreased							
Adenomatous goiter (AG)	n=743 6.5% (6.6%)	n=109 21.4% (21.9%)	n=112 10.4% (10.8%)	n=149 6.0% (6.1%)	n=271 6.1% (6.2%)	n=102 3.6% (3.6%)	**P<0.001**
Follicular lesions (FL)	n=301 2.6% (2.7%)	n=44 8.6% (8.8%)	n=43 4.0% (4.1%)	n=68 2.7% (2.8%)	n=79 1.8% (1.8%)	n=67 2.3% (2.3%)	**P<0.001**
Anaplastic thyroid cancer (ATC)	n=19 0.17% (0.17 %)	n=5 1.0% (1.0%)	n=3 0.3% (0.3%)	n=6 0.2% (0.2%)	n=3 0.07% (0.07%)	n=2 0.07% (0.07%)	**P<0.001**
Suspicious for malignancy	n=43 0.38% (0.38%)	n=7 1.4% (1.4%)	n=4 0.4% (0.4%)	n=2 0.08% (0.08%)	n=11 0.25% (0.25%)	n=19 0.7% (0.7%)	**P<0.001**
Others (malignant lesions)	n=27 0.24% (0.24%)	n=9 1.8% (1.8%)	n=7 0.6% (0.7%)	n=3 0.1% (0.1%)	n=5 0.1% (0.1%)	n=3 0.1% (0.1%)	**P<0.001**

[a] Percentages in parentheses have adequate FNAC as denominator. In the statistics column, P values correspond to the chi-square test that was performed with respect to the number of all FNAC, including inadequate. Statistics did not change using total adequate FNAC. Statistically significant P values are typed bold and, if borderline significant (P 0.10 to 0.05), they are also typed in *italics*. Statistical values do not change substantially if numbers predicted for the 5-year period 2008-2012 are considered. For instance, in the case of PTC with a predicted number of 93 cases (1.95% of 4768 predicted adequate FNACs), χ^2=8.39, P=***0.078***.

DISCUSSION

Here we have shown that in the metropolitan, semirural and rural areas served by our cytological unit (North-Eastern Sicily and Southern Calabria), PTC has become progressively more frequent during the 23-year period between 1988 and 2010 with a 9.5-fold average increase in the 18 years between 1990 and 2010. Such an increased frequency of PTC

Table 2. Pearson's correlation coefficient of the rate of the indicated cytological diagnoses in 11,389 thyroid nodules from 11,389 persons with the year of diagnosis during the period 1988-2010

		% of total FNAC
Colloid goiter (CG), n=9,136	r	0.785
	95% CI	0.760 to 1.608
	P	**<0.001**
Adenomatous goiter (AG), n=743	r	-0.78
	95% CI	-1.187 to -0.553
	P	**<0.001**
Follicular lesions (FL), n=301	r	-0.783
	95% CI	-0.470 to -0.221
	P	**<0.001**
Hürthle cell tumors (HCT), n=32	r	-0.043
	95% CI	-0.025 to 0.020
	P	0.844
Papillary thyroid cancer (PTC), n=200	r	0.396
	95% CI	-0.003 to 0.1
	P	***0.062***[a]
Anaplastic thyroid cancer (ATC), n=19	r	- 0.678
	95% CI	-0.077 to -0.026
	P	**<0.001**
Medullary thyroid cancer (MTC), n=12	r	-0.373
	95% CI	-0.036 to 0.002
	P	***0.080***
Suspicious for malignancy, n=43	r	-0.282
	95% CI	-0.086 to 0.018
	P	0.193
Others (chronic lymphocytic thyroiditis, CLT), n=700	r	0.924
	95% CI	0.299 to 0.437
	P	**<0.001**
Others (malignant lesions), n=27	r	-0.585
	95% CI	-0.125 to -0.029
	P	**0.003**

[a] Due to the two peaks of PTC in 1991 and 1994 (3.0% and 3.1% of total FNAC), correlation did not reach statistical significance. This was reached (r= 0.579, P= **0.024**) considering years 1996 through 2010. Statistically significant P values are typed bold and, if borderline significant (P 0.10 to 0.05), they are also typed in *italics*.

cannot be accounted for by the increased number of FNACs performed over the same 23-year period, the latter increase likely reflecting changes in health care level of access as well as public awareness of the importance of endocrine/thyroid 'check-up' and thyroid diseases. The discrepancy is evident in the new millennium (2001-2010), when PTC increased by an average of 3.4-fold over year 2000 but FNAC increased by an average of 1.6-fold.

