Increased annual frequency of Hashimoto’s thyroiditis between years 1988 and 2007 at a cytological unit of Sicily

Abstract

Like other auto-immune diseases, Hashimoto’s thyroiditis (HT) results from the interaction of genetic with environmental factors. Only few studies have evaluated the year-to-year change in frequency of HT over a wide period of time. The endocrine division of our Hospital has reported a great increase in the annual frequency of HT between 1975 and 2005, and a progressive decrease in both age at presentation and female to male (F/M) ratio starting in the mid-1990s. Between years 1988 and 2007, we have collected 8397 adequate examinations by fine needle cytoponctions and have noted a multiplication by 14 of the number of cytoponctions between 2007 and 1988. On this 20-year period, the number of cases of HT, De Quervain’s thyroiditis and Riedel’s thyroiditis were 490, 36, and 2 respectively. Cases of HT were one in 1988, but 90 in 2007 with a significant trend to increase over the time ($r = 0.919; p < 0.001$) and a significant trend to decrease in the age of cytology ($r = -0.466; p < 0.05$). In contrast, the number of cases of DQT was zero and one respectively, without significant trend to increase ($r = 0.29; p = 0.21$). The increase of HT cases started in 1996 (+350% compared to 1995). Until 1995, there was only one male case, but their number reached 22 in 2005–2007. These examinations by fine needle cytoponctions provide an independent confirmation of the studies of the same hospital division, providing arguments supplementary to the fact that modifications of the environment alone can explain the remarkable changes over a relatively short period of time.
aspiration cytology (FNAC) on 8397 persons referred for the evaluation of a solitary or dominant thyroid nodule (total FNAC and persons = 8520) with a 14-fold increase in 2007 over 1988. In this 20-year period, cases of HT, De Quervain’s thyroiditis (DQT) and Riedel’s thyroiditis (RT) were 490, 36 and two, respectively. HT cases were one in 1988 but 90 in 2007, with a significant upward temporal trend \((r = 0.466, P < 0.05)\). In contrast, DQT cases were zero and one, respectively, with no significant temporal trend \((r = 0.29, P = 0.21)\). The HT increase in frequency started in 1996 (+350% over 1995). Until 1995 there was only one man, but there were 22 men in 2005–2007. These FNAC data provide independent confirmation to the data from the endocrine division of the same hospital, further supporting the conclusion that only environmental modifications can explain these marked changes that have occurred in such a relatively short period of time.

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Keywords: Fine-needle aspiration cytology; Chronic lymphocytic thyroiditis; Thyroid nodules

1. Introduction

Recently, the Division of Endocrinology of our university hospital has reported on the great increase in the annual frequency of Hashimoto’s thyroiditis (HT) diagnosed in the 31-year period spanning 1975 and 2005 [1]. HT (also known as chronic lymphocytic thyroiditis) increased linearly over these 31 years \((r = 0.813, P < 0.001; n = 30 \text{ in } 1975 \text{ but } n = 484 \text{ in } 2005)\). The increase became evident starting in the mid-1990s and levelled off in the last 3 years, as the increase between 2003 and 2004 was 1% and the increase between 2004 and 2005 was 3%; in contrast, the increase between 1995 and 1996 was 64% [1]. Such augmented frequency was accompanied by a progressive decrease in both the female to male (F/M) ratio and age at presentation. The patients came from the Southern-Italy area served by our university hospital: the North-Eastern corner of our island (Sicily) and most of Calabria, which is the region across the Straits of Messina. Environmental modifications were claimed as responsible for those changes. Indeed, because the etiopathogenesis of endocrine and non endocrine auto-immune diseases results from interaction of two fundamental factors (genes and environment) [2], any modification of a given auto-immune disease that occurs in relatively short periods of time can be explained only in terms of changes of the environmental component [1].

This Cytology Unit, which is part of another department at the same university hospital, has also witnessed an increase in HT as diagnosed by the ultrasound-guided fine-needle aspiration cytology (FNAC) of the thyroid. Thyroid is only one of the tissues examined at this ambulatory facility that services outpatients coming from the aforesaid basin: North-Eastern Sicily and most of Calabria. Ultrasound-guided thyroid FNAC is requested for the diagnostic work-up of thyroid nodule(s), regardless of thyroid volume. Starting from 1988, the team, including the sonographer, has been the same; furthermore, from the same year, FNAC diagnoses were computer-stored. As described in more detail under Discussion, there is literature reporting the FNAC frequency of HT [3–23], but only one cytological paper [6] has addressed the year-to-year change of HT over a period of time longer than 10 years.

