In addition to increased diagnostic activity, other environmental factors may contribute to the rising incidence of papillary thyroid cancer

Rego-Iraeta A, Perez-Mendez LF, Mantinan B, Garcia-Mayor RV. Time trends for thyroid cancer in northwestern Spain: true rise in the incidence of micro and larger forms of papillary thyroid carcinoma. Thyroid 2009;19:333-40.

SUMMARY

BACKGROUND The incidence of thyroid cancer has been rising over the past three decades in the United States and in many other areas around the world. Although a variety of factors may be responsible for this trend, some have attributed it mainly to the increased utilization of sensitive diagnostic techniques such as neck ultrasonography and fine-needle aspiration biopsy. However, there is growing awareness that there may be other as yet unidentified factors that might be responsible for this increased incidence of thyroid cancer. The aims of this retrospective study were to define the incidence and prevalence of thyroid cancer in Vigo, Spain, from 1979 through 2001 and to investigate the relationship between the incidence and prevalence rates of thyroid cancer and the trends in tumor size and thyroid surgery over time.

METHODS Data were obtained from the Pathology Registry of the Vergo University Hospital, which belongs to the Spanish public health system that collects data on about 97% of the malignant tumors verified by microscopic examination. The study population comprises 322 cases of papillary, follicular, Hürthle-cell, and medullary thyroid cancer. Tumor stages were classified according to the 1992 tumor–node–metastasis (TNM) staging classification. Papillary thyroid cancers ≤1 cm were categorized as papillary thyroid microcarcinoma (PTMC).

RESULTS During the study period, 2345 patients had thyroidectomies, which represented a significant increase from 13.76 (95% confidence interval [CI], 12.35 to 14.56) to 23.83 (95% CI, 22.17 to 24.73) to 45.01 (95% CI, 42.45 to 46.39) cases per 100,000 persons each year from 1978 to 1985, 1986 to 1993, and 1994 to 2001, respectively. The proportion of thyroid cancers among patients who had a thyroidectomy increased from 9.92% in 1978 to 1985, to 12.31% in 1986 to 1993, and to 15.35% in 1994 to 2001, respectively (P = 0.015). Total thyroidectomy comprised 48% of the initial surgical procedures in 1978 to 1985, and 74% during 1994 to 2001. A total of 322 thyroid cancer cases were diagnosed from 1978 to 2001. Mean patient age at the time of diagnosis was 46.8 years (range, 8 to 91). The ratio of women to men was 3.6 to 1. Of the 322 cases, 245 (76%) were papillary, 44 (13.7%) follicular, 23 (7.1%) medullary, and 10 (3.1%) anaplastic thyroid cancers. The papillary-to-follicular cancer ratio was 5.8; when PTMC cases were excluded, this ratio was 2. PTMC cases increased significantly over time, rising to 16.7%, 23%, and 43% during 1978 to 1985, 1986 to 1993, and 1994 to 2001, respectively (Figure 1). The ratio of papillary thyroid cancer to follicular thyroid cancer increased significantly over time from 2.3 to 3.6 to 11.5, respectively; when PTMC was excluded, these ratios increased over time from 1.9 to 2.7 to 6.6, respectively.

Trends in thyroid cancer incidence in men and women and by age: The rates of thyroid cancer were considerably higher in women than in men. The overall incidence of thyroid cancer increased significantly in women from 1.61 to 4.43 to 10.29 cases per 100,000 from 1978 to 1985, 1986 to 1993, and 1994 to 2001, respectively (Figure 2). The age-standardized incidence rates (ASRs) over this period show the same tendency, with a

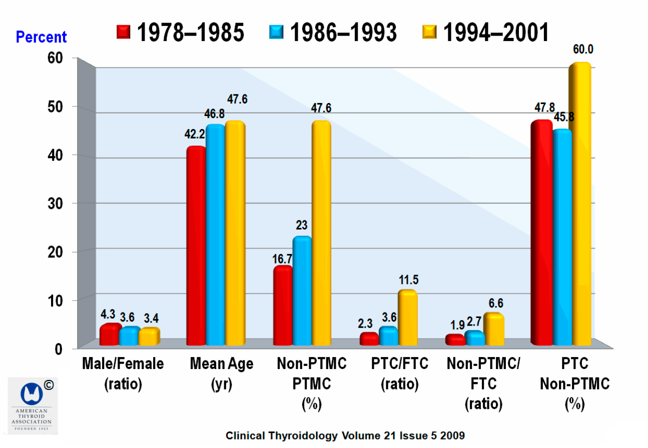

Figure 1. This figure summarizes the male-to-female ratio in thyroid cancer over time, the mean age of patients during this period, and the proportion of papillary and follicular thyroid cancers. FTC = follicular thyroid cancer; PTMC = papillary thyroid microcarcinoma; PTC = papillary thyroid carcinoma without PTMCs. The data in this figure are derived from Table 1 of Rego-Iraeta et al.