In the year 1989, the single PTC observed accounted for 1.1% of the 87 FNAC, while the 22 and 26 cases of years 2004 and 2006 accounted for 2.8% of 781 and 2.6% of 982 FNAC, respectively. In particular, in the years 2001-2007 the average increase over year 2000 was 2.1-fold, in contrast to the simultaneous average of 0.6-fold and 0.5-fold decrease for AG and FL, respectively. These opposite directions of changes of PTC *vs* AG and FL underscore that PTC follows different pathways of oncogenic transformation of the thyroid follicular cell leading to thyroid neoplasia.

As summarized in Table 4, a total of 16 studies (17 with ours) have evaluated the local epidemiology of thyroid cancer/PTC based on FNAC.[5-20] Of these, only ours and another three[5,6,13] have cohorts greater than 10,000, whereas nine have cohorts smaller than 1,000.[7,8,10,11,15,17-20] Moreover, only 7/16 studies including ours[6-8,10,12,13] spanned a period longer than 10 years, but only 2/16[6,13] and ours reported year-to-year changes. Finally, among the largest studies,[5,6,13] only ours covers the years after 2004.

One limitation of FNAC studies with long case series spanning a lengthy period is the changes in the diagnosis of thyroid nodules and their clinical management over time, which are highly dependent upon several variables such as: diagnostic criteria, terminology, management guidelines, adequacy of the sample and also the physical characteristics of the biopsied thyroid lesion and operator experience (i.e. the individual performing the biopsy and interpreting the cytomorphology). In our study, the same cytopathology team assessed all FNAB samples and employed the same technique for the collection and preparation of samples, thus neutralizing or reducing not only inter-observer variability but also the abovementioned limiting variables.[25]

When these largest studies are considered,[5,6,13] our rate of malignancy of 2.3% (Table 4, footnote) matches the 2.4% rate of the other Italian cohort,[5] is similar to the 3.4% of the Taiwanese cohort[13] but is somewhat lower than the 5.6% of the Dutch cohort[6]. Two-digit rates are almost invariably reported in cohorts smaller than 1,000 cases (Table 4), with the remarkable exception of the 2.3% rate observed in Greece,[8] a Southern European country like Italy.

CLT was the only lesion that showed the highest

Table 3. Demographics of the 200 cases of papillary thyroid cancer (PTC) diagnosed by fine-needle aspiration cytology in 11,389 persons during the years 1988-2010 and 5-year-classes thereof (except the last three years)

	1988-2010	1988-1992	1993-1997	1998-2002	2003-2007	2008-2010
Total FNAC (females, males)	11,389 (9,341, 2,048)	510 (426, 84)	1,076 (915, 161)	2,494 (2,097, 397)	4,440 (3,627, 813)	2,869 (2,276, 593)[c]
Number of PTC (PTC – per time period- as % of Total No. of PTC)	200 (100%)	7 (3.5%)	13 (6.5%)	32 (16%)	92 (46%)	56 (93)[c] (28%)
F: M ratio in PTC	3.8:1	7:0	5.5:1	4.3:1	4.7:1	2.1:1 (2.0:1)[c]
No. of PTC, m ± SD per year (all)	8.7 ± 8.1	1.4 ± 1.1	2.6 ± 2.1	6.4 ± 2.9	18.4 ± 5.5	18.7 ± 1.5 (18)[c]
% PTC in females as % total FNAC in females[a]	1.69%	1.64%	1.20%	1.24%	2.09%	1.67%
% PTC in males as % of total FNAC in males[b]	2.05%	0	1.24%	1.51%	1.97%	3.04%
PTC as % of all PTC	100 % [n=200]	3.5%	6.5%	16%	46%	28% (31.2%)[c]
PTC, age (years) of all patients	42.4 ± 15.1	41.1 ± 14.3	47.3 ± 17.2	41.7 ± 14.5	41.8 ± 15.0	42.8 ± 15.6
PTC, age (years) of female patients	42.9 ± 14.9	41.1 ± 14.3	47.7 ± 18.7	42.5 ± 13.9	42.6 ± 14.8	42.6 ± 15.1
PTC, age (years) of male patients	40.8 ± 16.2	N/A	45.0 ± 8.5	38.5 ± 18.2	38.5 ± 16.0	43.1 ± 17.1

