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EDITOR'S COMMENTS

This is the fourth 2009 issue of *Clinical Thyroidology*. As you may know, each issue will be sent to you as a separate list of articles that can be downloaded separately or as the entire document.

We wish to thank Dr. Ken Burman, the current President of the American Thyroid Association, for his contribution to this issue of *Clinical Thyroidology* in which he provided an expert opinion on the article by Somwaru et al.

FIGURES in *Clinical Thyroidology* You will notice that the articles contain figures with the ATA logo and a citation with the volume and issue numbers. We encourage you to continue using figures from *Clinical Thyroidology* in your lectures, which we hope will be useful to you and your students.

WHATS NEW The last page which lists new reviews has been expanded to REVIEWS & HOT ARTICLES. The last page now contains references to important reviews and very recent articles that look especially important to the editors.

EDITOR'S CHOICE ARTICLES are especially important studies that we recommend you read in their entirety.

We welcome your feedback and suggestions on these changes.

CONCISE REVIEW CITATIONS Beginning with the first review article for *Clinical Thyroidology* by Dr. Elaine Ron, authors can cite our CONCISE REVIEWS by using the electronic citation at the end of each review.

Ernest L. Mazzaferri, MD, MACP
Jennifer A. Sipos, MD

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Thyroid-function test abnormalities are common in elderly people taking thyroid hormone–replacement medications

Somwaru LL, Arnold AM, Joshi N, Fried LP, Cappola AR. High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. J Clin Endocrinol Metab 2009;94:1342-5.

SUMMARY

BACKGROUND Hypothyroidism requiring levothyroxine replacement therapy is common in the elderly population and not infrequently results in overtreatment or undertreatment. The aim of this study was to assess the frequency of and factors associated with thyroid hormone overtreatment and underreplacement.

METHODS The study subjects were from a cohort of 5201 adults enrolled from 1989 through 1990 in the Cardiovascular Health Study, which at baseline obtained a medical history, physical examination, assessment of health status and blood tests, including thyrotropin (TSH) and free thyroxine (FT_4). Among the original cohort, a subgroup of 3678 individuals had thyroid-function tests, and of this group, 339 (9.2%) were taking various thyroid hormone preparations. Those taking thyroid hormones were stratified into one of three groups: low TSH (TSH, ≤0.44 μIU/ml), euthyroid (TSH, 0.45 to 4.49 μIU/ml), and high TSH (≥4.5 μIU/ml). In addition, 321 of the 339 individuals taking thyroid hormones were stratified into five other groups: overt hyperthyroidism (TSH, ≤0.10 μIU/ml plus high serum FT_4); subclinical hyperthyroidism (TSH, 0.11 to 0.44 or ≤0.10 μIU/ml plus normal FT_4); euthyroid (TSH, 0.45 to 4.50 μIU/ml); subclinical hypothyroidism (TSH, 4.51 to 19.9 μIU/ml plus normal FT_4); or overt hypothyroidism (TSH, ≥20 μIU/ml or >4.50 μIU/ml plus low free FT_4). An additional 18 subjects were excluded because they did not fit into any of the categories.

RESULTS Of the 339 individuals taking thyroid hormones, 41% had a low serum TSH, 16% had a high TSH, and 43% were euthyroid (Figure 1). Among this group, 26% were taking thyroid hormone products with both levothyroxine ($L\text{-}T_4$) and triiodothyronine (T_3) and the rest were taking $L\text{-}T_4$ alone. The mean age of the latter group was 72.9 years, which was the same among all the thyroid status categories. More women were in the low TSH group than the euthyroid group (87.8 vs.72.9%; P = 0.03). Individuals with low serum TSH levels had lower weight (65.3 vs. 72.2 kg; P<0.001) and lower body-mass index (25.5 vs. 27.1 kg/m^2; P<006), and fewer had a medical diagnosis (P<0.05) and were taking fewer medications (P = 0.02) as compared with the euthyroid group. Serum TSH levels increased

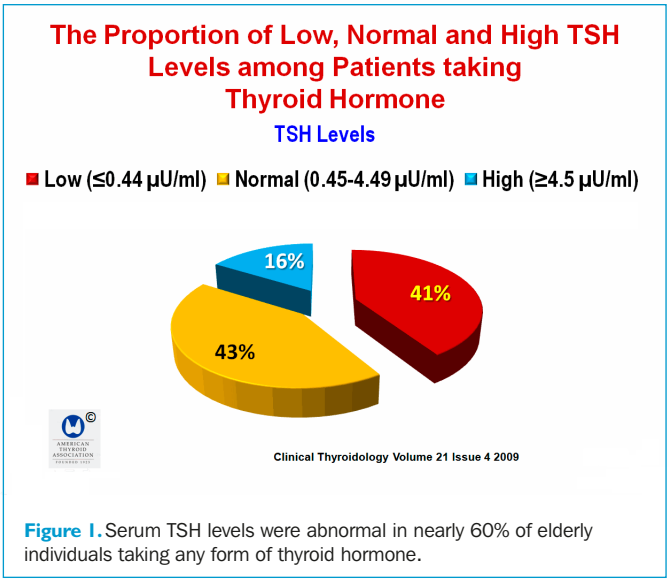

Figure 1. Serum TSH levels were abnormal in nearly 60% of elderly individuals taking any form of thyroid hormone.

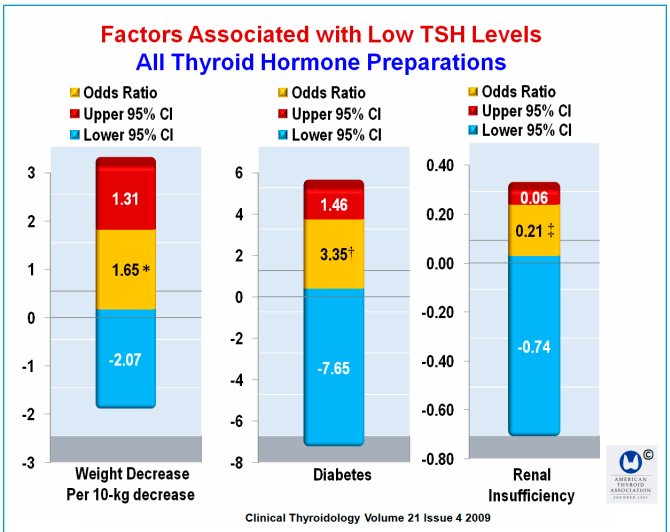

Figure 2. Results of multivariable analysis showing three independent variables associated with low serum TSH levels in individuals taking any form of thyroid hormone. *P<0.001, †P = 0.04 , and ‡P = 0.02, comparing individuals with low serum TSH levels with euthyroid individuals.

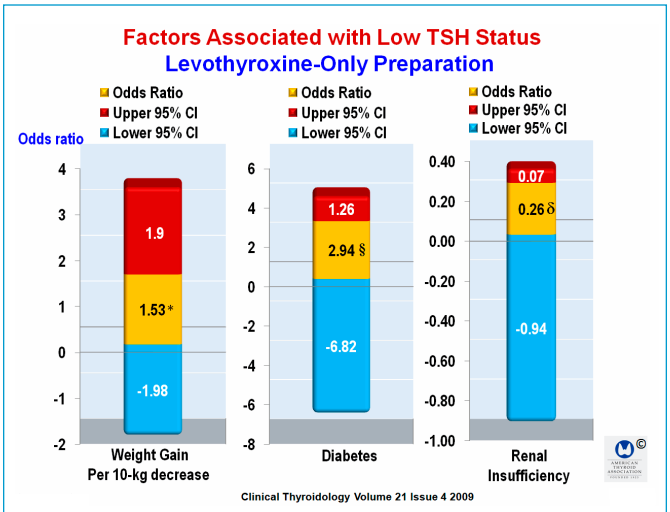

Figure 3. Results of multivariable analysis showing three Independent variables associated with low serum TSH levels in individuals taking levothyroxine as the only form of thyroid hormone. *P<0.001, §P = 0.01, and δP = 0.04, comparing individuals with low serum TSH levels with euthyroid individuals.

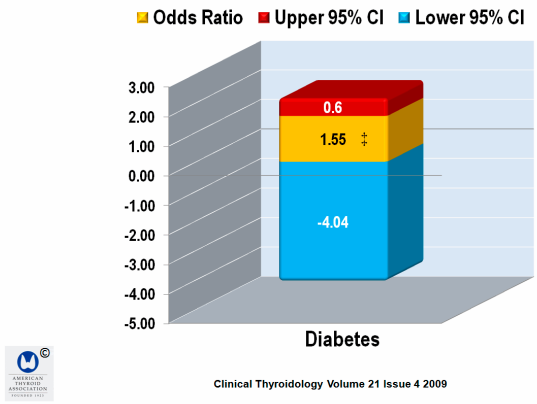

Figure 4. The only risk factor associated with a high TSH status is diabetes mellitus with any form of thyroid hormone preparation. ‡P = 0.02, comparing individuals with high serum TSH with euthyroid individuals.

