

Increasing Incidence of Thyroid Cancer in the United States, 1973-2002

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WHILE THE INCIDENCE OF many head and neck cancers in the United States is decreasing,¹ a number of registries have reported that the incidence of thyroid cancer is increasing.²⁻⁶ Some investigators have attributed the increase to environmental radiation,⁵ while others have found no obvious source.³ However, increasing cancer incidence can be either real or apparent because of increased diagnostic scrutiny. Supporting evidence for a real increase in incidence includes an increase in known or suspected risk factors for the cancer. If the increase were real, it would be expected across all stages, as opposed to a shift in the stage distribution toward earlier stages, as might be expected if there were changes in diagnostic criteria or increased diagnostic scrutiny. Moreover, the increase in incidence might be expected to be accompanied by increasing symptoms or associated mortality.

Although some thyroid cancers can spread and cause death, for many people thyroid cancer has also long been recognized to exist in a subclinical form. More than 50 years ago, pathologists reported that thyroid cancer (particularly papillary histology) was a common autopsy finding, despite its never having caused symptoms during a person's life.⁷ This finding has been replicated in several autopsy studies,⁸⁻¹¹ the most methodical of which was from Harach et al,¹² who systematically sectioned 101 thy-

Context Increasing cancer incidence is typically interpreted as an increase in the true occurrence of disease but may also reflect changing pathological criteria or increased diagnostic scrutiny. Changes in the diagnostic approach to thyroid nodules may have resulted in an increase in the apparent incidence of thyroid cancer.

Objective To examine trends in thyroid cancer incidence, histology, size distribution, and mortality in the United States.

Methods Retrospective cohort evaluation of patients with thyroid cancer, 1973-2002, using the Surveillance, Epidemiology, and End Results (SEER) program and data on thyroid cancer mortality from the National Vital Statistics System.

Main Outcome Measures Thyroid cancer incidence, histology, size distribution, and mortality.

Results 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 (95% confidence interval [CI], 2.2-2.6; $P < .001$ for trend). There was no significant change in the incidence of the less common histological types: follicular, medullary, and anaplastic ($P > .20$ for trend). Virtually the entire increase is attributable to an increase in incidence of papillary thyroid cancer, which increased from 2.7 to 7.7 per 100 000—a 2.9-fold increase (95% CI, 2.6-3.2; $P < .001$ for trend). Between 1988 (the first year SEER collected data on tumor size) and 2002, 49% (95% CI, 47%-51%) of the increase consisted of cancers measuring 1 cm or smaller; 87% (95% CI, 85%-89%) consisted of cancers measuring 2 cm or smaller. Mortality from thyroid cancer was stable between 1973 and 2002 (approximately 0.5 deaths per 100 000).

Conclusions The increasing incidence of thyroid cancer in the United States is predominantly due to the increased detection of small papillary cancers. These trends, combined with the known existence of a substantial reservoir of subclinical cancer and stable overall mortality, suggest that increasing incidence reflects increased detection of subclinical disease, not an increase in the true occurrence of thyroid cancer.

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roid glands in 2- to 3-mm slices. They found that 36% of people not known to have thyroid cancer during their lifetime nonetheless had 1 or more foci of thyroid cancer. However, because many of the cancers identified by Harach et al were small (far smaller than the 2-3 mm between the slices), they reasoned that many were missed by their technique. They went on to calculate that, if sectioned finely enough, virtually every person would be found to harbor a thyroid cancer.

As diagnostic techniques for thyroid cancer have become more sensitive, particularly with the advent of ultrasound

and fine-needle aspiration, it has become possible to detect this subclinical reservoir. Thus, while increasing incidence of thyroid cancer might reflect an increase in the true occurrence of disease, it might also reflect increased diagnostic scrutiny or changes in diagnosis.

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tic criteria. Examination of the reasons underlying an increase in the incidence of thyroid cancer is important, because if there is an increase in the true occurrence of disease, efforts should be made to address its cause and aid those at greatest risk of developing the disease. If the observed increase is based simply on increased diagnostic scrutiny, then the challenge to the health care community is how to identify which patients truly warrant treatment, with its attendant risks. To examine possible reasons for the observed increasing incidence of thyroid cancer, we describe trends in its incidence, histology, size distribution, and mortality in the United States, to determine whether the patterns suggest a real change in incidence or an apparent change based on increased diagnostic scrutiny.

