Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry

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Background. *The incidence of thyroid cancer has more than doubled in recent decades. Debate continues on whether the increasing incidence is a result of an increased detection of small neoplasms or other factors.*

Methods. *Using the Surveillance, Epidemiology and End Results database, we examined the overall incidence of thyroid cancer with variations based on tumor pathology, size, and stage, as well as the current surgical and adjuvant therapy of thyroid carcinoma.*

Results. *Thyroid cancer incidence increased 2.6-fold from 1973 to 2006. This change can be attributed primarily to an increase in papillary thyroid carcinoma, which increased 3.2-fold (*$P < .0001$*). The increase in papillary thyroid carcinoma also was examined based on tumor size. Tumors ≤1 cm increased the most at a total of 441% between 1983 and 2006 or by 19.2% per year, the incidence of papillary thyroid carcinoma also increased at 12.3%/year in 1.1–2-cm tumors, 10.3%/year in 2.1–5-cm tumors, and 12.0%/year for >5-cm tumors (all* $P < .0001$ *by Cochran–Armitage trend test). We also demonstrated a positive correlation between papillary thyroid carcinoma tumor size and stage of disease (Spearman,* $r = 0.285$, $P < .0001$*). Operative treatment for thyroid cancer also has shifted with total thyroidectomy replacing partial thyroidectomy as the most common surgical procedure.*

Conclusion. *Contrary to other studies, our data indicate that the increasing incidence of thyroid cancer cannot be accounted for fully by an increased detection of small neoplasms. Other possible explanations for the increase in clinically significant (>1 cm) well-differentiated thyroid carcinomas should be explored. (Surgery 2010;148:1147-53.)*

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In recent decades, the incidence of thyroid cancer has more than doubled in much of the developed world, including the United States,[1] Canada,[2] France,[3] and Australia.[4] Since the 1990s, thyroid cancer has become the fastest increasing cancer in women,[5] whereas the incidence of other neoplasms like lung, colon, and breast cancer has decreased.[6] Thyroid cancer remains the most common endocrine malignancy and accounts for 2.5% of all human cancers.[6]

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Numerous studies have described the increasing incidence of thyroid cancer; however, debate continues on whether these findings reflect a true increase of relevant disease or simply an improved diagnostic surveillance or pathologic recognition of incidental neoplasms with little clinical significance. Some groups have proposed that the increasing use of cervical ultrasonagraphy and fine needle aspiration contributes to the identification of clinically unimportant cancers. If this theory is true, then a greater proportion of earlier stage cancers should be noted. Davies and Welch support this theory by showing that neoplasms ≤1cm representing micropapillary thyroid cancer (microPTC) accounted for 49% of the overall increase of thyroid cancer in their study.[1] They did not, however, do any correlation of tumor size to stage of disease. A second report by Kent et al drew similar conclusions based on data demonstrating that

predominantly small cancers (<2 cm) accounted for the change.[2] An additional theory for the increasing incidence of thyroid malignancies is that an increased pathologic reporting of microPTC identified in thyroid specimens is removed for primarily benign disease. Incidental microPTC has been shown to be present in up to 13% of Americans by autopsy studies.[7] Others have suggested that the increase in thyroid cancer is real and have observed an increase in thyroid cancer of all stages. Enewold et al examined demographic changes in thyroid cancer and found a substantial increase in larger cancers (>2 cm).[8] Although the exact etiology of this trend is not yet known, some investigators have suggested that radiation or other unknown environmental factors are possible contributors to the increase in incidence of thyroid malignancy.[9,10]

Consensus exists that papillary thyroid cancer (PTC) accounts for the vast majority of the increase in thyroid cancer.[1,2,8] PTC is the most common type of thyroid cancer, accounting for 80% of cases with a 5-year survival rate of 90–95%.[11] Treatment for well-differentiated thyroid carcinoma typically consists of surgical resection with or without the addition of radioactive iodine ablation.

