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Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013

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IMPORTANCE Thyroid cancer incidence has increased substantially in the United States over the last 4 decades, driven largely by increases in papillary thyroid cancer. It is unclear whether the increasing incidence of papillary thyroid cancer has been related to thyroid cancer mortality trends.

OBJECTIVE To compare trends in thyroid cancer incidence and mortality by tumor characteristics at diagnosis.

DESIGN, SETTING, AND PARTICIPANTS Trends in thyroid cancer incidence and incidence-based mortality rates were evaluated using data from the Surveillance, Epidemiology, and End Results-9 (SEER-9) cancer registry program, and annual percent change in rates was calculated using log-linear regression.

EXPOSURE Tumor characteristics.

MAIN OUTCOMES AND MEASURES Annual percent changes in age-adjusted thyroid cancer incidence and incidence-based mortality rates by histologic type and SEER stage for cases diagnosed during 1974-2013.

RESULTS Among 77 276 patients (mean [SD] age at diagnosis, 48 [16] years; 58 213 [75%] women) diagnosed with thyroid cancer from 1974-2013, papillary thyroid cancer was the most common histologic type (64 625 cases), and 2371 deaths from thyroid cancer occurred during 1994-2013. Thyroid cancer incidence increased, on average, 3.6% per year (95% CI, 3.2%-3.9%) during 1974-2013 (from 4.56 per 100 000 person-years in 1974-1977 to 14.42 per 100 000 person-years in 2010-2013), primarily related to increases in papillary thyroid cancer (annual percent change, 4.4% [95% CI, 4.0%-4.7%]). Papillary thyroid cancer incidence increased for all SEER stages at diagnosis (4.6% per year for localized, 4.3% per year for regional, 2.4% per year for distant, 1.8% per year for unknown). During 1994-2013, incidence-based mortality increased 1.1% per year (95% CI, 0.6%-1.6%) (from 0.40 per 100 000 person-years in 1994-1997 to 0.46 per 100 000 person-years in 2010-2013) overall and 2.9% per year (95% CI, 1.1%-4.7%) for SEER distant stage papillary thyroid cancer.

CONCLUSIONS AND RELEVANCE Among patients in the United States diagnosed with thyroid cancer from 1974-2013, the overall incidence of thyroid cancer increased 3% annually, with increases in the incidence rate and thyroid cancer mortality rate for advanced-stage papillary thyroid cancer. These findings are consistent with a true increase in the occurrence of thyroid cancer in the United States.

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Supplemental content

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In the United States, thyroid cancer incidence rates have increased by 211% between 1975 and 2013, with papillary thyroid cancer (PTC), the most common and least-aggressive histologic type, accounting for most of the new cases.[1] Some investigators have suggested that overdiagnosis, or the increased ability to detect and diagnose small indolent tumors that would never otherwise cause symptoms or require treatment, explains a substantial proportion of the increase.[2-5]

However, growing evidence supports a true increase in the occurrence of thyroid cancer. An analysis of Surveillance, Epidemiology, and End Results (SEER) cancer registry data from 1980-2005 revealed substantial increases in the incidence of advanced-stage PTCs and PTCs greater than 5 cm in diameter; these tumors are generally large enough to be detected via palpation, to cause symptoms, or both.[6] The rates of increase for the largest (>5 cm) and the smallest PTCs (≤1 cm) were nearly equal among white women, a group considered to be particularly susceptible to overdiagnosis.[6] Although thyroid cancer mortality rates are much lower relative to incidence, providing the impression of stability over time,[2-5] thyroid cancer mortality rates have increased significantly since the late 1980s (0.7% per year; $P < .001$).[1] These trends are consistent with temporal changes in the prevalence of some risk factors, including obesity and noncurrent smoking.[7]

Because advanced-stage PTC is less amenable to treatment than localized PTC, the increasing mortality rates may be a direct consequence of the trends in advanced-stage PTC. To address this question, the current analysis used SEER data during 1974-2013 to compare thyroid cancer incidence and mortality trends by demographic and tumor characteristics at the time of diagnosis.

Key Points

Question What have been the trends in US thyroid cancer incidence and mortality, and have they differed by tumor characteristics at diagnosis?