[a]Pearson's correlation coefficient of the four percentages over time was not statistically significant (r= 0.427, P= 0.473).
[b]Pearson's correlation coefficient of the four percentages over time was trendwise significant (r= 0.962, ***P*<0.001**).
[c]In parenthesis, projection over the 5-year period 2008-2012, if trend persists.

fold increase of percentage change from 1988 to 2010 based on total FNAC. These data agree with a number of studies reported in the literature, particularly with the studies methodologically closer to ours.[26-28] Because the annual increase of CLT preceded the annual increase of PTC with an overall parallelism between the two curves (Figure 3), and because both CLT and PTC displayed a similar decrease of F:M ratio over the years (this study and Ref. 27), there are grounds to believe that environmental changes may have favored both thyroid autoimmune disease and PTC-oriented thyroid oncogenesis. However, thyroid autoimmunity responded to such environmental changes more quickly than thyroid oncogenesis, thus explaining why the increased frequency of CLT preceded the increased frequency of PTC.

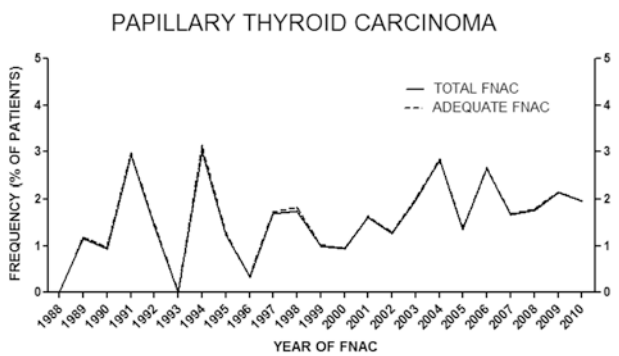

Figure 2. Prevalence of PTC as percentage of all adequate FNACs performed in each year. Prevalence does not change if expressed as % of nodules because the number of patients and number of nodules coincide. The steepest increase was between the years 2000 and 2004 (from n= 5 to n= 22, +4.4-fold, r= 0.933, 95% CI 0.28 to 0.99, P= **0.020**; from 0.93% to 2.82%, +3.0-fold, r= 0.903, 95% CI 0.10 to 0.99, P= **0.035**).

An association has been controversially suggested between CLT and PTC. Fiore et al[29] showed that the frequency of PTC in nodular-CLT patients was significantly higher compared with patients with non-CLT nodular goiter and was strongly correlated with TSH levels. These authors[29] hypothesized that higher TSH levels increase the probability that mutated oncogenes[30] may cause clinically detectable cancer. Moreover, rearrangements of RET oncogene (RET/PTC), which are frequently detected in PTC, may also be found in the thyroids of patients affected by CLT, with no histopathological evidence of PTC.[31]