Our study assessed trends in thyroid cancer incidence from 1973–2006 using the Surveillance, Epidemiology and End Results (SEER) database. We sought to provide a more comprehensive analysis of histopathologic markers of tumor severity and treatment modalities to determine whether an increase occurred in neoplasms of all stages or a shift toward earlier stage tumors.

MATERIALS AND METHODS

SEER database. We evaluated a retrospective cohort of patients from 1973 to 2006 in the SEER database of the National Cancer Institute. Our data included the following SEER population-based registries that began collecting data in 1973: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. These SEER-9 registries comprise approximately 10% of the U.S. population. All SEER data are deidentified. The University Hospitals/Case Medical Center institutional review board deemed this project to be exempt from review.

Case definition. Malignant thyroid cancer diagnoses were extracted from SEER, yielding 50,212 cases for this 33-year period. The histologic type of all cases has been coded according to The international classification of disease for oncology, 3rd ed. Histology categories are as follows: papillary (8050,8052,8130,8260,8340,8344,8450,8452), follicular (8290,8330-8332,8335), medullary (8345-8346,8510), and anaplastic (8012,8020-8021,8030-8032). Tumor size was coded in the SEER database beginning in 1983 and was measured in terms of the cancers' greatest dimension as recorded on surgical pathology reports. Subanalysis of PTC was restricted to the time period 1983–2006 and included 33,886 cases (67.5% of all cases). Tumor size for PTC was split into the following categories: ≤1 cm (microPTC), 1.1–2 cm, 2.1–5 cm, and >5 cm. Data on stage were determined for all cases using SEER Historic Stage A codes. Stages included local disease (tumor confined to the thyroid); regional disease (lymph node involvement); or distant disease (metastatic spread to distant organs). We converted the raw SEER Stage A data into a format more consistent with the classic TNM staging for thyroid carcinoma. Stage data were available for 29,425 (86.8%) patients with PTC.

Operative therapies were defined as follows: (1) partial thyroidectomy included lobectomy and isthmusectomy; (2) total thyroidectomy was restricted to cases in which either the entire thyroid was removed or a near total thyroidectomy was performed; (3) the operative approach not otherwise specified (NOS); and (4) no operative therapy was treated as such where indicated. We queried the SEER database regarding the use of adjuvant therapy for thyroid malignancies. The SEER database only captures those patients who received radiation therapy within 4 months of operation.

Data analysis. All data extraction was done using SEER*Stat version 6.5.2. Incidence rates were age-adjusted based on the 2000 U.S. population census and expressed per 100,000 individuals. All rates were estimated on a 2-year interval for the variable of interest. Incidence rates for thyroid cancer were determined over time for all cancers and for each histologic category (papillary, follicular, medullary, and anaplastic) from 1973 to 2006. Subanalysis of PTC was performed with regard to incidence rates of cancer based on size, stage, and surgical therapy. We compared trends in distribution of tumor size and surgical therapy for PTC between 1983 and 2006 as this timeframe coincided with size data becoming available. Correlation analysis for the distribution of PTC tumor size and stage was performed additionally between 1983 and 2006. Tumors that were classified as unstaged were omitted from the latter analysis. The Cochran–Armitage trend test was used to examine the incidence trends of over time. The association

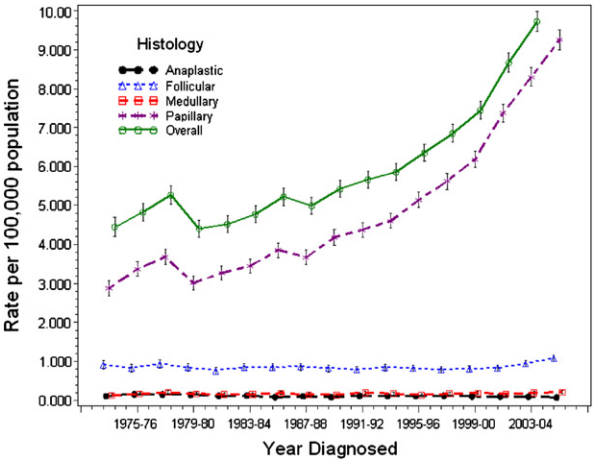

Fig 1. Trends in incidence of overall thyroid cancer cases (1973–2006). Data are age-adjusted to 2000 U.S. Census and stratified by histological subtype with 95% CI.