Hence, we wished to assess the yearly change in the FNAC prevalence of HT over a wide period of time in patients with thyroid nodules. By doing so, we wished to independently verify the data obtained by the endocrine division [1]. Accordingly, we quantified the annual frequency of HT and, for comparison, of the non-auto-immune thyroiditis, as well as the HT distribution between genders and age at presentation.

2. Patients and methods

2.1. Patients

Of 8520 FNAC performed on 8520 persons with a single or dominant thyroid nodule between January 2001, 1988 and December 31, 2007, there were 8397 adequate FNAC from 8397 persons, the results of which were computer-stored. We retrieved all cytological diagnoses of thyroiditis (HT, De Quervain’s thyroiditis [also known as subacute thyroiditis] and Riedel’s thyroiditis [also known as ligneous thyroiditis or invasive fibrous thyroiditis]). FNAC were adequate when a smear contained at least six groups (clusters) of well-preserved, well-visualized follicular cells, each group containing more than 10 cells. As said in the Introduction, the cytology team was composed by the same persons and used the same methodology. Cells were aspirated from the single or dominant thyroid nodule by the ultrasonographist (CS) using a 23-gauge needle attached to a 20-ml syringe. In patients with HT, an abnormal sonographic appearance of the thyroid, characterized by diffuse areas of decreased echogenicity, was noted. The indication for FNAC was based on the presence of nodules > 10 mm in diameter, echographically solid, regardless of thyroid volume. Alcohol-fixed and air-dried smears were stained by the Papanicolaou and the May–Grunwald and Giemsa methods. A minimum of five smears were prepared. The sonographist punctured, with a minimum of five passes, under continuous real-time sonographic guidance provided by 7.5 or 10 MHz high frequency transducers.

Diagnoses of HT, DQT and RT, made after FNAC evaluation, were based on the following cytopathologic features [24,25]. Diagnosis of HT was based on the presence of numerous lymphoid cells. These cells appeared activated and polymorphic with a mixed cell population of mature lymphocytes, centrocytes, centroblasts, few immunoblasts, in some cases, associated with germinal center formation. Moreover, there were plasma cells, few macrophages and, sometimes, large multinucleate histiocytes. Sometimes, the lymphoid cells were admixed within groups of epithelial cells, generally with Hurthle cell changes (oncocytic metaplasia). The aspiration in HT patients is less bloody than most of the thyroid aspiration biopsies. Seeing lymphocytes apparently infiltrating the cytoplasm of the epithelial cells was a particularly characteristic finding. Diagnosis of
DQT was based on the presence of numerous multinucleate histiocytes, few mixed inflammatory cells, abundant epithelioid 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 with HT, follicular center (immature) lymphocytes and Hurthle cells were unusual. We also have 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 leucocytes, lymphocytes and histiocytes. However, when the lined (wooden) fibrosis consent the penetration of the needle, the characteristic finding was the presence of fibroblasts, also in tissue fragments.

To substantiate the cytological diagnosis of HT, we retrieved the results for serum thyroglobulin and thyroperoxidase autoantibodies (TgAb and TPOAb) that had been assayed at our University hospital in the patients that we diagnosed as having HT based on FNAC. Starting from 1991, the kits used were the corresponding immunoradiometric assays (IRMA) kit by DiAsorin (Saluggia, Italy), with normal values of < 100 U/mL and < 10 U/mL, respectively.

2.2. Statistical analysis

Because all thyroid patients who come to us are referred for the cytological evaluation of their single or dominant thyroid nodule, the comparison between the series of HT collected at this Cytology Unit in 1988–2007 and the series of HT that had been collected at the endocrine division in 1975–2005 [1] is pertinent when concerning the following category of patients in the second series: HT patients, observed in 1988–2005, having one or more

Fig. 1. Yearly number of total FNAC (continuous line) and adequate FNAC (discontinuous line) performed at our cytological unit over the study period (1988-2007).