There are numerous environmental factors that

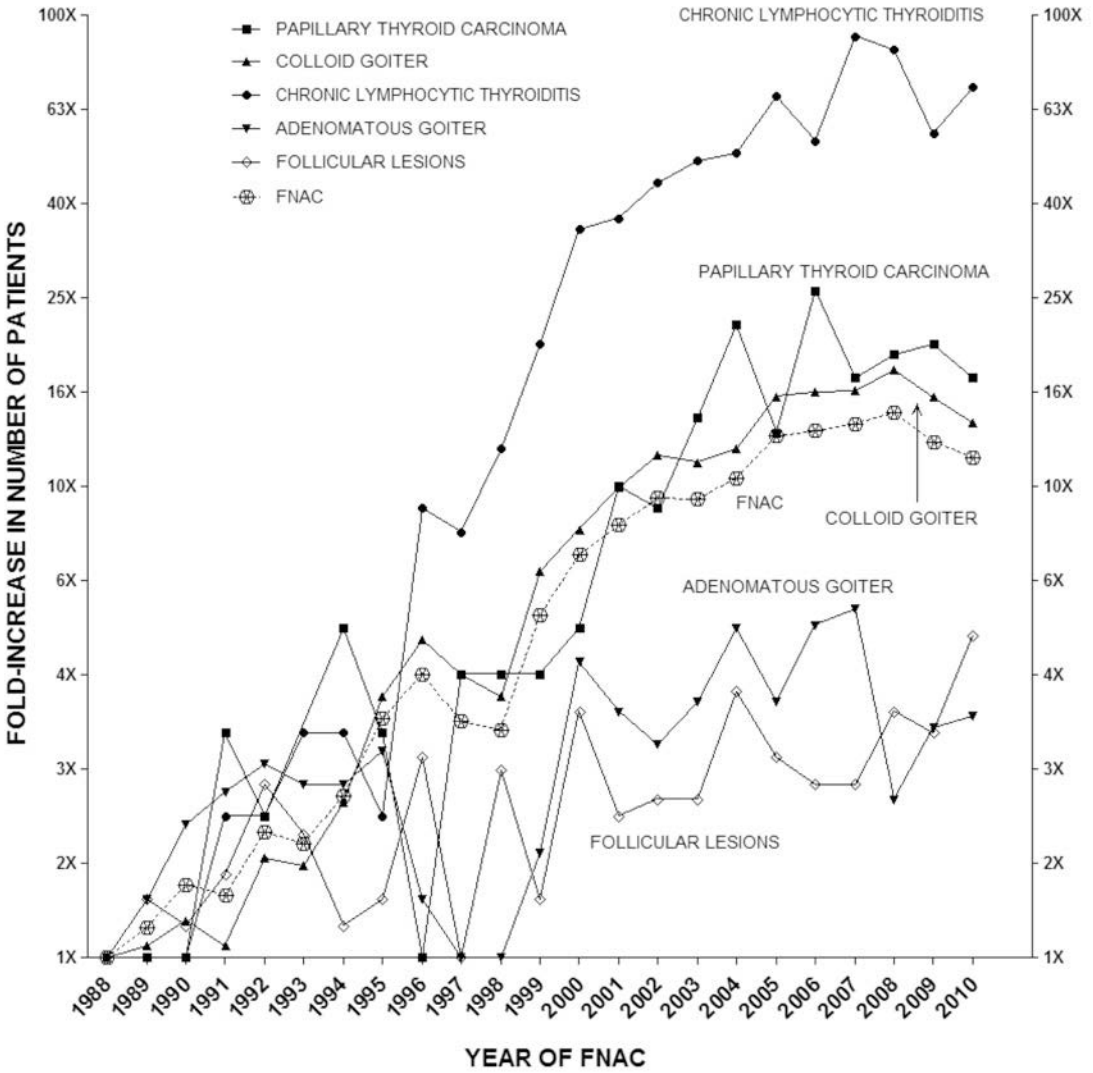

Figure 3. Fold increase in number of patients with the specified cytological diagnosis over the indicated study period (1988-2010). Note the $\log_{10}$ scale on the vertical axes.

may favor the development of thyroid nodules (including PTC) and their trends over time. Such factors include: low iodine as well as goitrogenic or non-goitrogenic natural substances contained in various foods (e.g. chlorate, thiocyanate, nitrates, isoflavones);[32,33] heavy metals and polluting chemicals that are increasingly known to affect thyroidal growth and homeostasis (e.g. polychlorinated biphenyls, phthalates, bisphenol A and other plasticizers). Compared to other areas mentioned in Table 4, in which some or all these factors could play an important role in PTC incidence, we think that another environmental factor is the presence of the Etna volcano in Eastern Sicily, precisely in the province of Catania which is just south of our province. This volcano hosts a major aquifer that provides drinking water and irrigation to large agricultural areas nearby. Various chemicals (including HCO_3, SO_4, calcium, fluoride, chloride, magnesium, boron, manganese, iron, vanadium and also ^{222}Radon) were found increased in water samples from various sources of this volcanic aquifer.[34] Finally, active volcanoes like Etna produce suspended particulate matter and gases that may contaminate the environment. However, investigation into the nature of these triggering environmental factors was not the goal of our present work.