METHODS

Data Source

Data on thyroid cancer incidence, histology, and size distribution were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The SEER program has collected population-based data on incident cancers from 9 cancer registries in distinct areas of the United States (5 states: Connecticut, Hawaii, Iowa, New Mexico, and Utah; and 4 metropolitan areas: Atlanta, Detroit, San Francisco, and Seattle). These areas represent approximately 10% of the US population and provide data from 1973 to 2002.

Thyroid cancer mortality for the same period was obtained from the Centers for Disease Control and Prevention's National Vital Statistics System, which provides information on the underlying cause of death obtained from death certificates filed in each state.

The Dartmouth institutional review board has deemed studies using deidentified, publicly available data (such as those used herein) to be exempt from institutional review board review.

Case Definitions

We restricted our analyses to the 4 major histological categories associated

with thyroid cancer: papillary, follicular, medullary, and anaplastic.¹³ We identified the categories using the codes from *The International Classification of Diseases for Oncology, 3rd Edition*¹⁴: papillary (8050, 8052, 8130, 8260, 8340-8344, 8450, 8452), follicular (8290, 8330-8332, 8335), medullary (8345, 8346, 8510), and anaplastic (8021). These codes encompassed 99.5% of cancers attributed in SEER to the anatomical site "thyroid." The remaining 0.5% of cases were excluded based on rarity, concern that the thyroid gland was not the location of the primary cancer (eg, fibrosarcoma, squamous cell carcinoma), or both.

Analyses

For all included histological categories, the overall incidence and mortality of thyroid cancer for each year from 1973-2002 were calculated. All rates were age-adjusted to the 2000 US population.

Incidence trends for each of the distinct histological categories were then examined. Because the medullary and anaplastic categories are so rare and behaviorally similar (poorly differentiated and aggressive), these were combined into a single category labeled "poorly differentiated."

Beginning in 1988, SEER began to collect data on thyroid cancer size, measured in terms of the cancers' greatest dimension as recorded on surgical pathology reports.¹⁵ We compared the size distribution of papillary cancer in the earliest available year (1988) with that of the most recent year (2002). Size data were available for more than 95% of cases in each year of our analysis.

Tests of trend and 95% confidence intervals (CIs) were performed using STATA version 9.0 (StataCorp, College Station, Tex); $P < .05$ was used to determine statistical significance.

RESULTS

Thyroid Cancer in 2002

In 2002 there were approximately 2400 cases of thyroid cancer diagnosed in the 9 SEER areas. Extrapolated to the nation, this translates into roughly 24 000 new

cases for the year. The median age at diagnosis was 46 years, up slightly from previous years (in 1995, the median age was 45 years). Thyroid cancer affected women more than men by a ratio of 2.7 to 1. The distribution of histological categories was as follows: 88% papillary, 9% follicular, and 3% poorly differentiated (medullary and anaplastic).

Incidence Trends, 1973-2002

As shown in FIGURE 1, 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 (95% CI, 2.2-2.6; $P < .001$ for trend). This 5.1 per 100 000 increase in the incidence of thyroid cancer is virtually entirely due to an increase in papillary cancer, which increased by 5 per 100 000, from 2.7 to 7.7 per 100 000—a 2.9-fold increase (95% CI, 2.6-3.2; $P < .001$ for trend). There was no significant change in the incidence of the less common histological categories: follicular, medullary, and anaplastic ($P > .20$ for trend).