Findings In this analysis of 77 276 thyroid cancer patients diagnosed during 1974-2013 and of 2371 thyroid cancer deaths during 1994-2013, average annual increases in incidence and mortality rates, respectively, were 3.6% and 1.1% overall and 2.4% and 2.9% for patients diagnosed with advanced-stage papillary thyroid cancer.

Meaning Thyroid cancer incidence and mortality rates have increased for patients diagnosed with advanced-stage papillary thyroid cancer in the United States since 1974, suggesting a true increase in the occurrence of thyroid cancer.

Methods

Data Sources

Thyroid cancer cases diagnosed during 1974-2013 were ascertained from the SEER cancer incidence file maintained by the National Cancer Institute.[8] The file includes information from 9 high-quality, population-based registries (SEER-9; California [San Francisco and Oakland], Connecticut, Georgia [Atlanta only], Hawaii, Iowa, Michigan [Detroit only], New Mexico, Utah, and Washington [Seattle and Puget Sound region]) that include approximately 10% of the US population. Demographic and cancer diagnosis information was available for each case. Data regarding nationwide and SEER-9 thyroid cancer deaths were derived from information recorded in death certificates and ascertained from the National Center for Health Statistics.[9]

The incidence-based mortality file uses cancer registry information from the SEER-9 cancer incidence file to link characteristics of the cancer at diagnosis with death certificate information.[10,11] Thus, unlike traditional mortality rates, incidence-based mortality rates can be examined according to variables recorded at diagnosis (eg, histology, stage, tumor size). The incidence-based mortality analysis was restricted to deaths during 1994-2013 and diagnoses during 1974-2013 to ensure maximum data for those deaths and to prevent underestimation of the incidence-based mortality rates in the earliest years.

Demographic Characteristics

Demographic characteristics of interest for this analysis included sex, race, and age at diagnosis. This information was originally abstracted from medical records and submitted to regional or state cancer registries. Information on age at thyroid cancer death was abstracted from death certificates.

Tumor Characteristics

Thyroid cancer cases (*International Classification of Diseases for Oncology, Third Edition*; topography code C73) were classified according to histologic type[12]: PTC (histologic codes 8050, 8260, 8340-8344, 8350, 8450-8460), follicular thyroid cancer (8290, 8330-8335), medullary thyroid cancer (8345, 8510-8513), anaplastic thyroid cancer (8020-8035), and others (including unspecified, poorly specified [eg, insular {8337}], and others).

SEER Historic Stage A was used to classify cases according to stage at diagnosis: localized (limited to the thyroid gland), regional (tumor extension beyond the limits of the thyroid gland or spread by more than 1 lymphatic or vascular supply route), distant (extracervical metastasis), and unknown stage.[13] Beginning in 2004, diagnosed cases additionally were classified as stage I-IV (or unknown) according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) tumor-node-metastasis (TNM) staging system (*AJCC Cancer Staging Manual, 6th Edition*), which accounts for age at diagnosis (<45 and ≥45 years for PTC and follicular thyroid cancer), tumor size (T stage), extent of spread to the regional lymph nodes (N stage), and presence or absence of distant metastases (M stage).[14] Although AJCC/TNM stage information was not available for the entire study period, it is the staging system most used for thyroid cancer in clinical practice and is more readily interpretable than SEER stage.

Tumor size has been recorded in SEER since 1983 using 3 different schemes: Extent of Disease-4 codes for 1983-1987, Extent of Disease-10 codes for 1988-2003, and Collaborative Staging codes for 2004-2013. These codes were combined to categorize cases diagnosed during 1983-2013 by tumor size.[15]

Data Analysis

Only microscopically confirmed cases and the first matching record were selected, and cases identified only from autopsy records or death certificates were excluded. Incidence and mortality rates were calculated using SEER*Stat version 8.3.2.[16] All rates were age adjusted to the 2000 US standard population and expressed per 100 000 person-years. Incidence-based mortality rates were calculated as number of thyroid cancer deaths among cases diagnosed in the SEER-9 registries over person-time at risk among individuals in the SEER areas. Standardized dimensions were used for the y-axes and x-axes, in which a slope of 10 degrees represented a change of 1% per year.[17] Rates for thyroid cancers with missing or unknown histology, stage, or size were calculated and plotted separately from the known values. Rate differences were calculated to evaluate the degree to which reductions or increases in rates for thyroid cancers with unknown stage or size may have affected trends for thyroid cancers with known values.