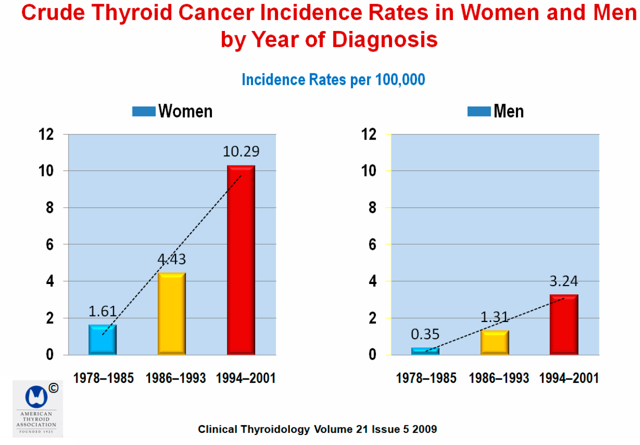

Figure 2. The unadjusted thyroid cancer incidence rate from 1978 through 2001 has been rising in Spain, particularly in women. The incidence rates were approximately threefold higher in women than in men. The line represents the rising incidence over time. The data in this figure are derived from Table 2 of Rego-Iraeta et al.

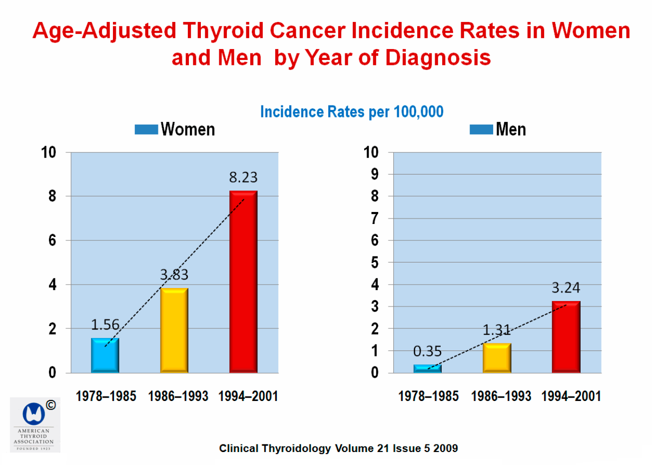

Figure 3. The age-adjusted increase in the incidence rates of thyroid cancer in women from 1978 through 2001 are approximately 2.5-fold those of men. The data in this figure are derived from Table 4 of Rego-Iraeta et al.

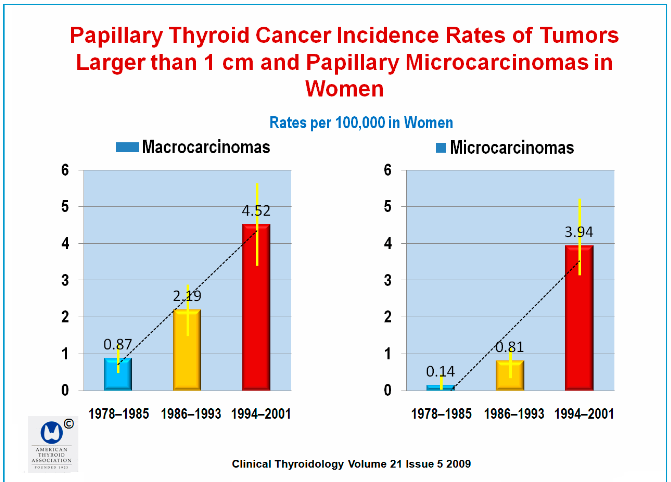

Figure 5. The incidence rates of tumors 1 cm or smaller (papillary thyroid microcarcinoma) and that of larger papillary thyroid carcinomas are almost the same. The bars = 95% CI, and the line = trend in the increase of macro- and microcarcinomas. The Data in men are comparable. The data in this figure are derived from Table 3 of Rego-Iraeta et al.

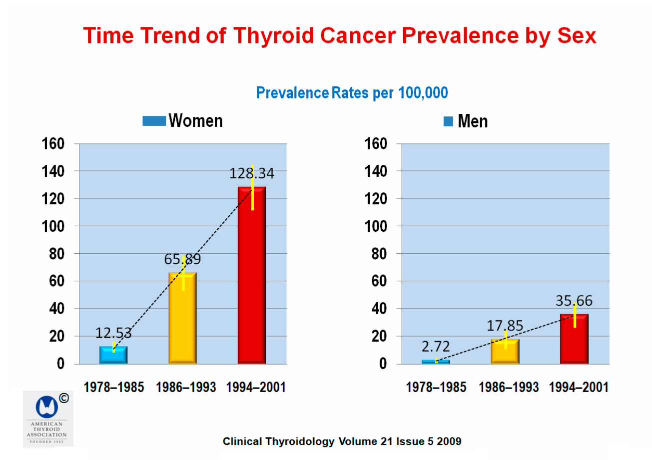

Figure 4. The age-adjusted prevalence rates of thyroid cancer in women are approximately threefold those of men. The yellow bars show the 95% confidence limits, and the line shows the approximately tenfold increase in the prevalence of thyroid cancer among woman and men during 1978 through 2001. The data in this figure are derived from Table 4 of Rego-Iraeta et al.

significant increase in women in the incidence of thyroid cancer of 1.56 per 100,000 each year (1978 to 1985) to 3.83 (1986 to 1993) and 8.23 (1994 to 2001); for men the incidences were 0.33, 1.19, and 2.65 (Figure 3). The prevalence rates of thyroid cancer have shown a comparable increase from 1978 to 2001. Figure 4 shows that the prevalence of thyroid cancer increased substantially between 1985 and 2001 in both sexes.