Papillary Cancer Size Distribution, 1988-2002

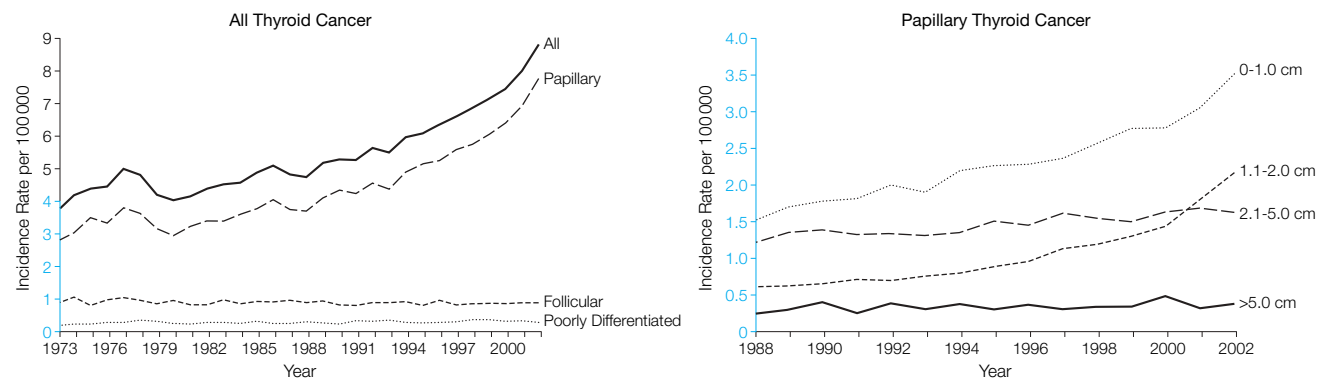
Since SEER began recording cancer size in 1988, incidence of papillary cancer has increased by 4.1 per 100 000. Figure 1 shows that the bulk of this increase is the result of increased detection of small cancers. Forty-nine percent (95% CI, 47%-51%) of the increase consisted of cancers measuring 1 cm or less; 87% (95% CI, 85%-89%) consisted of cancers measuring 2 cm or less.

Mortality, 1973-2002

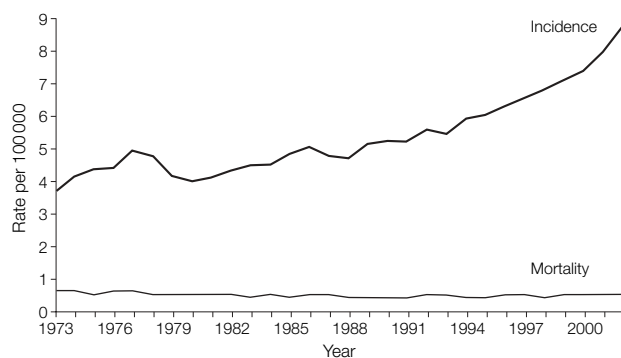
Despite increasing incidence, the mortality from thyroid cancer has remained stable (FIGURE 2). Thyroid cancer-specific mortality was approximately 0.5 deaths per 100 000 in both 1973 and 2002. (Mortality was 0.57 in 1973, decreased to 0.48 by 1980, and was 0.47 in 2002.) The proportion of deaths due to papillary type has not changed over time ($P > .20$ for trend).

COMMENT

We found that the incidence of thyroid cancer in the United States more than

Figure 1. Trends in Incidence of Thyroid Cancer (1973-2002) and Papillary Tumors by Size (1988-2002) in the United States

Poorly differentiated indicates anaplastic and medullary cancers.

Figure 2. Thyroid Cancer Incidence and Mortality, 1973-2002

doubled over the past 30 years and that 87% of the increase was due to the diagnosis of small papillary cancers. Mortality remained stable during this period. Given the known prevalence of small, asymptomatic papillary thyroid cancers at autopsy, we believe this suggests that increased diagnostic scrutiny has caused an apparent increase in incidence of cancer rather than a real increase.

For the forgoing findings to be explained by an increase in the true occurrence of disease, several conditions would need to be met. First, there would have to be a substantial increase in the major risk factor for the disease, ie, radiation. However, if anything, radiation exposure is less common today than it was in the past. The last major nuclear atmospheric tests in the United States were conducted in 1961.¹⁶ Therapeutic radiation for common benign diseases

of the head and neck has not been used since the late 1950s, when it was used for multiple conditions such as acne, adenoid hypertrophy, tinea capitis, and thymus enlargement.¹⁶ Second, detection and treatment would have to improve in order to keep mortality stable. These advances would need to match the pace of the underlying increase in disease burden; they could not be too slow or mortality would increase, and they could not be too fast or mortality would decrease.

Some might argue that, while there has been an increase in the true occurrence of disease, there has not been enough time for increased mortality to appear. However, for this to be an explanation for the trend here, the lead time would have to be extraordinarily long—greater than the 30 years in which mortality has been stable.