Table 4. Summary of the international literature on the detection of papillary thyroid cancer (PTC) in patients who underwent fine-needle aspiration cytology (FNAC) for single or multiple thyroid nodules over a period comparable to that of the present study[a]

Continent, Country	Year(s) of study	Reference	FNAC	Frequency of PTC (% of total FNAC)
Europe, Italy	1988 – 2010 (23 years)	Rizzo, 2012 (this study)	11,389 FNAC on 11,389 patients with single or dominant nodule who underwent **US-FNAC**. Adequate FNAC = 11,258 (98.8%, on 11,258 patients). The number of adequate FNAC increased linearly from a minimum of 73 in 1988 to a maximum of 1,069 in 2008, a 15-fold change (r = 0.956, *P< 0.001*).	**PTC**= 200/11389 (1.8%)[b] In percentage the increase was from 0% in 1988 to 1.97% in 2010 (P= ***0.062*** by correlation), with a peak of 2.6% in 2006. Moreover, colloid goiter and chronic lymphocytic thyroiditis were the only categories that increased at a linear rate in percentage (P <**0.001**)
Europe, Italy	1997 – 2004 (8 years)	Rago, 2010[5]	FNA cytology in 47,775 nodules from 34,266 patients.	2.4% were indicative or suspicious for carcinoma
Europe, The Netherlands	1989 – 2003 (15 years)	Netea – Maier, 2008[6]	Between 1989 and 2003 a total of 44,141 FNAB were performed. The number of FNABs performed each year progressively increased from 1,093 in 1989 to 4,123 in 2003.	A diagnosis of thyroid cancer (TC) was made in 2,493 cases (5.6%) based on FNAB. The number of TCs at cytopathological examination also increased yearly by 9.5% (P <**0.0001**). Therefore, the proportion of TC diagnosed or suspected at cytological examination among all of the performed FNAB did not change during the study period (P = ***0.07***). However, there was a slight increase in incidence of **PTC** of 2.1% per year (P <**0.001**) particularly in stage I tumors, possibly, in part, because of a marked increase in use of FNAB.
Europe, Czech Republic	1986 – 2002 (17 years)	Martinek, 2004[7]	In the period 1986–2002, 781 FNACs on 245 persons with focal lesions in the thyroid gland. Adequate aspirates in 213 persons.	**PTC** in 28/245 cases (11.4%). Percentage of **PTC** on adequate FNAC= 13.1% (28/213).
Europe, Greece	1993 – 2003 (11 years)	Zagorianakou, 2005[8]	A total of 900 patients, between 1993 and 2003, who had palpable or visible thyroid nodule by ultrasonography, underwent FNA. In 179 (19.9%) FNA was inadequate.	**PTC** in 21/900 cases (2.3%). Percentage of **PTC** on adequate FNAC= 2.9% (21/721).
N. America, USA (Massachusetts)	1995 – 2003 (9 years)	Frates, 2006[9]	2,208 patients had at least one thyroid nodule larger than 10 mm in maximal diameter and underwent **US-guided FNAC**. Adequate cytology = 1,985.	**PTC** in 261/2,208 cases (11.8%). Percentage of **PTC** on adequate FNAC= 13.1% (261/1,985).
N. America, USA (New York)	1986 – 1996 (11 years)	Charles, 1997[10]	Review of 422 patients who underwent thyroid surgery. All patients had FNAB prior to surgery. Adequate cytology = 400.	**PTC** in 81/422 patients (19.2%) on FNAC. Percentage of **PTC** on adequate FNAC= 20.2% (81/400).
N. America, USA (Miami and Nashville)	2003 – 2009 (7 years)	Lew, 2011[11]	A retrospective review of prospectively collected data of 797 consecutive patients with dominant nodules >1 cm who underwent FNA and thyroidectomy.	147/797 (18.4%) positive for malignancy, 85/797 (10.7%) suspicious for **PTC**.