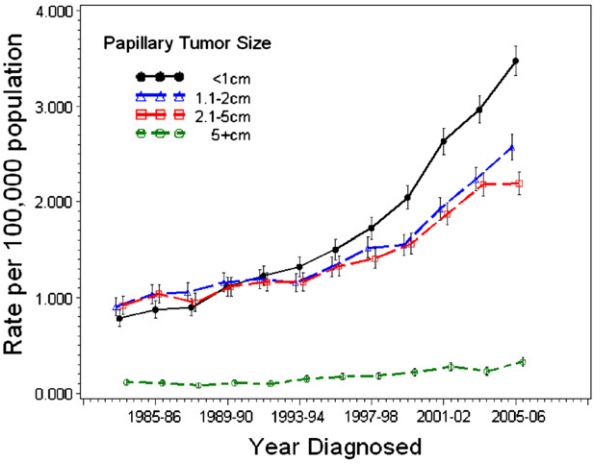

Fig 2. PTC incidence rates by tumor size (1983–2006). Data are age-adjusted to the 2000 U.S. Census with 95% CI.

between 2 factor variables was estimated using χ^2 analysis.

The Spearman correlation test was used to analyze the association between PTC tumor size and stage. Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC). All tests were two-sided and a P value <.05 was considered statistically significant.

RESULTS

Incidence trends for all thyroid malignancies: 1973–2006. From 1973 to 2006, a statistically significant increase occurred in the age-adjusted incidence rate of thyroid carcinoma from 4.3 cases per 100,000 in 1973–1974 to 11.1 cases per 100,000 in 2005–2006, representing a 2.6-fold increase (Fig 1) ($P < .0001$). PTC had the largest increase in age-adjusted incidence rates with 2.88 per 100,000 in 1973-1974 to 9.25 per 100,000 in 2005–2006, representing a 3.2-fold increase ($P < .0001$). Medullary (0.13 per 100,000 in 1973–1974 to 0.21 per 100,000 in 2005–2006) and follicular (0.91 per 100,000 in 1973–1974 to 1.08 per 100,000 in 2005–2006) carcinomas displayed more modest but statistically significant increases in age-adjusted incidence rates ($P < .0005$). No increase in anaplastic cancer was noted (0.11 per 100,000 in 1973–1974 to 0.08 per 100,000 in 2005–2006) ($P > .05$).

PTC: 1983–2006. As mentioned previously, PTC had the greatest increase in age-adjusted incidence rates with 2.88 per 100,000 in 1973–1974 to 9.25 per 100,000 in 2005–2006 representing a 3.2-fold increase ($P < .0001$). This change in incidence of PTC accounted for 96% of the overall increase in thyroid cancer (net increase in PTC of 6.37 per 100,000 divided by a combined increase in PTC, follicular thyroid carcinoma, and medullary thyroid carcinoma of 6.62 per 100,000). When we analyzed this increase in PTC incidence based on tumor size, we found an increase in age-adjusted incidence rates in each tumor size category of PTC. The largest increase was among the microPTC (≤1 cm) neoplasms (Fig 2). MicroPTC (≤1 cm) increased 441% between 1983 and 2006, or 19.3%/year (0.79 per 100,000 in 1983–1984 to 3.48 per 100,000 in 2005–2006; $P < .0001$). This increase was followed by a 12.3%/year increase in 1.1–2-cm neoplasms (0.91 per 100,000 in 1983–1984 to 2.57 per 100,000 in 2005–2006; $P < .0001$), a 10.3%/year increase in 2.1–5-cm neoplasms (0.92 per 100,000 in 1983–1984 to 2.19 per 100,000 in 2005–2006; $P < .0001$), and lastly a 12.0%/year increase in neoplasms >5-cm (0.12 per 100,000 in 1983–1984 to 0.33 per 100,000 in 2005–2006; $P < 0.0001$).