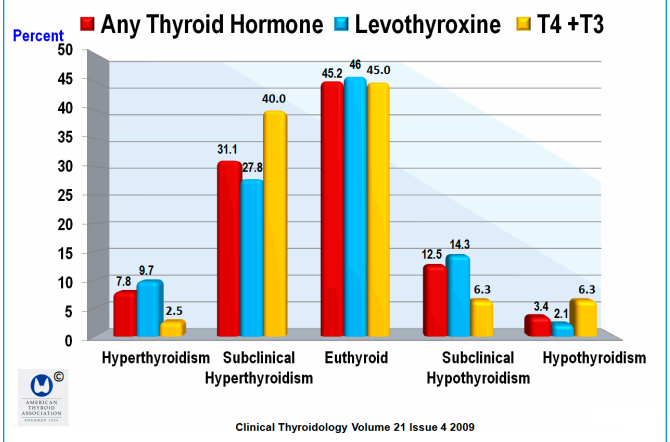

Figure 5. There are no significant differences in thyroid testing status among individuals taking one of three different forms of thyroid hormone.

65% for every 10-kg decrease in weight. Individuals with diabetes mellitus were more likely and those with renal insufficiency were less likely to have low TSH levels (P = 0.02).

Multivariable-adjusted models found weight, diabetes mellitus, and renal insufficiency to be independently and significantly associated with low TSH status. Serum TSH levels decreased 65% for every 10-kg decrease in weight, and those with diabetes were more likely to have low TSH levels, although low TSH levels were less likely with renal insufficiency (Figure 2). The results were similar when levothyroxine alone was taken (Figure 3). The prevalence of euthyroidism was the same among all thyroid hormone preparations (Figures 2 to 4). Diabetes mellitus was the only statistically significant predictor of a high TSH both for all thyroid hormone preparations (P = 0.004) and for levothyroxine alone (P = 0.02) (Figure 4). The prevalence of euthyroidism was similar among all thyroid hormone preparations (Figure 5).

CONCLUSION Thyroid-function test abnormalities are common in elderly people taking thyroid hormone–replacement therapy.

COMMENTARY

Somwaru et al. have performed an interesting and important study that assessed the frequency of abnormal serum TSH concentrations in a large cohort of older individuals. Using baseline serum samples stored between 1989 and 1990 from the Cardiovascular Health Study, they measured serum TSH in 339 subjects who were taking exogenous thyroid hormone(s) (9.2% of the entire study population) and divided the results into separate groups. Surprisingly, only 43% of the serum TSH concentrations fell within the normal range, with 41% having decreased serum TSH values and 16% having elevated serum TSH values. There were more women who had a low serum TSH than had a normal TSH. Using further statistical analyses, they observed that lower body weight, renal insufficiency, and diabetes mellitus were independently associated with lower serum TSH values. Curiously, diabetes mellitus was also associated with an increased likelihood of having an elevated serum TSH. The authors appropriately conclude that this high frequency of abnormal TSH values stresses the importance of close monitoring of patients receiving exogenous thyroid hormone(s), especially individuals with diabetes, renal insufficiency and low body weight. It is important to normalize serum TSH concentrations to decrease the risks of cardiovascular and osseous abnormalities; it is assumed that the goal TSH in these patients taking thyroid hormone–replacement preparations is within the normal reference range (1).

There are additional issues, however, that should be mentioned, many of which are also noted by the authors. The underlying cause for hypothyroidism was not mentioned except to indicate that none of the patients had thyroid cancer. However, it is not noted whether any patients were taking exogenous levothyroxine for suppressive purposes for thyroid nodule(s), a process that has largely become obsolete (2, 3). TSH was also measured only once, and it is not known whether the TSH values remained abnormal in patients for the duration of the study. Further, 26% of the patients taking exogenous thyroid hormone(s) were taking a combination of levothyroxine and triiodothyronine. It is now recommended that only exogenous levothyroxine be used for replacement purposes (http://hyper.thyroidguidelines.net/hormone). The inclusion of patients who ingest a combination of levothyroxine and triiodothyronine makes it difficult to interpret the TSH values, since the triiodothyronine component has a shorter half-life and can suppress the TSH for several hours following its ingestion, whereas during the remainder of the day the TSH may not be as suppressed or could even be normal. The timing of the ingestion of thyroid hormones in relationship to the measurement of serum levels is not reported. The associations noted above for decreased serum TSH concentrations with the presence of lower weight, renal insufficiency and diabetes mellitus still held when users of only levothyroxine (not with triiodothyronine) were reanalyzed. However, the relationship of elevated serum TSH with ingestion of exogenous levothyroxine now became statistically

nonsignificant. The authors also could not comment on whether nonthyroidal illness was contributing to the presence of perturbed thyroid-function tests, especially in patients with renal insufficiency and diabetes mellitus, although this seems relatively unlikely to affect a substantial number of individuals, given the outpatient nature of the study.

It is also worthwhile to comment that the normal TSH range they chose is 0.45 to 4.49 μIU/ml and the NHANES study has now suggested that the normal TSH reference range is approximately 0.45 to 4.12 μIU/ml (median, 1.39) (4), implying that an even higher percentage of subjects(in the Somwaru et al. study) may have elevated TSH values. It appears that free T_4 levels were measured only in subjects with serum TSH less than 0.1 μIU/ml or higher than 4.5 μIU/ml, and it is possible individuals with TSH values outside these parameters may have had abnormal serum FT_4 values. Serum T_3 or FT_3 levels and thyroid antibodies were not analyzed in this study.

The issue of age and thyroid-function tests also requires comment. Participants in this study were 65 years or older. The mean age was 72.9, but a further breakdown of age categorization is not given. However, it is now believed that the TSH reference range is higher in elderly subjects. Perhaps an elevated serum TSH, in approximately the 5 to 10 μIU/ml range, may be beneficial rather than harmful in individuals over age 85 and should not be treated with levothyroxine, with the implication that perhaps in patients taking thyroid hormone–replacement preparations a serum TSH in this level would not require an increase in levothyroxine dosage (5, 6).

In summary, Somwaru et al. have advanced our understanding of patients taking exogenous levothyroxine by emphasizing that goal serum TSH values are achieved in only approximately 43% of these patients. They correlated decreased serum TSH with lower body weight, renal insufficiency, and diabetes mellitus and an elevated TSH with diabetes mellitus (only in patients taking a combination of levothyroxine and triiodothyronine). The ATA guidelines suggest that serum TSH should be measured in patients taking thyroid hormone–replacement preparations on a periodic basis, and specifically when there has been a change in weight or in older individuals (http://hyper.thyroidguidelines.net/care). Following equilibration and normalization of serum TSH, periods between visits and serum measurements can be lengthened to every 6 to 12 months, unless clinical circumstances change. When the levothyroxine dose or brand of levothyroxine is changed, TSH measurements should be repeated in 6 to 8 weeks. The explanation for the high frequency of perturbed TSH concentrations in the population studied by Somwaru et al. is not known, but previous clinical studies have suggested a similarly high frequency (4, 7). The importance of periodic assessment of serum TSH in patients with hypothyroidism who are taking levothyroxine cannot be overemphasized.

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The utilization of sensitive diagnostic procedures does not completely explain the observed increased incidence in papillary thyroid cancer over three decades

Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, Devesa SS. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev 2009;18:784-91.

SUMMARY

BACKGROUND The incidence rates of thyroid cancer in the United States, Europe and other developed areas have been steadily increasing over the past three decades. This is mainly the result of a large rise in the incidence of papillary thyroid cancers smaller than 2 cm, which some have concluded is caused by the use of sensitive diagnostic tools such as ultrasonography and fine-needle aspiration biopsy that does not reflect an increase in the true occurrence of thyroid cancer but instead represents subclinical tumors that do not reflect the true incidence of clinically significant thyroid cancer. However, others have challenged this view in terms of the source and clinical consequences of this finding. The authors of the present study hypothesized that additional studies will be necessary to settle this debate if an analysis of the incidence patterns of thyroid cancer cannot be completely explained by enhanced detection. That is, if the detected cancers are not only localized but are in some cases more advanced, then the underlying cause or causes for the increased incidence of papillary thyroid cancer remain uncertain.