Fig. 2. (Top panels) Yearly number of De Quervain’s thyroiditis (DQT) (left) or Hashimoto’s thyroiditis (HT) (right) diagnosed at our cytological unit over the indicated study period (1988–2007). (Bottom panels) Prevalence of DQT (left) or HT (right) as percentage of all adequate FNAC performed at each year.

En haut : nombre annuel de thyroïdite de De Quervain (DQT) (à gauche) ou de thyroïdite d’Hashimoto (HT) (à droite) diagnostiqué dans notre unité de cytologie pendant la période d’étude (1988–2007). En bas : prévalence de la DQT (à gauche) ou de l’HT (à droite) en pourcentage de toutes les cytoponctions interprétables réalisées chaque année.
Comparaison de deux séries locales de patients présentant une thyroïdite de Hashimoto, observée dans une unité de cytolgie (FNAC) ou le service d’endocrinologie (Endo) dans le même hôpital universitaire.

Table 1
Comparison between two local series of Hashimoto’s thyroiditis patients observed in the year period 1988–2007 (Cytology Unit series) or 1975–2005 (Endocrinology Division series) at the same university hospital.

<table>
<thead>
<tr>
<th></th>
<th>Cytological series</th>
<th>Endocrine series</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Male to Female</td>
</tr>
<tr>
<td>Number</td>
<td>490</td>
<td>2371</td>
</tr>
<tr>
<td>Female/Male ratio</td>
<td>8.4/1</td>
<td>9.7/1</td>
</tr>
<tr>
<td>Age at observation</td>
<td>46.6 ± 15.0 (47)</td>
<td>49.9 ± 4.3 (49.5)</td>
</tr>
<tr>
<td>% of all diagnoses</td>
<td>4.1 ± 2.6 (4.3)</td>
<td>8.9 ± 7.7 (4.5)</td>
</tr>
</tbody>
</table>

a The Endocrinology Division series had been published in [1]. The following variants, based on thyroid scintigraphy/ultrasonography, had been considered in that series: (i) atrophic; (ii) non goitrous, non nodular (thyroid size normal, absence of nodules); (iii) non goitrous, nodular (thyroid size normal, presence of one or more nodules); (iv) goitrous, non nodular (thyroid size increase, absence of nodules); and (v) goitrous, nodular (thyroid size increased, presence of one or more nodules). Data tabulated in the column “Nodular variant” are combined from variants (iii) and (v).

b In the cytological series, the numerator is the diagnosis of Hashimoto’s thyroiditis and the denominator is all cytological diagnoses at each of the 20 years comprised between 1975 and 2005 (see Fig. 1 and Table 1 of [1]), and percentages are averaged as m ± SD (median). In the endocrine series, the numerator is diagnosis of Hashimoto’s thyroiditis and the denominator is all thyroid diseases diagnosed at each of the 31 years comprised between 1975 and 2005 (see Fig. 1 and Table 1 of [1]), and percentages are averaged as m ± SD. In the column “nodular variant” of the present Table, only the patients with the two HT variants associated with thyroid nodule(s), as specified in the above footnote, were taken into account.

Overall, there were 36 cases of DQT (Fig. 2, left) and only two cases of RT (one in 1994 and one in 2004; data not shown). Thus, the approximate RT/DQT ratio was 1/18. DQT showed no significant temporal trend over the 20-year period of time when expressed either as absolute numbers (r = 0.293, 95% CI −0.17 to 0.65, P = 0.21) or percentages of all adequate FNAC diagnoses at each year (r = −0.273, 95% CI −0.64 to 0.19, P = 0.24) (Fig. 2, left).

3. Results

3.1. Generalities and non-Hashimoto’s thyroidites

The number of adequate FNAC increased linearly from a minimum of 73 in 1988 to a maximum of 1006 in 2007, a 14-fold change (r = 0.954, 95% CI 0.88 to 0.98, P < 0.001) (Fig. 1). Statistics did not change considering total FNAC (adequate + inadequate specimens), as numbers were 75 in 1988 and 1017 in 2007, and Pearson’s coefficient of correlation was 0.955 (95% CI 0.89 to 0.98, P < 0.001). Dividing the 20-year period in four classes of equal duration, adequate FNAC were 498 in 1988–1992, 1040 in 1993–1997, 2459 in 1998–2002 and 4400 in 2003–2007. The highest increase between two subsequent years occurred between years 1998 and 1999 (+75%), while the smallest increase occurred between 2005 and 2006 as well as between 2006 and 2007 (+3% both).