A correlation was found between PTC tumor size and Stage A classification (Table I) (Spearman correlation coefficient 0.285; $P < .0001$). For microPTC (≤1 cm), 81% of neoplasms were localized and confined to the thyroid. Of the microPTC cases, 17.7% exhibited regional lymph node metastases and 1.3% demonstrated distant metastatic metastases. As we examined the other tumor size categories, a trend emerged showing that as tumor size increased so did the overall stage and the likelihood of distant metastatic disease. Thus, as shown in Table I, patients with neroplasms >5 cm in size had both the greatest rate of regional lymph node metastases (51.6%) and distant metastases (12.1%).

Table I. Correlation of SEER stage A classification to PTC tumor size (1983–2006)

Tumor size	*Localized* n *(%)*	*Regional* n *(%)*	*Distant* n *(%)*	*Total*
≤1 cm	8,607 (81.0%)	1,886 (17.7%)	136 (1.3%)	10,629 (100%)
1.1–2 cm	5,356 (59.0%)	3,493 (38.5%)	223 (2.5%)	9,072 (100%)
2.1–5 cm	4,381 (50.5%)	3,903 (45.0%)	387 (4.5%)	8,671 (100%)
>5 cm	382 (36.3%)	543 (51.6%)	127 (12.1%)	1,053 (100%)

Finally, the type of surgical resection for PTC demonstrated an increase in the percentage of patients who underwent total thyroidectomy performed over time (27% in 1987–1988 to 82.6% in 2005–2006; $P < .0001$) (Fig 3). Thus, a downward trend in the percentage of partial thyroidectomies performed over time was observed (20.5% in 1987–1988 to 13.5% in 2005–2006; $P < .0001$). Prior to 1987, the most common operative designation was surgery NOS that has decreased over time (96% in 1983–1984 to 0.8% in 2005–2006; $P < .0001$), reflecting possibly coding disparities in the SEER database during earlier collection periods.

Finally, the type of operative resection for PTC showed an increase in the rate of total thyroidectomy performed over time (0.95 per 100,000 in 1987–1988 to 1.63 per 100,000 in 2005–2006; $P < .0001$) (Fig 3). The rate of partial thyroidectomies performed over time remained unchanged (0.74 per 100,000 in 1987–1988 to 1.25 per 100,000 in 2005–2006; $P < .97$). Prior to 1987, the most common operative designation was NOS that has decreased over time (3.2 per 100,000 in 1983–1984 to 0.29 per 100,000 in 2005–2006; $P < .0001$), again reflecting possibly coding disparities in the SEER database during earlier collection periods.

Adjuvant therapies for all PTC tumors: (1983–2006). We queried the SEER database looking for the use of adjuvant therapy for thyroid malignancies. One limitation of this query is that the SEER database only captures those patients who received radiation therapy within 4 months of operation. A total of 33,886 cases of PTC were included in the SEER database. Most PTC received no form of adjuvant radiation therapy (53.6%; $n = 18{,}178$). Among the 46.4% of patients who received some form of adjuvant radiation therapy for PTC, the distribution was as follows: radioisotope therapy (I-131) (37.1%; $n = 12{,}580$), radiation therapy designated as "other" with no additional information available (3%; $n = 1{,}023$), external beam radiation therapy (2.3%; $n = 765$), and radioactive implants (1.4%; $n = 471$). Remaining forms of radiation therapy designations (combination of beam, implants and isotopes, and radiation therapy NOS) represented only 1.1% of the postoperative population; $n = 373$). Cases also were present in which therapies were recommended but potentially not given (1.1%; $n = 381$), were refused (0.16%; $n = 54$), or were unknown (0.18%; $n = 61$).