METHODS This study was based on an in-depth analysis of 48,403 patients with thyroid cancer in whom the cancer was diagnosed from 1980 through 2005. Data from this group were collected from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program using data from nine population-based registries in Connecticut, Iowa, New Mexico, Utah, Hawaii, Detroit, San Francisco–Oakland, Atlanta, and Seattle–Puget Sound (the SEER-9 registries), which include approximately 10% of the U.S. population. In 1992, four registries from San Jose–Monterey, Los Angeles, rural Georgia, and Alaska Natives were added to the registry, thus expanding the coverage to 14% of the U.S. population (the SEER-13 registries). The analysis included data from the early years of the SEER-9 database, which provided racial categories of only white and black, and from the SEER-13 database, which became available in 1992, providing data on Hispanic ethnicity and Asian/Pacific Islanders (APIs) who have a high rate of thyroid cancer. The analysis was restricted to patients with malignant thyroid tumors that were microscopically confirmed and not diagnosed solely at autopsy or identified only through death certificates. On this basis, 887 patients (1.8%) were excluded from the analysis, leaving 47,516 patients, 39,706 of whom had papillary thyroid cancer. Thyroid cancer incidence rates vary by sex and race/ethnicity, factors that influence access to and utilization of health care, which were not taken into account in previous studies when evaluating trends in thyroid cancer incidence. This study thus examined thyroid cancer incidence rates by demographic and tumor characteristics based on 48,403 patients with thyroid cancer diagnosed from 1980 through 2005.

For a long-term trend analysis of thyroid cancer incidence rates in white patients, regardless of Hispanic ethnicity, and black patients, the years of diagnosis in the SEER-9 database were grouped into seven calendar-year categories: 1980–1983, 1984–1987, 1988–1991, 1992–1995, 1996–1999, 2000–2002, and 2003–2005. For a shorter-term analysis of whites stratified by Hispanic ethnicity and APIs, only the last four calendar-year categories, 1992–1995 to 2003–20005 were used. Tumor size has been recorded since 1983 in the SEER database, before which this was unavailable in 23% of thyroid tumors. Tumor stage was stratified into three groups: localized, regional, or distant disease at the time of diagnosis. All incidence rates were age-adjusted to the year 2000 U.S. population and expressed as rates per 100,000 person-years.

RESULTS BY HISTOLOGY By far the most common form of thyroid cancer among all sex and race/ethnic groups was papillary thyroid cancer (65 to 88%), followed by follicular cancer (9 to 23%); the rates were twofold to threefold greater in women (Figure 1). The incidence rates tended to be higher among white than among black patients and among white non-Hispanics than among white Hispanics or APIs. From 1980–1983 to 2003–2005, the incidence rates of papillary cancer tripled among white and black women ($P<0.001$) and doubled among white and black men ($P<0.001$). From 1992–1995 to 2003–2005, the incidence rates of papillary thyroid cancer increased among every sex and race/ethnic group, ranging from 23% ($P = 0.07$) among API men to 104% ($P<0.01$) among black women (Figure

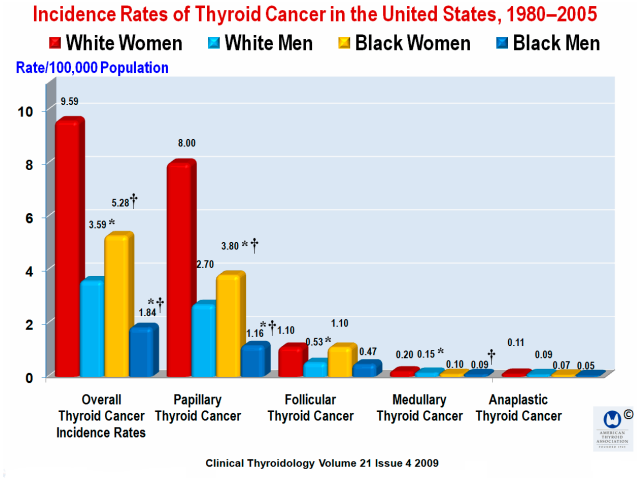

Figure 1. The incidence rates of thyroid cancer in the United States adjusted to the 2000 population and stratified according to tumor histology. Data are derived from the SEER-9 registries from 1980 through 2005.*$P<0.01$ as compared with same-race women. †$P<0.05$ as compared with same-sex white patients. This figure is derived from Table 1 in Enewold et al.

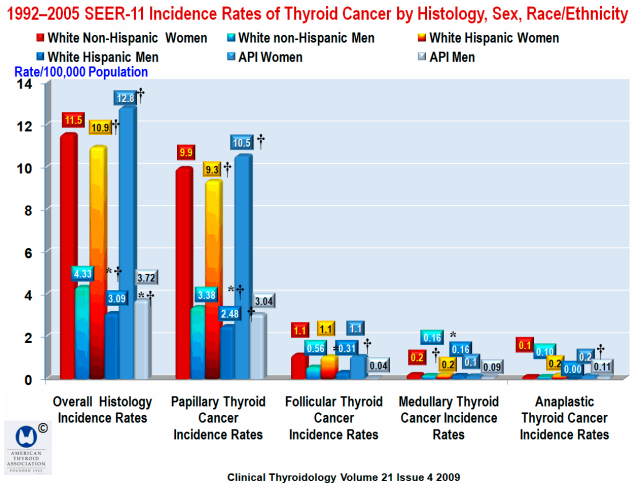

Figure 2. The incidence rates of thyroid cancer by sex and race/ethnicity, and histology, 1992-2005 in SEER-11 registries (this is SEER-13 registries excluding the Alaska Natives and rural Georgia registries).*P<0.01 as compared with same-sex/ethnicity for women. †P<0.05 as compared with same-sex white non-Hispanic patients. This figure is derived from Table 2 in Enewold et al.

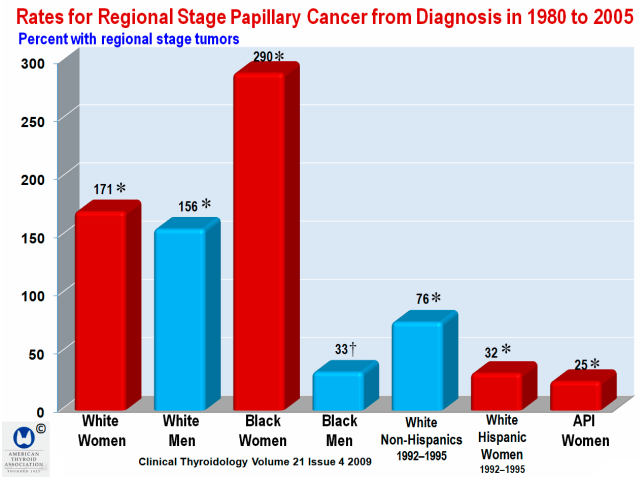

Figure 4. The rates for regional staged papillary thyroid cancer are shown over a >20-year period from 1980 to 2005. P<0.01 for rising incidence rates, except for regional tumors among black men (P>0.40). Papillary cancer distant stage rates more than doubled among whites and among Asian Pacific Islanders (APIs) from 1980 to 1983. Regional tumor rates were stable among white Hispanic and APIs.

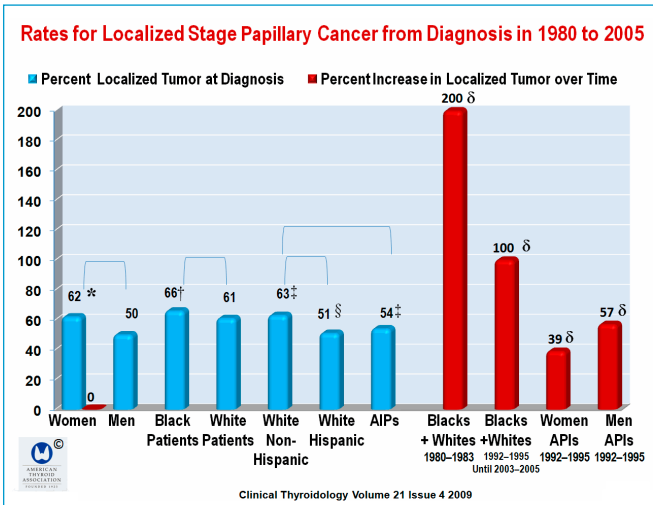

Figure 3. Incidence rates for localized papillary thyroid cancers. *P<0.01 for women versus men. †P<0.01 for black versus white patients. ‡P<0.01 for white non-Hispanics versus white Hispanics. §P<0.01 for white non-Hispanics versus Asian Pacific Islanders (API). δP<0.01 for percent increase in localized tumor over the times noted in the horizontal axis.

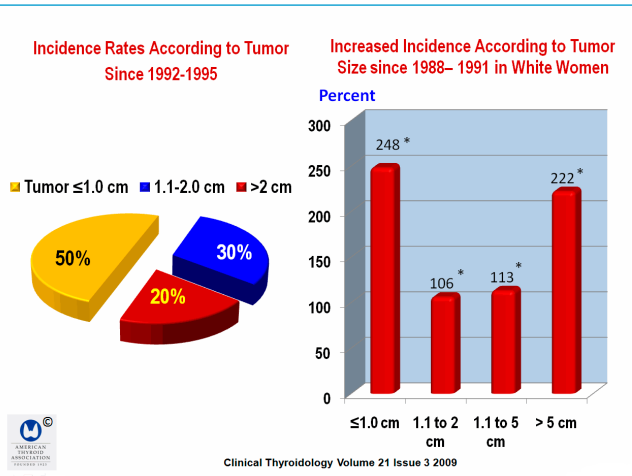

Figure 5. The increased incidence rates according to tumor size since 1988–1991 are for white women with papillary thyroid cancer. P*<0.01 for all four size groups. Rates among white men and black women were similar. During the years of study, the rates for most tumor sizes also increased among white Hispanics, Asian Pacific Islanders and black men. About 50% of the overall increase in papillary cancers since 1992–1995 was due to the increasing rates of cancers ≤1.0 cm, 30% to cancers 1.1 to 2 cm, and 20% to cancers >2 cm.