The National Cancer Institute's Joinpoint Regression Analysis program, version 4.2.0, was used to calculate annual percentage changes (APCs) and 95% CIs to quantify trends in incidence and mortality overall and by demographic and tumor characteristics using *t* tests to determine whether APCs were statistically significantly different from zero.[18] The program also selected the best-fitting log-linear regression model to identify calendar years (ie, the joinpoints) when APCs changed significantly, allowing for the minimum number of joinpoints necessary to fit the data.[18] Statistical significance was assessed at an α level of $P < .05$, and all hypotheses were 2-sided.

Results

Of the 79 409 thyroid cancer cases diagnosed among residents of the SEER-9 areas during 1974-2013, 77 276 (97%) met the case definition and were included in the incidence analysis (**Table 1**). Women (58 213 [75%]) and white patients (63 479] 82%) comprised the majority of the cases. Mean (SD) age at diagnosis was 48 (16) years. The most common histologic types were PTC (84%) and follicular thyroid cancer (11%). Of the eligible cases, 2371 died of thyroid cancer during 1994-2013 and were included in the incidence-based mortality analysis. Of the deaths, 57% occurred among women and 81% among white patients. Compared with all cases, patients who died of thyroid cancer were more likely to have been diagnosed at older ages; with non-PTC histologies; and with advanced-stage tumors, larger tumors, or both. Among those who died of thyroid cancer, the median time between thyroid cancer diagnosis and death was 25 months; 19% survived more than 10 years after diagnosis. Among PTC patients who died of thyroid cancer, 27% survived more than 10 years after diagnosis.

Of the 77 276 cases occurring during 1974-2013, 10% were diagnosed in years prior to the availability of tumor size data starting in 1983, and 51% were diagnosed prior to the availability of AJCC/TNM stage information starting in 2004 (Table 1). Of the 2371 incidence-based mortality deaths occurring during 1994-2013, 3% were diagnosed in years prior to the availability of tumor size data and 66% were diagnosed prior to the availability of AJCC/TNM stage information. During the years in which specific tumor characteristics were reported to the registries, SEER stage (1974-2013) was unknown for 2% of cases and 5% of deaths, tumor size (1983-2013) was unknown for 13% of cases and 31% of deaths, and AJCNN/TNM stage (2004-2013) was unknown for 5% of cases and 6% of deaths.

A comparison of the agreement between SEER Historic Stage A, tumor size, and AJCC/TNM stage among PTC cases diagnosed between 2004 and 2013 by age (<45 and ≥45 years) is shown in eTable 1 in the Supplement. In general, more advanced stage was associated with larger tumor size. There was greater agreement of SEER stage with size and AJCC/TNM stage for patients aged 45 years and older compared with younger patients, which reflects the differences in AJCC/TNM staging guidelines for PTC patients diagnosed before and after age 45 years.[14]

Trends in thyroid cancer incidence by demographic and tumor characteristics are described in **Table 2**, with joinpoints denoted as trends 1 to 5. Trends by selected tumor characteristics are shown graphically in **Figure 1**. Thyroid cancer incidence rates increased over the study period (from 4.56 [95% CI, 4.40 to 4.73] per 100 000 person-years in 1974-1977 to 14.42 [95% CI, 14.20 to 14.64] per 100 000 person-years in 2010-2013), increasing 3.6% (95% CI, 3.2% to 3.9%) per year, on average. Rates increased 6.7% (95% CI, 6.1% to 7.2%) per year during 1997-2009, but did not increase during 2009-2013 (APC, 1.8% [95% CI, −0.7% to −4.4%]). Thyroid cancer incidence rates increased for all sex, race, and age groups. Significant increases were observed for PTC (APC, 4.4% [95% CI, 4.0% to 4.7%]), follicular thyroid cancer (APC, 0.6% [95% CI, 0.2% to 0.8%]), and medullary thyroid cancer (APC, 0.7% [95% CI, 0.2% to 1.1%]). PTC incidence increased significantly for every stage and tumor size category. During 2009-2013, incidence rates did not increase significantly for overall, localized, stage I, or small (≤2 cm) PTCs, while there was no evidence of a reduction in the increase for regional, distant, or large PTCs.