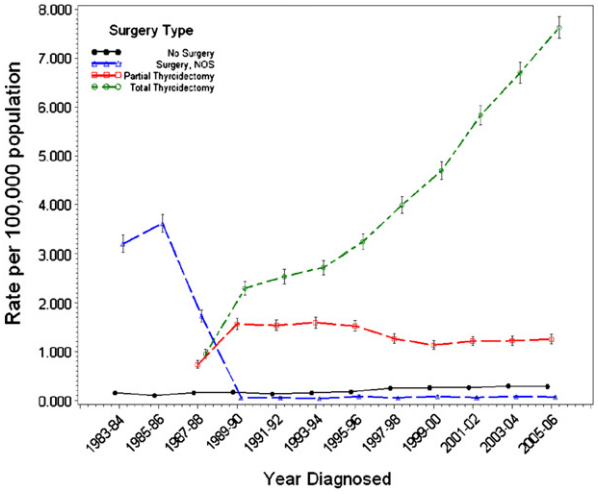

Fig 3. Surgical therapy for papillary thyroid cancers (1983–2006). Data are age-adjusted to 2000 U.S. Census with 95% CI.

DISCUSSION

Our findings demonstrate that thyroid cancer is increasing rapidly and that this increase in age-adjusted incidence can be accounted for primarily by PTC, which accounts for 96% the overall increase in the general incidence of thyroid carcinoma. These findings agree with several previous studies that PTC is responsible for the general increase in the incidence of thyroid cancer.[1,2] Interestingly, in our current review, follicular and medullary types of thyroid cancer also show a small but statistically significant increase, although this increase accounted for only 4% of the overall increase in thyroid cancer. The purpose of our study was to determine whether the increase in thyroid cancer reflected a shift toward cancers at earlier stages or an increase in cancers of all stages. When looking at tumor size, our findings show a significant increase in PTC of all size categories (≤1 cm, 1.1–2 cm, 2.1–5 cm, >5 cm).

We also showed that the size of PTC correlated positively (Spearman correlation coefficient 0.285; $P < .0001$) with the stage of disease as shown in Table I. Our data are consistent with and build on 2 smaller studies that show a direct positive correlation between the tumor size and depth of invasion as well as the presence of lymph node metastasis.[12,13] Both studies showed that, as tumor size increased to greater than 1 cm, an exponential increase was noted in the amount of spread of disease outside the thyroid. These data suggest that increases in medium- and large-size neoplasms reflect an increased burden of regional and distant metastatic disease. Interestingly, our data revealed that, although neoplasms ≤1 cm are unlikely to have distant spread (only 1.3%), they accounted for 15.6% of all distant stage disease. This finding is likely because 36% of all neoplasms in the SEER database were <1 cm in size.

Incidence rates for PTC neoplasms increased across all size groups. We observed that the rate of increase was the greatest for microPTC at 19.3%/year compared with that of larger cancers that varied between 10.3%/year and 12.3%/year. The observed increase in neoplasms larger than 1 cm was remarkably consistent and averaged 11.3%/year. As we stated in our introduction, most surgeons and endocrinologists believe that the general increase in the incidence of thyroid cancer is a result of improved radiographic detection of small microPTC. Although this belief has been accepted widely, little solid data are available to validate it. Based on our current study, improved detection techniques may explain the 8.0%/year difference between the increase in microPTC compared with the average increase in neoplasms larger than 1 cm; however, changes in the methods of detection cannot explain the overall increase in all sizes of PTC.

To elaborate, several reports have proposed that improved detection of small neoplasms accounted for the increase in thyroid cancer. Using the SEER database, Davies and Welch calculated that 87% of the increase in PTC consisted of cancer less than 2 cm in size.[1] Kent et al. using the Ontario Cancer Registry found similarly that cancers less than 2 cm seemed to account for the increase in thyroid cancer.[2] Based on these findings, these authors concluded that the widespread adoption of ultrasonography and fine-needle aspiration on thyroid nodules explained the increase of thyroid cancer. Hall et al. also examined the trend in the usage of neck imaging and found an association between the incidence of thyroid cancer and the use of diagnostic imaging tests.[14] We believe that these reports failed to consider the increase in larger but less common cancers.