2). Because papillary cancer was increasing more rapidly than all other forms of thyroid cancer, it was the most common form of thyroid cancer, thus permitting stratification by other patient and tumor variables as well histology alone. Follicular cancer rates were more variable, increasing only moderately among API men and to 104% (P<0.01) among black women.

RESULTS BY TUMOR STAGE Although the incidence rates for papillary cancer increased for tumors of all stages, it increased most regularly for localized tumors among all racial/ethnic groups. The rate of localized tumors was greater among women than among men (62% vs. 50%) and among black than among white patients (66% vs. 61%), and among white non-Hispanics (63%) as compared with white Hispanics (51%) or APIs (54%) (P<0.01 for all) (Figure 3). The most common tumor stage at the time of diagnosis was thus localized for all racial/ethnic groups, except for white Hispanic and API men, among whom regional stage was most frequent. The rates of localized tumor among white and black patients increased approximately 200% (range, 186 to 232%) since 1980–1983 and 100% (range, 97 to 155%) from 1992–1995 to 2003–2005. Since 1992–1995, the incidence rates of localized papillary cancer among APIs increased 39% in

women and 57% in men (all P<0.01) (Figure 3). During the more than 20-year period from 1980–1983 to 2003–2005, regional tumor rates increased 171% and 156% among white women and men, respectively, and 290% and 33% among black women and men, respectively (Figure 4). Since 1992–1995, regional tumor rates increased 49% to 76% among white patients and non-Hispanics, 32% among white Hispanic women, and 25% among API women and were stable among white Hispanic and API men (Figure 4). Distant stage tumor rates more than doubled among white patients since 1980–1983, increasing >130% since 1980–1983

RESULTS BY TUMOR SIZE Although the incidence rates for tumors of all sizes increased, the increases were most rapid for the smaller tumors (Figure 5). Since 1988–1991, the earliest years that tumor size was adequately recorded, the tumor rates among white women increased 248% for tumors ≤1 cm, 106% for tumors 1.1 to 2 cm, 113% for tumors 1.1 to 5 cm, and 222% for tumors >5 cm (all P<0.01). (Figure 5) The tumor size increases among white men and black women were similar. The rates for most tumor sizes also increased among white Hispanics, APIs, and black men during this period. Approximately 50% of the overall increase in papillary thyroid cancer since 1992–1995 was the result of increasing rates of very small cancers (≤1.1 to 2 cm) and 20% among tumors >2 cm. The size-specific increases in tumor incidence among white men and black women were similar. During the period studied, the rates for most tumor sizes also increased among white Hispanics, APIs, and black men. From 1992 to 1995, approximately half of the increase in papillary thyroid cancers was due to increasing rates of very small cancers (≤1.0 cm), 30% to cancers 1.1 to 2 cm, and 20% to cancers >2 cm (Figure 5).

RESULTS BY AGE-SPECIFIC TIME TRENDS The age-specific time trends in papillary thyroid cancers were consistently apparent across all age, sex, and race/ethnic groups, except for the youngest (<20 years) and oldest (≥80 years) patients, who comprised only 2% and 3%, respectively, of each race/ethnic group. Among women, the highest incidence rates occurred among those who were 40 to 59 years of age, but the steepest increases in tumor incidence were observed among those of 60 through 79 years. However, both the highest age-specific time trends for papillary cancer and the largest increases over time tended to be among older men.

CONCLUSION Increased medical surveillance and the use of more sensitive diagnostic procedures do not completely explain the observed increases in papillary thyroid cancer rates, leaving other possible explanations for the observed increase in papillary thyroid cancer over the past three decades.

COMMENTARY

The incidence of thyroid cancer in the United States has been increasing steadily over the past three decades. Why this has occurred has become a matter of debate. Davies and Welch (1) recently investigated the size distribution of papillary thyroid cancers in approximately 2,400 thyroid cancer cases in the SEER-9 registry from the years 1988 to 2002, 88% of which were papillary thyroid cancers. They found a 2.4-fold increase (P<0.001 for trend) in the incidence of thyroid cancer, which was virtually completely due to an increase in papillary cancer that increased by 5 per 100,000 persons, from 2.7 to 7.7, thus representing a nearly 3-fold increase in the incidence (P<0.001 for trend). However, there was no significant change in the incidence of follicular, medullary, and anaplastic thyroid cancer (P>0.2 for trend). The bulk of the increased was from the detection of small cancers: 49% (95% confidence interval, 47 to 51) were from cancers 1 cm or less and 87% from tumors 2 cm or less. Papillary thyroid cancer mortality was found to be stable between 1973 and 2002, with approximately 0.5 deaths per 100,000. The authors concluded that the increasing incidence of thyroid cancer 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. The authors opined that knowing the underlying cause of the increasing incidence is important because if this is a true occurrence of disease, then efforts should be made to address its cause and aid those at greatest risk of the disease, but if it is based simply on increased diagnostic scrutiny, then the challenge to the health care community is how to identify patients who truly warrant therapy.

In another study, Kent et al. (2) used the Ontario Cancer Registry to investigate the relation between incidence rates and tumor size, age, and sex, and also found a significantly higher number of differentiated thyroid cancer, from 403 cases in 1990 to 990 in 2001—a 146% increase in 12 years, or 13% per year. In all, papillary thyroid cancer comprised approximately 95% of the cases. An analysis that grouped tumor size into small (≤2 cm), medium (2 to 4 cm), and large (>4 cm) found a significant increase in the incidence rate for the small-tumor group (P = 0.001) and the large-tumor group (P = 0.023), but not the medium-sized-tumor group. The overall incidence rates were significantly lower among men (22.1%) as compared with women (77.4%), but there was no significant difference when tumor size was compared among men and women or among patients 45 years of age or younger. Both studies concluded that the more frequent use of medical imaging has led to an increased detection rate of small, subclinical tumors, which accounts for the high incidence of papillary thyroid cancer. Of note, both studies were done without reference to patient race/ethnic demographics, which are important because thyroid cancer incidence rates vary by sex and race/ethnicity, which are factors that also influence access to and utilization of health care. One would thus expect reduced incidence rates in men, especially Hispanics and blacks, and higher rates in APIs with a known high incidence of thyroid cancer.

Enewold et al. began with the hypothesis that if the increase in thyroid cancer incidence was all due to improved disease detection, then one would expect more rapid increases in small, early-stage tumors than large late-stage tumors, and as a result, the incidence rates for large late-stage tumors should decline and

the rates of tumors with all other histologies should increase, except for anaplastic thyroid cancer. However, the Enewold study found trends in disease incidence that did not completely support this hypothesis. There were consistent increases in the incidence rates for papillary cancer only. Although the greatest increases were observed among smaller, early-stage papillary thyroid cancers, there were no declines in larger, more advanced tumors, while tumors of all sizes increased over time. For example, the incidence rates of the smallest tumors (≤1 cm) increased 248%, and in those with the largest tumors (>5 cm), it increased 222%. Moreover, the incidence rates for all tumor stages at the time of diagnosis increased among white women.

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The best results for remnant ablation is achieved with 50 mCi of ^{131}I in almost 90% of patients with papillary thyroid cancer

Kusacic Kuna S, Samardzic T, Tesic V, Medvedec M, Kuna K, Bracic I, Despot M, Dodig D. Thyroid remnant ablation in patients with papillary cancer: a comparison of low, moderate, and high activities of radioiodine. Nucl Med Commun 2009;30:263-9.

SUMMARY

BACKGROUND Patients with papillary thyroid cancer larger than 1 cm ordinarily undergo total thyroidectomy and are usually treated with ^{131}I to destroy the normal thyroid remnant and occult locoregional lymph-node metastases. The amount of ^{131}I given postoperatively is generally selected empirically and arbitrarily, with patients being treated with ^{131}I in amounts ranging from 30 to 100 mCi (1110 to 3700 MBq) to ablate the thyroid remnant, 150 mCi (5550 MBq) to treat patients with macroscopic lymph-node metastases, and 200 mCi (7400 MBq) for lung metastases. There are relatively few studies that compare the efficacy of different activities of ^{131}I for remnant ablation. This is a retrospective study aimed at identifying the smallest amount of ^{131}I that is required to obtain a reasonably high success rate for remnant ablation in patients with papillary thyroid cancer.