Table 4. (Continued) Summary of the international literature on the detection of papillary thyroid cancer (PTC) in patients who underwent fine-needle aspiration cytology (FNAC) for single or multiple thyroid nodules over a period comparable to that of the present study[a]

Continent, Country	Year(s) of study	Reference	FNAC	Frequency of PTC (% of total FNAC)
Oceania, Australia (region of Tasmania)	1988 – 1998 (11 years)	Burgess, 2006[12]	A total of 3,452 individuals underwent a thyroid procedure, comprising 1,968 surgical and 1,756 FNAB cytologic procedures in 1,532 patients. Thyroidectomy and thyroid FNAB increased by 7% and 49.7% per annum, respectively.	184 patients were diagnosed with TC (confirmed by histology), of whom 121/1,532 (7.9%) had **PTC**. The likelihood of diagnosing a PTC in any given thyroidectomy specimen increased from 3.3% in 1988 to 7.7% in 1998. Diagnoses of **PTC** in patients previously assessed by FNAB increased by 99.7% per year (P **<0.005**).
Asia, Taiwan	1986 – 1999 (14 years)	Lin, 2005[13]	21,748 patients examined in one medical center (FNAC considered the first-line examination procedure).	Malignancy on cytology = 740 / 21,748 (3.4%). Particularly, 424 / 21,748 patients (1.94%) were confirmed by histology.
Asia, Korea	1999 – 2001 (3 years)	Ko, 2003[14]	Among 1,613 consecutive FNAs of the thyroid, 207 patients (12.8%) who underwent both FNAs and surgery were selected for review. Adequate cytology= 1,532 (95%).	Malignancy in 118/1,613 (7.4%) FNAs. Of 207 thyroid lesions who underwent both FNAs and surgery, 98 were **PTC** (98/1,613= 6.1%).
Asia, Korea	2000 – 2001 (2 years)	Nam-Goong, 2004[15]	317 nodules (all impalpable) from 267 patients who underwent **US-FNAC**. Cytological diagnosis included 101 inadequate specimens (32%)	42/317 (nodules) were **PTC** (13.2%). Percentage of **PTC** on adequate FNAC= 19.4% (42/216).
Asia, Korea	2003 – 2006 (4 years)	Choi, 2008[16]	2,614 patients underwent **US-guided FNAC**, of whom 392 (15.0%) were inadequate. 343/2,614 underwent thyroidectomy.	- 311/2,614 (11.8%) malignant or suspicious for malignancy; - 73/2,614 were indeterminate; - 1,838/2,614 benign. - 198/343 were **PTC** on histology.
Asia, Korea	03/2006 – 02/2008 (2 years)	Choi, 2008[17]	658 FNAC in 658 patients. Inadequate specimens were 96 (13.7%).	- 79 (12%) positive malignancy of whom 46 underwent thyroidectomy (43/79 were **PTC** at histology); - 22 indeterminate cytology.
Asia, China	12/1999 – 12/2003 (4 years)	Cheung, 2007[18]	Total FNAC= 179 Inadequate FNAC= 32 (17.9%).	27/179 (15.1%) **PTC** or suspicious for **PTC.**
Asia, Yemen	1997 – 2001 (5 years)	Al-Hureibi, 2003[19]	243 FNAs due to thyroid swellings.	4 (1.6%) suspicious for **PTC**, 7 (2.9%) **PTC**.
Africa, Kenya	10/1994 – 04/2002 (7.58 years)	El Hag, 2003[20]	303 patients with thyroid swellings underwent FNA	Neoplasia (13.9%).

[a]These studies were retrieved through a PubMed search by entering the strings: "Papillary thyroid carcinoma AND FNA" or "Thyroid carcinoma AND FNA" or "Thyroid cancer AND FNA" or "Thyroid nodule AND FNA".

[b]To permit comparison with other cohorts of this table, rate of malignancy is 2.32% (1.8% PTC + 0.17% ATC + 0.11% MTC + 0.24% OML), while rate of malignancy and suspicious for malignancy combined is 2.56% (2.32% + 0.24%). Interestingly, results in our study reported in Table 1 on MTC show a lower frequency of MTC with respect to the Czech Republic and Korea, a higher frequency with respect to Taiwan, China and the USA, and similar results with respect to The Netherlands.

The authors have no conflict of interest to declare.

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