In order to maintain the 5-year-interval of the previous periods, below are given data for the 5-year period 2003–2007 of the cytological series.

Overall, there were 36 cases of DQT (Fig. 2, left) and only two cases of RT (one in 1994 and one in 2004; data not shown). Thus, the approximate RT/DQT ratio was 1/18. DQT showed no significant temporal trend over the 20-year period of time when expressed either as absolute numbers (r = 0.293, 95% CI −0.17 to 0.65, P = 0.21) or percentages of all adequate FNAC diagnoses at each year (r = −0.273, 95% CI −0.64 to 0.19, P = 0.24) (Fig. 2, left).
3.2. *Hashimoto’s thyroiditis*

Overall, there were 490 cases of HT (438 women and 52 men, resulting in a F/M ratio of 8/1) (Table 1). Combining this number with the aforementioned total number of DQT and RT, the approximate RT/DQT/HT ratio was 1/18/250. From the yearly distribution of HT shown in Fig. 2 (right), it is evident the linear increase in the annual frequency of HT when expressed either as absolute numbers ($r = 0.919$, 95% CI 0.80 to 0.97, $P < 0.001$) or percentages of all adequate FNAC diagnoses at each year ($r = 0.932$, 95% CI 0.83 to 0.97, $P < 0.001$). The number of cytological diagnoses of HT was between 0 and 3 years until 1995, but it was 9 in 1996 (+350% increase over the two cases seen in 1995) and peaked at 90 in 2007 (+81% over 2006, and +8900% over 1988). Up to 1995, HT accounted for no more than 2% of the FNAC diagnoses at each year. However, starting in 1997 and with the single exception of 2006, HT accounted for greater than 6% of the FNAC annual diagnoses, peaking at 9% in the year 2007.

The number of HT diagnoses was six (years 1988–1992), 25 (1993–1997), 148 (1998–2002) and 311 (2003–2007) (Table 2). In terms of mean ± SD, the number of HT diagnoses was $1.2 ± 0.8$ (1988–1992), $5.0 ± 3.2$ (1993–1997), $29.6 ± 13.2$ (1998–2002) and $62.2 ± 17$ (2003–2007) ($P < 0.001$ by ANOVA). Such 52-fold increase in the period 2003–2007 over the period 1988–1992 is overtly disproportionate compared with the corresponding 9-fold increase in the number of adequate FNAC. When expressed in terms of percentage...
of total FNAC diagnoses (adequate + inadequate) in the corresponding 5-year period, HT diagnoses were 1.2, 2.2, 6.0 and 7.1%.

Changes in the gender composition and age are illustrated in Fig. 3. Concerning gender, the number of males in the last 4 years exceeded that of the preceding 16 years (n = 28 vs 24). Comparison with the endocrine series of HT, particularly with the nodular variant, can be appreciated in Tables 1–3. In either the cytological or endocrine series, the F/M ratio was <10/1, the mean and median age ranged from 47 to 50 years, and HT accounted for a median of about 4.5% of the cytological or clinical thyropathies (Table 1). In addition to a progressive increase in the percentage, there was a progressive decrease in the F/M ratio and age at presentation in either series (Table 2), as also shown by the correlations summarized in Table 3. Mean and median age were ≥50 years between 1988 and 1997, but ≤48 years after 1998 in either series of HT patients.

Serum thyroid autoantibodies data were available for 305/490 HT patients. However, as stated under Materials and Methods, assays for TgAb and TPOAb had been performed in the same laboratory using the same kit, which is important considering the different kits that are commercially available, each with its own reference range. Overall, 264 out of 305 HT patients (87%) tested positive for TgAb, TPO Ab or both.

In brief, there was a fair agreement between the cytological and the endocrine series of HT patients.

### 4. Discussion

Clinicroadiological and hormonal parameters overlap in HT and other thyroid lesions [26]. Similarly, the sonographic appearance of lymphocytic thyroiditis may vary, likely reflecting the phase and severity of the disease process. Negative serology can cause a diagnostic dilemma, but it is known that intrathyroidal immune destruction occurs much earlier than serological evidence of antibodies [27]. However, in our series, negative serology occurred in only 13% of patients.