METHODS The study cohort comprised consecutive patients with papillary thyroid cancer treated in the Department of Nuclear Medicine and Radiation Protection at Clinical Hospital Centre in Zagreb, Croatia. All the patients were initially treated with total or near-total thyroidectomy and 24 to 120 mCi of ^{131}I (888 to 4440 MBq) after thyroid-hormone withdrawal, without a preceding diagnostic whole-body scan. Scintigraphic imaging was performed in all patients 72 hours after treatment with ^{131}I. Therapeutic outcome was first evaluated with whole-body scintigraphy 6 to 9 months after initial ^{131}I therapy and again 1 year thereafter, using 1 to 5 mCi (37 to 185 MBq) of ^{131}I in patients prepared with thyroid-hormone withdrawal; the second evaluation was performed 12 months later.

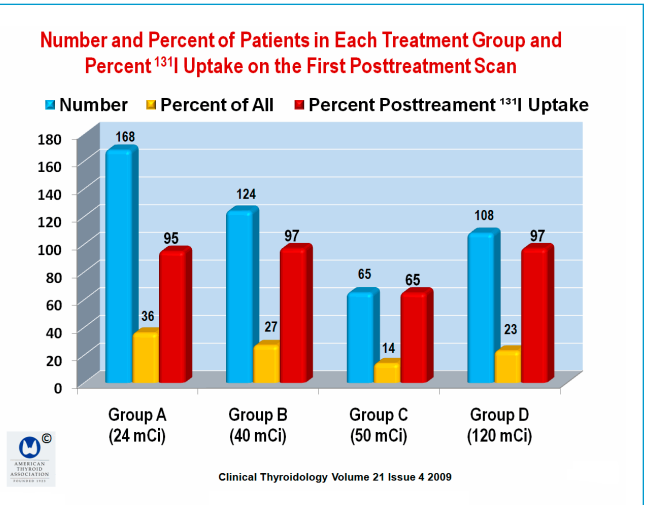

Figure 1. The four treatment groups (A through D) were treated with 24, 40, 50 and 120 mCi, respectively. Uptake of ^{131}I on the initial posttreatment whole-body scan was elevated in all four groups, ranging from 95% to 97%.

Initially, it was usual practice to administer 120 mCi of ^{131}I for remnant ablation; however, over a period of several years, the nuclear medicine physicians began using progressively smaller amounts of ^{131}I for this purpose. To compare the therapeutic efficacy of different amounts of ^{131}I, patients were retrospectively

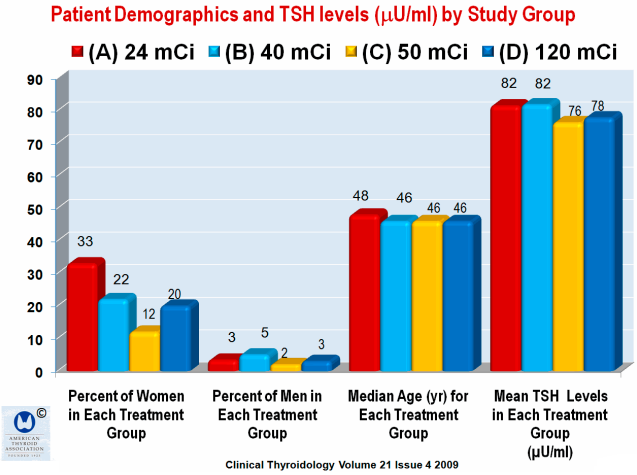

Figure 2. Patient demographics, including sex, median age at the time of diagnosis, and mean serum TSH levels were not significantly different among the four treatment groups.

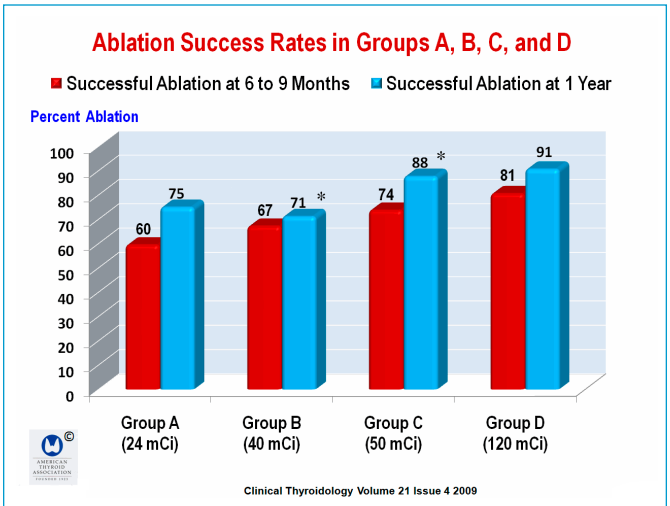

Figure 3. The remnant ablation success rate as determined by a 4-mCi diagnostic whole-body ^{131}I scan at 6 and 9 months of follow-up in groups B (40 mCi) and C (50 mCi) were not statistically significant; however, at the 1-year follow-up, ablation rates were significantly lower in group B than in group C. *P = 0.002. There were no significant differences in the rates of remnant ablation in groups C and D in the 6-year and 9-month follow-ups.

divided into four treatment groups according to the amount of ^{131}I that had been administered: 24 mCi (group A), 40 mCi (group B), 50 mCi (group C), and 120 mCi (group D) (Figure 1).

RESULTS In all, 466 patients comprised the study group—404 (87%) women and 62 (13%) men; the median age of the entire group was 47 years (range, 14 to 78). There were 168 (36%) patients in group A, 125 (27%) in group B, 65 (14%) in group C, and 108 (23%) in group D (Figure 1). Among the four study groups, there were no significant differences between mean age, sex, and thyrotropin (TSH) levels (mean [±SD] TSH was 81.6±37.6, 81.9±37.2, 76.4±393.9, and 77.9±383 μIU/ml; P = not significant, comparing the four groups A through D, respectively) (Figure 2). The postablative ^{131}I scintigraphic imaging 72 hours after initial treatment showed radionuclide accumulation in the thyroid bed in the majority of patients: 160 in group A (95.2%), 121 in group B (96.8%), 65 in group C (100%), and 105 in Group D (97.2%) (Figure 1). Six to 9 months after ^{131}I ablation, the whole-body scan was free of ^{131}I uptake in the neck region in 60%, 67%, 74%, and 82% in groups A, B, C, and D, respectively; and 1 year after follow-up, successful ablation was found in 75%, 71%, 88%, and 82% (Figure 3).

The difference in successful remnant ablation at 6 and 9 months in groups B (40 mCi) and C (50 mCi) were not statistically significant; however, at 1-year follow-up the rates were significantly lower in group B as compared with group C (71% vs. 88%; P = 0.001) (Figure 3); however, in groups C and D, there was no significant difference in the rates of remnant ablation (74% vs. 80.6%) in the first follow-up, nor were there significant differences in the second follow-up in groups C and D (87.7% vs. 71.2%) (Figure 3).

CONCLUSION Fifty mCi appears to be the optimal amount of ^{131}I to achieve a successful rate (90%) of remnant ablation.

COMMENTARY

The amount of radioiodine required for postoperative remnant ablation has been a matter of controversy for decades. The amounts of ^{131}I are generally selected empirically and arbitrarily. Two systematic reviews (1, 2) found that large amounts of ^{131}I, of approximately 100 mCi, are more efficient for remnant ablation than are lower activities of approximately 30 to 50 mCi, particularly after less than total thyroidectomy. The authors of both systematic reviews concluded that patients with differentiated thyroid cancer should routinely be treated with higher amounts of ^{131}I following total thyroidectomy. However, the authors opined that it is not possible to reliably determine whether 30 mCi achieves results similar to those with 100 mCi and that large randomized trials are needed to resolve the issue to guide clinical practice. Such studies are now available.

In a randomized clinical trial aimed at finding the smallest effective amount of ^{131}I for remnant ablation, Bal et al. (3) stratified 565 patients by 5-mCi (185-MBq) increments of ^{131}I into eight study groups treated with 15 to 50 mCi. Patients receiving at least 25 mCi of ^{131}I had a threefold greater chance of achieving successful remnant ablation than did patients receiving smaller amounts of ^{131}I (60% vs. 81%, P = 0.006). The authors concluded that the therapeutic efficacy of 25 mCi or more ^{131}I was equal to 50 mCi.

Another randomized clinical trial by Mäenpää et al. (4) of 160 adults with papillary or follicular thyroid cancer found, after randomly assigning patients to receive either 30 or 100 mCi of ^{131}I, that there was no conclusive evidence that 100 mCi is more effective for ablation of the thyroid remnant than 30 mCi, and that 100 mCi is associated with more adverse effects. In each of the above-mentioned studies patients were prepared with thyroid-hormone withdrawal.