Trends in thyroid cancer incidence by histopathology: The increase in papillary thyroid cancer is the result of an increased incidence of both PTMC and papillary thyroid cancer, which occurs in both men and women (Figure 5).

CONCLUSION The increasing incidence of thyroid cancer in Spain is equal to the rise in papillary microcarcinoma, and there has not been a shift over time in the thyroid cancer tumor size except for that of papillary microcarcinoma. In addition to increased diagnostic activity, these trends may reflect the contribution of other environmental factors

COMMENTARY

The incidence of thyroid cancer in the United States and in many regions around the world has been steadily increasing over the past three decades. The American Cancer Society estimates that 37,340 new cases occurred in 2008, about 75% of which were in women, and the rates were twice as high among white patients as black patients. Why this increase in thyroid cancer has occurred has engendered considerable debate. Davies and Welch (1) investigated the size distribution of papillary thyroid cancers in approximately 24,000 thyroid cancer cases in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) thyroid cancer registry from the years 1988 to 2002, 88% of which were papillary thyroid cancers. They found that the incidence of thyroid cancer increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002, a 2.4-fold increase ($P<0.001$ for trend) that was virtually completely due to papillary cancer, which increased from 2.7 to 7.7 per 100,000, a nearly threefold increase ($P<0.01$ for trend). There was no significant change in the incidence of follicular, medullary, and anaplastic thyroid cancer ($P>0.2$ for trend). The authors found that between 1988 and 2002, the bulk of the increasing incidence was from the detection of small papillary thyroid cancers. In all, nearly half of the tumors (49%) were ≤1 cm and 87% were ≤2 cm. Still, the papillary thyroid cancer mortality rates from 1973 through 2002 were stable, at approximately 0.5 death per 100,000. The authors concluded that this is predominantly due to the increased detection of small papillary cancers, which, combined with the flat mortality rates, suggests that this is an artifact produced by a reservoir of subclinical disease, not a true occurrence of thyroid cancer.

Several others have reached similar conclusions. Kent et al. (2), in a study from Canada, also found that carcinoma increased over the 12-year period. A significantly higher number of small (≤2 cm), nonpalpable tumors were resected in 2001 than in 1990 ($P = 0.001$), while the incidence of tumors 2 to 4 cm in diameter remained stable. When they examined the differences in tumor-detection rates by age and sex, they found a disproportionate increase in the number of small tumors among women and patients older than age 45 years. As a result, the authors suggested that more frequent use of medical imaging has led to an increased detection rate of small, subclinical tumors, which in turn accounts for the higher incidence of differentiated thyroid carcinoma

The study by Rego-Iraeta et al. has, according to the authors, three main points: (1) the increased incidence of thyroid cancer occurred equally in papillary microcarcinoma and in tumors larger than 1 cm; and (2) except for papillary microcarcinoma, there has not been a shift over the past two decades in thyroid tumor size in patients living in Spain; and (3) there has not been a similar increase in thyroid tumors of other histologic types. The authors suggest that these trends may reflect the contribution of other environmental factors in addition to enhanced diagnostic activity. The authors reach a conclusion similar to that of Enewold et al., (3) which also found that the SEER incidence rates of the smallest tumors (≤1 cm) increased 248% and increased 222% in those with the largest tumors (>5 cm). They found that 50% of the overall increase in papillary cancer incidence rates collected from the SEER program were due to tumors ≤2.0 cm, and 30% could be attributed to cancers 1.1 to 2.0 cm, and 20% to cancers >2 cm. When they made the assumption that all the increases in thyroid cancer were caused by the very small tumors, they could estimate that about 50% could be attributed to enhanced diagnostic accuracy; however, if there were changes in other potential risk factors, then the estimate for the role of early detection causing the increased incidence of thyroid cancer would be considerably lower. Among white women, the rate of increase for cancers >5 cm almost equaled that for the smallest papillary cancers. They concluded that medical surveillance and more sensitive diagnostic procedures cannot completely explain the observed increases in papillary thyroid cancer rates and that other possible explanations should be explored.

This and the study by Enewold provide strong support for the notion that the increase in thyroid cancer that has occurred over the past three decades may be due to one or more environmental factors that have yet to be identified.

Ernest L. Mazzaferri, MD, MACP

References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.

2. Kent WD, Hall SF, Isotalo PA, et al. Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. CMAJ 2007;177:1357-61.

3. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev 2009;18:784-91.