According with our experience, we can consider two typical cytologic findings of HT:

- (A) only lymphoid cells (tissue), with characteristic coagulative necrosis;
- (B) lymphoid tissue or cells admixed with Hurthle cells and, very scantily, colloid.

Moreover, we saw category (A) in a 30% of cases. Association between HT and papillary thyroid carcinoma was noted in 8.2% of all patients affected by HT; all the patients of this association were women.

In our series of thyroid FNAC, HT is more frequent than RT by two orders of magnitude and DQT by one order of magnitude. Our rate of 0.4% of DQT matches the 0.4% rate reported in one English study [5], while the 14/1 ratio between HT and DQT in
Table 4
Summary of the international literature on the detection of chronic lymphocytic thyroiditis (Hashimoto’s thyroiditis) in patients who underwent FNAC for nodular goiter over a period comparable to that of the present study*.

<table>
<thead>
<tr>
<th>Continent, Nation</th>
<th>Year(s) of study</th>
<th>Reference</th>
<th>FNAC</th>
<th>Frequency of HT (%)</th>
<th>Comments (other thyroidites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe, Italy</td>
<td>1988–2007</td>
<td>Rizzo et al., 2009 (this study)</td>
<td>8520 patients with single or dominant nodule who underwent US-FNAC. FNAC adequate in 8397 patients</td>
<td>1.3% in 1988 progressively increased to 8.8% in 2007 (P &lt; 0.001). Data unchanged based on adequate FNAC: 1.4% in 1988 → 8.95% in 2007 (P &lt; 0.001)</td>
<td>Rate of DQT = 0.4%; rate of RT = 0.02% (HT/DQT ratio = 14/1; HT/RT ratio = 250/1)</td>
</tr>
<tr>
<td>Europe, Czech Republic</td>
<td>1991–1998</td>
<td>Cap et al., 1999</td>
<td>2100 patients (&gt; 90% with single or multiple thyroid nodules). Results reported for 1950 patients</td>
<td>10.8% (11.8% of adequate FNAC)</td>
<td>FNAC diagnosis of DQT = 1.0% (HT/DQT ratio = 12/1)</td>
</tr>
<tr>
<td>Europe, Poland</td>
<td>1994–2005</td>
<td>Slowinska-Klencka et al., 2006</td>
<td>23173 cytological reports. The 1.6-fold increase in the number FNAC performed between 1994 (n = 1480) and 2005 (n = 2326) is disproportionate compared to 6-fold increase in the corresponding number of patients with HT (n = 38 in 1994 but 226 in 2005)</td>
<td>“Frequency of chronic thyroiditis increased from 2.6 in 1994 to 9.7% in 2005 (P &lt; 0.001)”</td>
<td></td>
</tr>
<tr>
<td>North America, Canada</td>
<td>1987–1994</td>
<td>MacDonald and Yazdi, 1999</td>
<td>1638 FNAC</td>
<td>11.2%</td>
<td></td>
</tr>
<tr>
<td>North America, USA</td>
<td>1988–1992</td>
<td>Sidaway et al., 1997</td>
<td>133 FNAC</td>
<td>4.5% (6.4% of adequate FNAC)</td>
<td></td>
</tr>
<tr>
<td>North America, USA</td>
<td>1993–1997</td>
<td>Tambouret et al., 1999</td>
<td>246 FNAC. Mean age and F/M ratio of patients 52.3 years and 2/1</td>
<td>3.8% (4.5% of adequate FNAC)</td>
<td></td>
</tr>
<tr>
<td>Africa, Sadan</td>
<td>Not specified</td>
<td>Bashier et al., 1996</td>
<td>94 patients with single or multiple thyroid nodules</td>
<td>1.06% (1.12% of adequate FNAC)</td>
<td></td>
</tr>
<tr>
<td>Africa, Nigeria</td>
<td>1995–2004</td>
<td>Nggada et al., 2006</td>
<td>69/116 patients “with thyroid node(s)” for whom data are provided</td>
<td>2.9% of adequate FNAC</td>
<td>Rate of DQT = 2.9% (HT/DQT ratio = 1/1)</td>
</tr>
<tr>
<td>Africa, Ethiopia</td>
<td>1986–1991</td>
<td>Mengistu, 1993</td>
<td>61/340 patients “with thyroid node(s)” for whom data are provided</td>
<td>1.6% (2% of adequate FNAC)</td>
<td>No distinction between types of thyroiditis</td>
</tr>
<tr>
<td>Africa, Kenya</td>
<td>2001</td>
<td>Sang et al., 2007</td>
<td>42 patients with nodular thyroid disease seen between June and August 2001. F/M ratio = 7/1</td>
<td>2.4% (2.6% of adequate FNAC)</td>
<td>No distinction between types of thyroiditis</td>
</tr>
</tbody>
</table>
Table 4 (Continued)