A study by Barbaro et al. (5) of 16 patients prepared with recombinant human TSH (rhTSH) and treated with 30 mCi of ^{131}I found that remnant ablation was achieved in 81% of patients pretreated with rhTSH and 75% treated with thyroid-hormone withdrawal.

A randomized study by Pacini et al. (6) using rhTSH or thyroid-hormone withdrawal in preparation for a 100-mCi treatment of remnant ablation used several criteria for successful ablation: no visible uptake in the thyroid bed, or if visible, radioiodine uptake less than 0.1% on neck scans performed 8 months after therapy. The criteria were satisfied in 100% of the patients in both groups. A secondary criterion for ablation—an rhTSH-stimulated serum thyroglobulin concentration of <2 ng/ml—was fulfilled in 96% of euthyroid (rhTSH) patients and 86% of hypothyroid (withdrawal) patients (P = 0.234). Moreover, euthyroid patients treated with rhTSH received a one-third lower radiation dose to the blood, as compared with the radiation received by patients in the hypothyroid group. This study demonstrates comparable remnant ablation rates in patients prepared for ^{131}I remnant ablation with 100 mCi by either administering rhTSH or withholding thyroid hormone.

Recommendation 36 of the 2009 ATA guidelines (7) for the management of thyroid cancer suggests that the minimum activity (30 to 100 mCi) necessary to achieve successful remnant ablation should be used, particularly for low-risk patients.

The study by Kusacic Kuna et al. shows that 50 mCi provides an optimal result, although the end points for remnant ablation were not as stringent as the studies cited above. Nonetheless, the rate of successful remnant ablation was significantly higher with 50 mCi as compared with 120 mCi, which is especially remarkable considering the high level of ^{131}I uptake on a diagnostic whole-body scan obtained immediately after surgery indicating the presence of large thyroid remnants. Given the major concern about whole-body radiation and second cancers as the result of ^{131}I therapy, it is prudent to follow the ATA guideline suggesting the use of the smallest amount of ^{131}I that is effective. Preparing the patient with rhTSH provides even less whole-body radiation.

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Self-reported hypothyroidism is increased in women with breast cancer treated with surgery, chemotherapy, and radiotherapy

Reinertsen KV, Cvancarova M, Wist E, Bjoro T, Dahl AA, Danielsen T, Fossa SD. thyroid function in women after multimodal treatment for breast cancer stage II/III: comparison with controls from a population sample. Int J Radiat Oncol Biol Phys 2009. S0360-3016(08)03860-1 [pii];10.1016/j.ijrobp.2008.11.037 [doi]

SUMMARY

BACKGROUND There is a relationship between breast cancer, thyroid dysfunction, and malignant thyroid tumors. However, it is uncertain whether this is due to a genetic link between breast cancer and thyroid tumors or the result of thyroid-tissue injury inflicted by radiotherapy, chemotherapy, or antiestrogens. Although radiation-induced thyroid damage may be the key factor in this situation, it is difficult to be certain, because external-beam radiation techniques have changed considerably in the past few years, during which standardized radiation-field techniques have been gradually altered to offer greater accuracy and individualization of the radiation fields for patients receiving adjuvant radiotherapy. The aim of this study was to assess the prevalence of thyroid disease, particularly hypothyroidism, in women who have received multimodal treatment of stage II/III breast cancer as compared with that in the general population. A secondary aim was to compare the thyroid effects between standardized radiation-field techniques (T-RT) and CT-based treatment fields (CT-RT).

METHODS The study subjects were women with breast cancer treated with radiotherapy after surgery for stage II/III breast cancer at the Norwegian Radium Hospital during the years 1998 through 2002. To assess the late effects of treatment, patients were invited in 2004 to participate in a follow-up questionnaire and thyroid blood testing. The inclusion criteria for the study were age ≤75 years, no evidence of residual breast cancer or other cancers except basal-cell cancer, in situ cancer of the uterine cervix, or prior surgery for contralateral stage I breast cancer. Surgery consisted of modified radical mastectomy or breast-conserving surgery with axillary dissection. Postoperative adjuvant treatment was given according to national guidelines. As a result, during 1999, adjuvant chemotherapy for women <55 years of age changed from nine 3-week cycles of chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) to six 3-week cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). From 2001, adjuvant FEC chemotherapy was also given to those between the ages of 55 through 64 years with hormone receptor–negative disease. Patients with inoperable tumors received preoperative chemotherapy before modified radical mastectomy and axillary dissection and were treated with the FEC regimen or were randomly assigned to receive four to eight 3-week cycles of epirubicin 90 mg/m^2 or paclitaxel 200 mg/m^2. Patients with hormone receptor–positive tumors or unknown receptor status were advised to take tamoxifen 20 mg daily for 5 years. Before 2000, radiotherapy (RT) was based on a standardized T-RT field, but since 2000, treatment was based on computed tomography images (CT-R. For each patient with breast cancer, five cancer-free and age-matched women were randomly selected as controls from a national Norwegian Health study.

RESULTS From 2004 through 2005, 318 of 418 eligible patients (77%) participated in the study, but three were subsequently excluded from the survey because of lack of blood samples in 2 and detection of new metastasis in 1. In 2007, 308 living patients were invited to participate in a new follow-up study. In

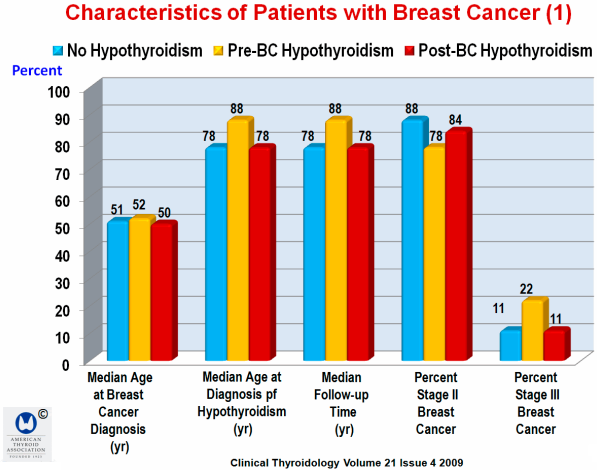

Figure 1. The baseline characteristics of the study population with breast cancer (BC) are derived from Table 1 of the study by Reinertsen et al.

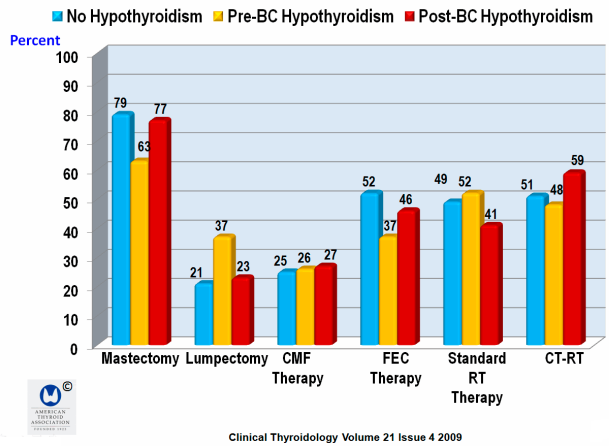

Figure 2. The surgical and medical treatment of patients with breast cancer is shown. BC = breast cancer; CMF = cyclophosphamide, methotrexate, and fluorouracil; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; RT = radiotherapy; Standard RT therapy = radiotherapy with a fixed radiation field; CT-RT = therapy with radiotherapy fields based on computed tomography imaging.

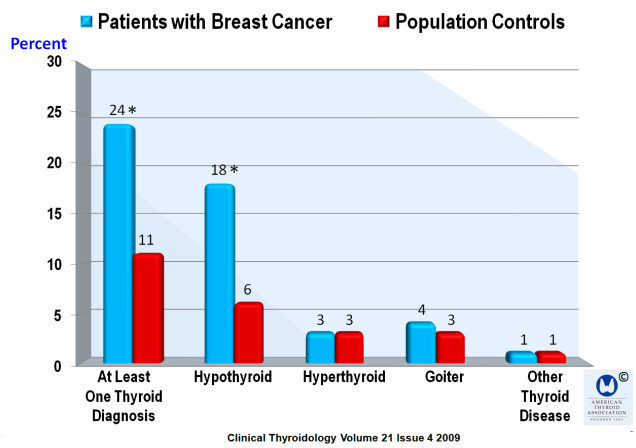

Figure 3. The prevalence of thyroid disease is based on patient self-reporting. *P<0.001 for patients versus controls.