Some recent reports suggest that an increase in more advanced stage thyroid cancers also may have occurred in addition to the increase in earlier stage. Enewold et al. performed a detailed demographic analysis showing an increase in PTC of all sizes in Caucasian females, Caucasian males, and African-American females.[8] Chen et al. similarly found an increase in differentiated thyroid cancer of all sizes with the most rapid increase occurring in females.[15] These studies raise the question of whether improved detection techniques really can explain the trend. Our study builds on these publications detailing the overall trends in incidence in thyroid cancer as well as a detailed analysis of PTC. Our analysis includes a greater time period of analysis of data on tumor size (1983–2006) compared with previous studies that focused on (1988–2002 or 1988–2005). Furthermore, we confirmed a positive correlation between cancer size and stage in the SEER database.

Changes in the pathologic criteria for thyroid cancer also have been postulated to contribute to the increase incidence of PTC. The pathologic reclassification of the follicular variant of thyroid cancer in 1988 as part of PTC instead of part of follicular thyroid cancer has been suggested to contribute to the this apparent increase in PTC.[16] In our data, the follicular variant accounted for only 3.8% of all cases of PTC indicating that it could have played only a minor role.

Our data showing an increase in PTC of all sizes and stages suggest that some environmental or other unknown factor may be contributing to the increase in thyroid cancer. Radiation exposure is most highly associated with thyroid cancer, and a well-documented increase is noted in thyroid cancer in areas of radioactive exposure.[10] Some authors have suggested that iatrogenic exposure to radiation during imaging by computed tomography, especially in children when radiation sensitivity of the thyroid gland is greater, could contribute to the increase in thyroid cancer[9]; however, a link between this form of "diagnostic" radiation exposure and the increase in thyroid cancer remains unproven. Additional factors that have been associated with an increased risk of thyroid cancer include changes in body mass index,[17] fertility drugs,[18] and changes in menstrual cycles.[19]

Our data show a shift in the type of surgical procedure used to treat thyroid cancer from 1973 to 2006. Total thyroidectomy has replaced all other forms of partial thyroidectomy (lobectomy ± isthmusectomy, subtotal thyroidectomy, etc) as the

most common operative treatment for thyroid cancer. We believe this reflects a change in the standard of care toward the use of total thyroidectomy for all neoplasms greater than 1 cm in size.[20] In addition, in regard to the surgical management of microPTC (neoplasms <1 cm in size), the current American Thyroid Association guidelines in recommendation point #26 state that "Thyroid lobectomy alone may be sufficient treatment for small (<1 cm) low-risk, unifocal, intrathyroidal papillary thyroid carcinomas in the absence of prior head/neck irradiation or radiologically or clinically involved cervical nodal metastases." Finally, from 1983–1990 the number of operations in which the extent was NOS declined rapidly. We believe that this finding represents a change in the way the type of operative therapy was recorded in the SEER database.

In regard to adjuvant therapy, from 1983 to 2006, 53.6% of patients with PTC did not receive any form of radiation therapy. Of those patients who received adjuvant radiation therapy, radioisotope therapy (37.1%) was the most common form of treatment. The role of adjuvant radiation therapy in the treatment of well-differentiated thyroid carcinoma continues to be an active area of research. Our data collected here in SEER may provide a snapshot of its overall usage in the treatment of PTC from 1983 to 2006 in the United States.

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DISCUSSION

Dr Sareh Parangi (Boston, MA): Thank you for this very nice presentation. I have 2 questions. First, in regard to your 16% rate of distant—was that distant disease in tumors less than 1 cm in size? Has that been reported elsewhere?