<table>
<thead>
<tr>
<th>Continent, Nation</th>
<th>Year(s) of study</th>
<th>Reference</th>
<th>FNAC</th>
<th>Frequency of HT (%)</th>
<th>Comments (other thyroidites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia, Japan</td>
<td>1984–1988</td>
<td>Konno et al., 1989&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Konno et al., 1989&lt;sup&gt;b&lt;/sup&gt;</td>
<td>384 patients with “thyroid diseases”</td>
<td>35%</td>
</tr>
<tr>
<td>Asia, Kuwait</td>
<td>1986–1993</td>
<td>Kapila et al., 1995</td>
<td>Kapila et al., 1995</td>
<td>415 FTNAC. Contrasting 1993 with 1986, the increase of new HT cases (n = 114 vs 67, +70%) outnumbered the increase in new FNAC performed (n = 655 vs 574, +14%) F/M ratio was 66/1 in 1986 but 31/1 in 1992 and 37/1 in 1993. No data on age, except stating that “it was (their) impression that over the last 2 years in Kuwait chronic lymphocytic thyroiditis (HT) presents at an earlier age…”</td>
<td>14.3% Increase in the last 2 years (1992 = 95/533 or 17.8%, 1993 = 114/655 or 17.4%, compared to 67/574 or 11.7% in 1986)</td>
</tr>
<tr>
<td>Asia, Saudi Arabia</td>
<td>1994–2002</td>
<td>El Hag et al., 2003</td>
<td>El Hag et al., 2003</td>
<td>303 patients with “thyroid swelling” F/M ratio and mean age of HT and DQT combined was 12/1 and 30 years, respectively</td>
<td>16.2% (16.6% of adequate FNAC) DQT rate = 1.02% (HT/DQT rate = 16/1)</td>
</tr>
<tr>
<td>Asia, India</td>
<td>1993–2003</td>
<td>Khan et al., 2004</td>
<td>Khan et al., 2004</td>
<td>2888 thyroid lesions</td>
<td>6.2% (6.6% of adequate FNAC)</td>
</tr>
<tr>
<td>Asia, India</td>
<td>2 years</td>
<td>Kini et al., 2006</td>
<td>Kini et al., 2006</td>
<td>172 patients observed in 2 years “suspected of having thyroid pathology”</td>
<td>52.3% (53.3% of adequate FNAC)</td>
</tr>
<tr>
<td>Asia, India</td>
<td>2004–2006</td>
<td>Handa et al., 2008</td>
<td>Handa et al., 2008</td>
<td>434 patients with thyroid lesions. Mean age of HT patients was 32.7 ± 11.8 years, and the F/M ratio was 29/1</td>
<td>27.4% (28.9% of adequate FNAC)</td>
</tr>
<tr>
<td>Asia, Malaysia</td>
<td>1992–1997</td>
<td>Jayaram et al., 1999</td>
<td>Jayaram et al., 1999</td>
<td>1853 patients with thyroid lesions (79% with single nodule)</td>
<td>4.2% (4.5% of adequate FNAC) DQT rate = 0.8% (HT/DQT ratio = 6/1)</td>
</tr>
<tr>
<td>Asia, Hong Kong (China)</td>
<td>1993–1997</td>
<td>Yeoh and Chan, 1999</td>
<td>Yeoh and Chan, 1999</td>
<td>1236 FNAC of thyroid nodules</td>
<td>4.8% (5.3% of adequate FNAC)</td>
</tr>
<tr>
<td>Asia, China</td>
<td>Not specified</td>
<td>Dong et al., 2008&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dong et al., 2008&lt;sup&gt;b&lt;/sup&gt;</td>
<td>271 “patients with thyroid nodules detected by physical examinations”</td>
<td>26.6%</td>
</tr>
<tr>
<td>Asia, Iran</td>
<td>1997–2004</td>
<td>Bazrafshan et al., 2008</td>
<td>Bazrafshan et al., 2008</td>
<td>476 patients with solitary or dominant nodules</td>
<td>6.5% (7.5% of adequate FNAC)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Within a given continent, articles are grouped taking into account geographic areas and year of study.