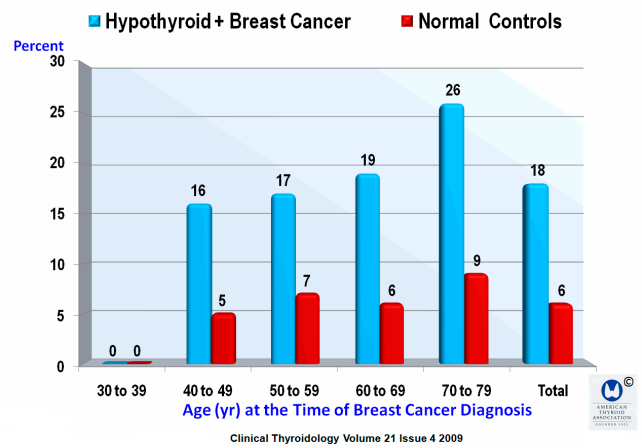

Figure 4. The prevalence of hypothyroidism increased steadily with age in patients with breast cancer.

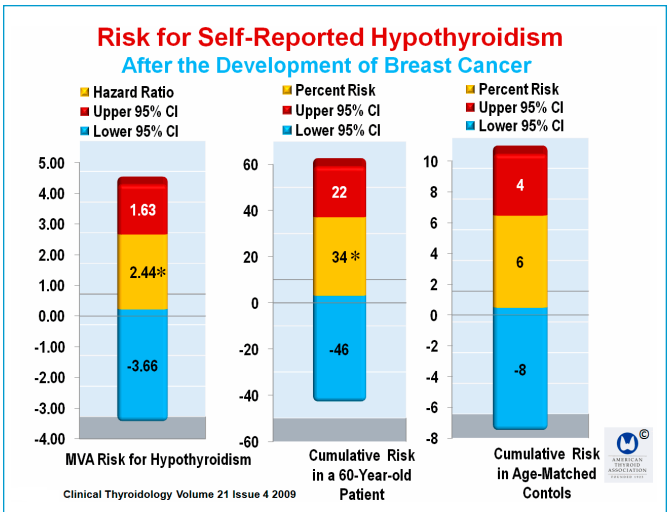

Figure 5. The risk for hypothyroidism is assessed by multivariate analysis (MVA) and as a cumulative risk in a 60-year-old patient with breast cancer as compared with five age-matched cancer-free women for each patient with breast cancer. *P<0.001.

addition, 145 additional patients not identified in 2004 were also invited to participate. In 2007, 336 patients (74%) had returned at least one completed questionnaire and had blood samples taken. Thus, a total of 403 patients participated in the study, but 16 participated only in 2004, 88 participated only in 2007 and 248 participated in both 2004 and 2007.

The major patient and treatment characteristics of all patients with breast cancer are shown in Figures 1 and 2. In all, 24% of the patients with breast cancer reported a diagnosis of at least one thyroid disorder, as compared with 11% in the general population. Hypothyroidism was the most common thyroid disorder in both the patients and controls (18% vs. 6%, P<0.001), whereas the prevalence of other thyroid diseases in the two groups were comparable (Figure 3). Hypothyroidism was progressively more prevalent in older patients (Figure 4). Prior to the diagnosis of breast cancer, 24 patients (7%) had a diagnosis of hypothyroidism, as compared with 6% of the controls; However, a median of 35 months (range, 5 to 88) after breast surgery, the diagnosis of hypothyroidism was twice as likely in patients as compared with controls (hazard ratio [HR], 2.44; 95% confidence interval [CI], 1.63 to 3.66) (Figure 5). Although univariate analysis found that the diagnosis of hypothyroidism was associated with a physician visit within the past year and a higher level of education, the hazard ratio was not affected when adjusted to these two variables. The cumulative risk for postoperative hypothyroidism in a 60-year-old patient was 34% (95% CI, 22 to 46), as compared with 6% in the control group (95% CI, 4 to 8). (Figure 5) There was a trend for increased occurrence of postsurgical hypothyroidism in patients treated with CT-RT as compared with 18 patients treated with T-RT (P = 0.08), which remained unchanged after adjustment for age.

Among the patients who reported no thyroid disease, 10% of the patients with breast cancer had elevated serum thyrotropin (TSH) levels, as compared with 7% in the control group (P = not significant) but biochemical hypothyroidism was present in none of the former and only 1% of the latter. Paradoxically, positive serum thyroid peroxidase antibody (TPOAb) tests were more common among patients with breast cancer than among patients with hypothyroidism (P<0.01); however, TPOAb was positive more often in patients in whom hypothyroidism developed before breast cancer than after (26% vs. 41%, P = not significant)

CONCLUSION Self-reported hypothyroidism is increased in women with breast cancer treated with surgery, chemotherapy, and radiotherapy.

COMMENTARY

Hypothyroidism is a potential complication of radiotherapy when the thyroid is included in the treatment fields. The main finding in the study by Reinertsen is that the rate of self-reported hypothyroidism was significantly increased in patients with breast cancer as compared with the general population, whereas prior to the diagnosis of breast cancer the prevalence of hypothyroidism was similar to that of age-matched cancer-free controls. Although there was a trend for ($P = 0.08$) for an increase in hypothyroidism in patients treated with a standardized radiation as compared with CT-guided field, the difference was not statistically significant.

A systematic review by Jereczek-Fossa et al. (1) suggested that radiotherapy-induced thyroid abnormalities remain underestimated and underreported. The sequelae of radiation therapy may include primary or central hypothyroidism, thyroiditis, Graves' disease, euthyroid Graves' ophthalmopathy, benign adenomas, multinodular goiter and radiation-induced thyroid carcinoma. However, primary hypothyroidism is the most common radiation-induced thyroid dysfunction, affecting 20% to 30% of patients following radiotherapy to the neck region, with approximately half of the events occurring within the first 5 years after therapy. The authors of this study acknowledged that the contribution of other treatment methods such as chemotherapy and endocrine therapy, as well as patient- and tumor-related factors is less clear. Their recommendation was to obtain a history for symptoms of thyroid dysfunction, clinical examination, and measurement of thyroid hormones and serum TSH. Several other studies have made similar observations and have recommended similarly appropriate surveillance for this group of patients (2). A study of 10 patients by Hancock et al. (3) found a marked dose-dependent effect of radiation therapy on the development of hypothyroidism.

Smith et al., in the most recent and largest study (4) of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER)-Medicare registry, identified 38,255 women 65 years of age or older with stage 0 to III breast cancer from 1992 to 2002 that was treated with radiotherapy to a supraclavicular field, which typically includes a portion of the thyroid. When the incidence of hypothyroidism in this irradiated cohort was compared with that in 111,944 cancer-free controls, the study found, after adjusting for sociodemographic and clinical characteristics, that the risk for hypothyroidism was not increased in irradiated patients. However, all patients, regardless of radiotherapy status, were more likely to have hypothyroidism as compared with cancer-free controls (HR, 1.21; 95% CI, 1.17 to 1.25). The authors concluded that development of hypothyroidism is fairly common in older breast cancer survivors, and supraclavicular irradiation does not appear to amplify risks, but suggested that further studies of the role of routine thyroid-function monitoring in all patients with breast cancer regardless of treatment may be warranted, given the excess risks as compared with the general population.

It is difficult to make a recommendation on the basis of the study by Reinertsen, mainly because the incidence of hypothyroidism was self-reported, and there may have been ascertainment bias among patients with breast cancer who might have had their thyroid function checked more often than is usual for the general population. Whether this group of irradiated patients with breast cancer should receive more surveillance for hypothyroidism than that in the general population remains uncertain. Still, routine testing for thyroid dysfunction, especially hypothyroidism, is well within the standard of care for postmenopausal women.

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Tumor histology is not an independent determinant of the prognosis of differentiated thyroid cancer

Verburg FA, Mader U, Luster M, Reiners C. Histology does not influence prognosis in differentiated thyroid carcinoma when accounting for age, tumour diameter, invasive growth and metastases. Eur J Endocrinol 2009;160:619-24.

SUMMARY

BACKGROUND Papillary and follicular thyroid cancer are often considered together in analyses of differentiated thyroid cancer; however, follicular cancer generally has a more aggressive course with less favorable survival rates. On the other hand, some studies suggest that the two tumors have inherently similar biologic behavior when adjusted for patient age, tumor stage and initial therapy. The aim of this study was to investigate whether there are differences in tumor-specific survival when adjusted for initial staging.

METHODS This is a retrospective study of papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) that was treated at the University of Würzburg from January 1978 through December 2002. The 2002 cutoff was selected to ensure a minimum follow-up of 5 years. All patients were treated with total thyroidectomy and ^{131}I for remnant ablation except for patients with isolated papillary thyroid microcarcinoma (tumors ≤1 cm). Patients were usually treated with 40 to 95 mCi (1500 to 3500 MBq) of ^{131}I according to the thyroid remnant size. Patients had follow-up 6 to 12 months after the initial treatment when ^{131}I whole-body scintigraphy and thyroglobulin (Tg) measurements were performed after levothyroxine withdrawal or recombinant human thyrotropin (rhTSH) stimulation. Persistent or recurrent disease was treated with 190 mCi (7000 MBq) of ^{131}I. Within the first 5 years after initial therapy, patients who were considered to be free of disease had one more whole-body diagnostic scans and serum Tg measurements after thyroid-hormone withdrawal or rhTSH stimulation. Thereafter, serum Tg measurements were made during thyroid-hormone suppression of TSH and neck ultrasonography, and computed tomography scans or magnetic resonance imaging was performed as indicated. Tumor staging was done according to the World Health Organization standard at the time of surgery. Tumor size was measured on the primary tumor specimen. Patients had to undergo lymph-node surgery to be considered free of lymph-node metastases.