Mr. John D. Cramer (Cleveland, OH): That was 16% of all distant stage disease, so out of 100% of distant stage disease, the percentage of the contribution it comes from is small. But it is less than 1% of all cancers that are 1 cm in size.

Dr Sareh Parangi (Boston, MA): Thank you very much for that clarification.

The second question I had was, if you broke up your new cancers by female versus male to see if you could, in fact, tease out some of the issues you brought up, such as fertility drugs or estrogen or things that may, in fact, disproportionately affect the female population?

Mr. John D. Cramer (Cleveland, OH): Yes, we did use some of the demographic analysis. Some of that, we are saving for further studies. But I think I can briefly comment on some of the trends that we were seeing.

So we did see that thyroid cancer in females was increasing a little bit more rapidly than in males. And I think we are still really working on that data.

Dr Richard A. Prinz (Chicago, IL): You have done a lot of work on this, and I always like it when it seems to mirror my own thoughts and experiences on a topic. I do have some questions that may be a little bit off the mark.

First of all, you showed us a slide that, in the early 1980s, no treatment was more common than any of the surgical treatments you showed. And, being old enough to be there operating in the 1980s, I did not appreciate that going on whatsoever. So maybe you can comment on that.

Then, you are mentioning the adjuvant therapy that occurs. And, in many situations, patients will have their operation at one center and then get their radioiodine or other treatments elsewhere. So that is very difficult to track in your database. So maybe your conclusions on that should be tempered a little bit.

Mr. John D. Cramer (Cleveland, OH): So, on your first point, the operative treatment that was not otherwise specified was surgery in the early 1980s, so there was an operation there. And that really declined, I think, reflecting changes in how SEER is recording those factors. It was not operative resection that was not done. The rate of patients receiving no operative treatment was a low percentage of the overall trend.

And the second point on radiation within the SEER database, we really do not know how SEER is detecting all different locations that radiation could have been given at community centers or different centers. I am really not sure on that point.

Dr Martha A. Zeiger (Baltimore, MD): Thank you very much for the clarification. I think a lot of us have wondered whether or not it is due to increased ultrasound use.

I have a comment and a question. My comment is that, if you look historically at pathology of thyroid tumors, years ago, the most common was papillary thyroid cancer, followed by follicular cancer. And then we had this mixed follicular-papillary thyroid cancer.

Nowadays, the most common is papillary thyroid cancer, followed by a follicular variant of papillary thyroid cancer. You hardly ever see follicular cancer. We will know that there is tremendous inter- and intraobserver variability that has been proven. A lot of pathologists will call one tumor a cancer and another pathologist will call it benign, and the same pathologists will even disagree with themselves if they are blinded.

The question to you is, were these all classical papillary thyroid cancer, or was there follicular variant of papillary thyroid cancer? In which case, I would question whether or not, if you took all these tumors and had pathologists review them, all pathologists would agree upon the diagnosis.

Mr. John D. Cramer (Cleveland, OH): So we did look a little bit at the classification of the follicular variant of papillary thyroid cancer in this period. We concluded that it accounted for about 4% of all the papillary thyroid cancer that was reported in the database. So based on that, we thought that it was, if anything, playing a small contribution to the overall changes that we are seeing.

We did not really do much further analysis of that other than just trying to capture what percentage of all cancers did correspond to that follicular variant in the database.

Dr Electron Kebebew (Bethesda, MD): One comment and a question to follow. A study done by Chen and colleagues that was published in Cancer is very much a similar analysis as yours. And they found that age greater than 45 that the increase was actually much higher, which would suggest a latency period, perhaps environmental radiation exposure. Have you done a similar analysis?

Mr. John D. Cramer (Cleveland, OH): Yes. We have looked at some of the age data on this. And we found that patients less than 30 actually had relatively little change in the overall incidence of thyroid cancer, whereas patients that were greater than 30 did have a much greater increase in the incidence of thyroid cancers. Specifically, I think, the age group 45–60 really had the most rapid rate of increase.