<sup>b</sup> Articles written in local language (Polish, Japanese or Chinese). Tabulated data taken from the abstracts written in English and/or illustrative material.

our series is comparable to the 12/1 and 16/1 ratios found in the cytological series from the Czech Republic [4] and Saudi Arabia [18] (Table 4 and Fig. 4). The number of HT and DQT cases that we observed in the years between 1988 and 1995 were similar (14 and 11, or 1.7 and 1.6 yearly, respectively). In the following 12 years, the cases of DQT were 25 (2.1 per year) but the cases of HT were 476 (39.7 per year) with a linear increase from nine in 1996 to 90 in 2007. This datum matches the observation done on HT patients of the endocrine division, in whom the increase in annual frequency started in the year 1995 and continued at a linear rate until 2005, the last year considered, with an 8-fold increase in 2005 over 1995 [1].

Similarly to the endocrine series, in which the 13-fold increase in the annual frequency of year 2005 compared to year 1988 could not be accounted for by the mere 2-fold increase in the annual number of all thyroid diagnoses between the same 2 years, in the cytological series the 67-fold increase between 2005 and 1998 cannot be accounted for by the 13-fold increase in the number of all FNAC diagnoses between the same 2 years. Noteworthy, the ratio between the two fold-increases in the endocrine series (13/2 = 6.5) compares fairly with the equivalent ratio in the cytological series (67/13 = 5.2). In the endocrine series, the annual frequency appeared to have reached a plateau, because the increase between 2003 and 2004 was 1% and the
increase between 2004 and 2005 was 3%. However, in the cytological series, this plateau is not so evident (change between 2003 and 2004, 2004 and 2005, 2005 and 2006, and 2006 and 2007 equal to +4, +31, −19 and +67%). Thus, it will be of interest to continue monitoring the phenomenon in the subsequent years.

The parallelism with the endocrine series is completed by:

- the progressively greater proportion of men with HT;
- the progressively younger age of patients.
The first point could partially be explained by a change in mentality or social background associated with improvement of economical status, leading more men to the attention of the endocrinologists. Secondly, it is worthy of note that, in the endocrine series [1], mean age showed a noticeable decrease to 37.1 years in the period 1991–1993; this was matched, in the present cytological series, by a decrease to 36.8 years in the period 1994–1995 (Fig. 3).

As summarized in Table 4 (and illustratively in Fig. 4), we are aware of a number of cytological studies that have evaluated the local “epidemiology” of HT [3–23]. However, only a number of these studies were conducted in a reasonably large series of patients with non-toxic nodular goiter over a reasonably wide period of time, and only a few [4,5,12,16,18] quantified concurrently other thyroidites. From Table 4 and Fig. 4, it is clear that ours is the study with the largest year span (20 years), preceding the 12-year span of a Polish study [6], though the size of our series ranks second after this Polish study [6]. Overall, our data agree with a number of those reported in the literature, particularly with the study methodologically close to ours [6].

5. Conclusion

In conclusion, extending on a wider temporal scale a number of FNAC observations reported in the world literature, we confirm that the annual frequency of HT has increased. This confirmation also applies to the HT patients observed at the endocrine division of our university hospital [1]. Because the annual increases of HT over a time span of just 2 decades is also accompanied by other changes (that is, earlier age at presentation and greater representation of the male gender), as some of us have recently reported [1], of the two ethiopathogenetic factors of auto-immune diseases only the environmental ones (as opposed to the genetic ones) can be accountable for the increased frequency of HT as well as simultaneous presentation. Special studies will be required to identify these exogenous factors.

Conflicts of interest

The authors declare that there is no conflict of interest associated with this manuscript.

References