RESULTS The study subjects were 875 patients with PTC (71%), and 350 with FTC (29%). There were 628 (72%) women with PTC and 228 (65%) with FTC; the mean age was 46.1 years (range, 5 to 87) in the PTC patients and 52.2 years (range, 8 to 81) in the FTC patients (P<0.001, comparing PTC with FTC) (Figure 1). Mean follow-up was 10.8 years in the PTC group and 10.9 years in the FTC group. Mean (±SD) tumor diameter in PTC and FTC was 19.2±0.6 and 31.7±1.3 mm, respectively (P<0.001). Tumor was multifocal in 92 (10.5%) and 51 (14.5%) (P = 0.047), metastatic to lymph nodes in 78 (8.9%) and 18 (5.1%) (P = 0.02), and metastatic to distant sites in 64 (7.3%) and 55 (15.7%) (P<0.001) in the two histologic tumor types, PTC and FTC, respectively. The median follow-up for the entire cohort was 9.9 years, without a significant difference in the length of follow-up in the two groups of patients. Tumor-specific mortality of PTC and FTC were considerably different: the 20-year survival rates were 90.6% for PTC and 73.7% for FTC (P<0.001). If distant metastases were excluded from the analysis, the 20-year disease-specific mortality rates in FTC patients was 80.2%, which was significantly lower than that for PTC (93.1%) (P<0.001). Moreover, in patients with distant metastases, there were no significant difference between PTC and FTC (P = 0.16). In Cox regression, the independent

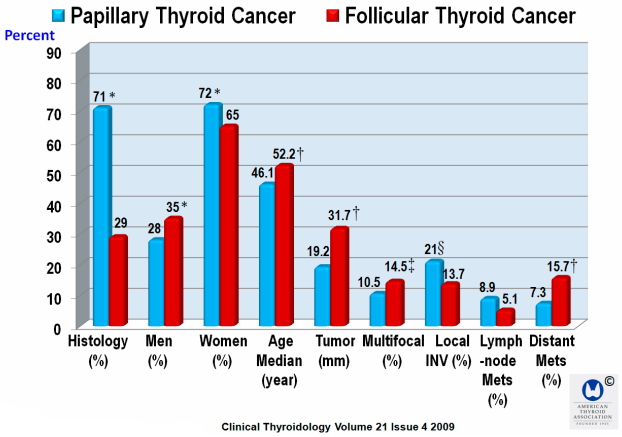

Figure 1. The comparison of characteristics between papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC). *P = 0.02, †P <0.001, ‡P = 0.047, §P = 0.006, all comparing papillary with follicular thyroid cancer. INV = local tumor invasion, Mets = metastases.

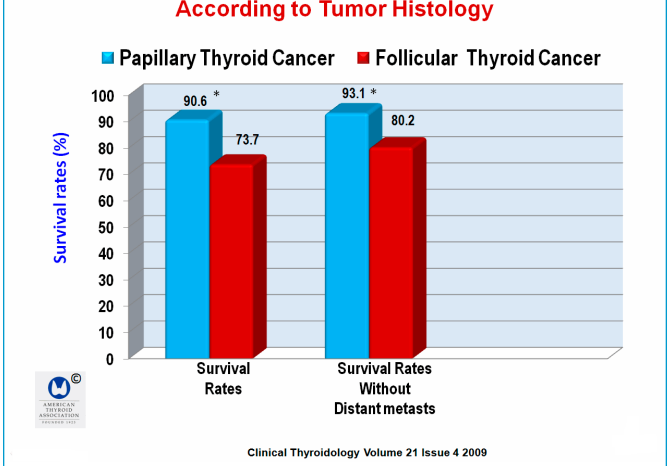

Figure 2. 20-year cancer-specific survival rates for papillary and follicular thyroid cancer with and without distant metastases. *P<0.001 comparing papillary with follicular thyroid cancer.

variables for survival were the presence of distant metastases (P<0.001), age (P<0.001), tumor size (P = 0.001), and extrathyroidal invasion (P = 0.007) at the time of diagnosis. In addition, Kaplan–Meier curves did not show significant differences between PTC and FTC for patients younger than 45 years of age with isolated nonmetastatic tumors <1 cm (P = 0.81) (Figure 2). Likewise patients 45 or older with stage IV tumors did not show significant differences in survival.

CONCLUSION The independent risk factors for tumor-specific survival were distant metastases, patient age, tumor size, and extrathyroidal invasion, but not tumor histology.

COMMENTARY

Although papillary and follicular thyroid cancer are often grouped together as a single entity referred to as differentiated thyroid cancer, the two histologically unique tumors have major genetic, biologic, and clinical differences that clearly set them apart from one another. The most obvious clinical difference is that cancer-specific mortality of follicular cancer is about twofold to threefold that of papillary cancer. A study by Hundahl et al. (1) of 53,856 cases of thyroid cancer treated in the United States from 1985 through 1995 found 10-year relative survival rates of 93% for papillary and 85% for follicular thyroid cancer—that is, cancer-mortality rates of 7% and 15%, respectively. This is in the approximate range reported by Verburg et al., who found 20-year cancer-specific survival rates of 90.6% for papillary and 73.7% for follicular thyroid cancer. The more important question is whether this is the result of inherent biologic characteristics of the tumor or as yet unidentified clinical factors. For uncertain reasons, the incidence rate of papillary cancer is approximately threefold that of follicular cancer (2). Follicular cancer tends to be diagnosed later in life, is more common in men, and is generally a larger tumor with more distant metastases at the time of diagnosis as compared with papillary cancer. On the other hand, papillary tumors tend to be more invasive and multifocal, with more locoregional lymph-node metastases than occur with follicular cancer. These obvious tumor differences lie at the surface of a much deeper and thorny set of issues. For example, the various RET/PTC oncogenes associated with papillary cancer are found in younger patients and specific RET/PTC rearrangements are associated with radiation-induced tumors, whereas as BRAF oncogenes are associated with aggressive papillary tumors such as tall-cell-variant papillary cancer, which has high recurrence and mortality rates. In contrast, encapsulated papillary cancer has almost no cancer-specific mortality. Follicular thyroid cancer, which is usually encapsulated, may have minimal tumor capsular invasion that usually portends relatively benign clinical behavior (3), while poorly differentiated follicular thyroid cancer has serious prognostic connotations (4). These tumor features must be taken into account when asking whether follicular histology per se determines the patient's outcome expressed as 20-year cancer-specific survival.

Verburg et al. found that patients with follicular cancer were on average older and were more likely to be men, and had larger primary tumors that were more often multifocal and metastatic to distant sites as compared with papillary cancer, which tended to have more extrathyroidal invasion, more lymph-node metastases, and fewer distant metastases. None of these features are strikingly different from that generally reported in the literature. The main finding of the study was that multivariate analysis identified four independent variables that predicted follicular cancer mortality: distant metastases, patient age, tumor size, and tumor invasion; however, tumor histology was not among the features predicting survival. The main conclusion of the article is that tumor-specific mortality is the same for papillary and follicular thyroid cancer when the analysis is controlled for the four factors found on multivariate analysis.

Others have found that 30-year cancer-specific mortality rates were greatest in patients with follicular cancer and that cancer mortality was most likely in the presence of adverse prognostic factors, such as advanced age, large tumor size, and distant metastases. This same study found that mortality rates for papillary and follicular thyroid cancer were similar (10% vs. 6%, P = not significant) if distant metastases were excluded from the analysis. Still others have found that histologic grade and invasive tumor is important for follicular outcome (4, 5).

Verburg et al. suggest that there are several sources of concern in their study. They were unable to confirm some of the data because in the earlier part of the study, pathology reports were rather scarce. Also, a large number of patients did not have information on the presence or absence of lymph-node metastases; and over time, there may have been shifts in tumor treatment. The authors also acknowledge that it is still not clear why patients with follicular cancer present with more advanced disease than do patients with papillary thyroid cancer.

Nonetheless, it is important to know that features such as patient age, tumor stage, and initial treatment have a major impact on the clinical outcome of both papillary and follicular cancer, which to some extent puts less emphasis on tumor histology alone when attempting to estimate the risks of tumor recurrence and cancer-specific mortality.

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DISCLOSURE

Dr. Mazzaferri receives honoraria from Genzyme for providing lectures.

Dr. Sipos receives honoraria from Abbott and Genzyme for providing lectures.

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Discounted Registration Deadline: August 31, 2009

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