Another possible explanation is that increasing incidence in the face of stable mortality represents a new category of thyroid cancer—symptomatic but not lethal. That is, there might be a growing number of people with thyroid cancer who are symptomatic but who will not die from their disease. The SEER data provide some evidence that this could explain, at best, only a small portion of the increase. One marker of increased symptoms from papillary cancer relates to the incidence of metastatic disease; however, this changed little over our analysis period (the incidence of metastatic papillary cancer increased by 0.15 per 100 000, while the overall incidence of papillary cancer increased by 5 per 100 000). Local symptoms from papillary cancer largely relate to size, resulting in dysphagia and orthopnea, and would generally be seen in cancers larger than 5 cm. The incidence of these large cancers also changed little (<3% of the increased incidence from 1988 to 2002 involved cancers of this size). Small cancers can become locally invasive and cause dysphagia or orthopnea, but this type of progression typically occurs when they are of the poorly differentiated type, and these categories of cancer (anaplastic and medullary) have also remained stable.

Alternatively, these changes could be explained by a change in the pathological criteria for thyroid cancer. The World Health Organization histological criteria for diagnosis of papillary thyroid cancer remained the same between 1988

and 2002, a period during which incidence of this category nearly doubled.¹⁷ While one might argue that the criteria could nevertheless have changed in practice, the finding that one third of adults harbor subclinical papillary cancer was based on pathological criteria from the early 1980s—making it difficult to believe that the pathological threshold for papillary cancer has decreased substantially since then.

Thus, we believe increased diagnostic scrutiny is the most likely explanation for the apparent increase in incidence. Advances in imaging and diagnostic techniques have made it more likely that cancers from this subclinical reservoir are detected. Because many of these cancers would likely never have caused symptoms during life, epidemiologists have labeled the phenomenon “overdiagnosis”—a term perhaps most familiar in the setting of prostate cancer.¹⁸

The case for overdiagnosis is strengthened because almost all the increased incidence is attributable to the detection of small cancers best discovered by use of the new technologies—ultrasound and fine-needle aspiration. In the 1980s, ultrasound came into widespread use.¹⁹ While thyroid ultrasound cannot diagnose a thyroid nodule as malignant, it can detect nodules as small as 0.2 cm. Thus, ultrasound is much more sensitive than physical examination alone, which only detects nodules that are nearly an order of magnitude larger, and physical examination has relatively low sensitivity (detects only about 40% of nodules >1.5 cm).²⁰ The second technology is fine-needle aspiration, which became widely adopted in the 1990s. Fine-needle aspiration allows for cytological assessment of a thyroid mass and can be performed quickly during an office visit.²¹ It has largely replaced nuclear medicine scans, much more involved tests that required dietary restrictions prior to the test, took several hours to complete, and frequently produced indeterminate results. The combination of the ability to detect small nodules and then aspirate their contents has clearly facilitated the diagnosis of these smaller cancers.

Overdiagnosis is a cause for concern because it makes it hard to identify which patients need treatment. In our data, most patients diagnosed with thyroid cancer underwent total thyroidectomy. This was the case even if the cancer was papillary and very small—75% of those with papillary cancers found to measure less than 1 cm underwent the procedure. Total thyroidectomy carries small but significant risks of operative complications, including permanent hypoparathyroidism and damage to the recurrent laryngeal nerve, which can result in chronic aspiration and compromised voice quality. Additionally, thyroidectomy commits the patient to a lifetime of thyroid replacement therapy and, as of recently, a recommendation of long-term surveillance for recurrent disease.

Furthermore, there are reasons to worry that the problem of identifying which patients need treatment will only get worse. Masses in the thyroid gland, which might prompt testing for thyroid cancer, are very common. Twenty percent of US adults have a palpable lesion of the thyroid gland, and 67% have a mass that can be visualized on ultrasound.²² While thyroid ultrasound has traditionally been performed in the radiology department, it is increasingly performed in the physician's office. If ultrasound continues to grow as an office-based adjunct to physical examination, there could be a dramatic increase in the number of nodules—and, ultimately cancers—identified.

We found an increase in the apparent incidence of thyroid cancer without any clinical impact on mortality. Further studies will be needed to determine if a more cautious diagnostic approach—perhaps simply providing follow-up for symptomatic thyroid nodules—is worthwhile. In addition, papillary cancers smaller than 1 cm could be classified as a normal finding.

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Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis: Davies, Welch.
Study supervision: Welch.

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