Thyroid cancer incidence-based mortality rates were underestimated in the earliest calendar years, but consistent with observed nationwide and SEER-9 thyroid cancer mortality rates during 1994-2013 (**Figure 2**; eTable 2 in the Supplement). Thyroid cancer incidence-based mortality increased, on average, 1.1% (95% CI, 0.6% to 1.6%) annually during 1994-2013 (**Table 3**; Figure 2), from 0.40 (95% CI, 0.36 to 0.44) per 100 000 person-years in 1994-1997 to 0.46 (95% CI, 0.43 to 0.50) per 100 000 person-years in 2010-2013. Positive APCs were observed for most demographic subgroups and statistically significant for patients who were female, white, black, and diagnosed after age 79 years. By histologic type, the annual increase in incidence-based mortality rates was restricted to patients diagnosed with PTC (1.7% [95% CI, 0.6% to 2.9%). Positive APCs were observed for PTCs of all known stages at diagnosis, but were statistically significant only for patients with distant disease (APC, 2.9% [95% CI, 1.1% to 4.7%]), stage IV disease (APC, 12.9% [95% CI, 7.2% to 19.0%]), or both (Table 3;

Table 1. Thyroid Cancer Incidence (1974-2013) and Incidence-Based Mortality (1994-2013): The SEER-9 Registry Database

Characteristic	Incidence				Incidence-Based Mortality			
	Thyroid Cancer		Papillary Thyroid Cancer		Thyroid Cancer		Papillary Thyroid Cancer	
	Cases, No. (%)[a]	Rate (95% CI)[b]	Cases, No. (%)[a]	Rate (95% CI)[b]	Deaths, No. (%)[c]	Rate (95% CI)[b]	Deaths, No. (%)[c]	Rate (95% CI)[b]
Overall	77 276 (100)	7.98 (7.93-8.04)	64 625 (100)	6.66 (6.61-6.71)	2371 (100)	0.44 (0.42-0.46)	1063 (100)	0.20 (0.19-0.21)
Sex								
Male	19 063 (24.7)	4.20 (4.14-4.26)	15 074 (23.3)	3.28 (3.23-3.33)	1017 (42.9)	0.44 (0.41-0.47)	464 (43.7)	0.20 (0.18-0.22)
Female	58 213 (75.3)	11.63 (11.53-11.72)	49 551 (76.7)	9.92 (9.83-10.01)	1354 (57.1)	0.44 (0.41-0.46)	599 (56.3)	0.19 (0.18-0.21)
Race								
White	63 479 (82.1)	8.18 (8.12-8.24)	53 219 (82.4)	6.85 (6.80-6.91)	1914 (80.7)	0.43 (0.41-0.45)	841 (79.1)	0.19 (0.18-0.20)
Black	4582 (5.9)	4.88 (4.73-5.03)	3473 (5.4)	3.64 (3.52-3.77)	143 (6)	0.32 (0.27-0.38)	48 (4.5)	0.11 (0.08-0.15)
Other[d]	8442 (10.9)	9.14 (8.95-9.34)	7305 (11.3)	7.85 (7.66-8.03)	312 (13.2)	0.59 (0.52-0.66)	173 (16.3)	0.33 (0.28-0.38)
Age at diagnosis, y								
<20	1794 (2.3)	0.62 (0.59-0.65)	1512 (2.30)	0.52 (0.49-0.55)	NR[e]	NR[e]	NR[e]	NR[e]
20-39	23 877 (30.9)	8.00 (7.89-8.09)	21 106 (32.7)	7.06 (6.97-7.16)	102 (4.3)	0.02 (0.02-0.02)	47 (4.4)	0.01 (0.01-0.01)
40-59	32 188 (41.7)	13.28 (13.14-13.43)	27 727 (42.9)	11.45 (11.32-11.59)	631 (26.6)	0.11 (0.10-0.12)	314 (29.5)	0.06 (0.05-0.06)
60-79	16 877 (21.8)	13.15 (12.95-13.35)	12 825 (19.8)	9.92 (9.75-10.10)	1148 (48.4)	0.22 (0.21-0.24)	515 (48.4)	0.10 (0.09-0.11)
≥80	2540 (3.3)	8.81 (8.47-9.16)	1455 (2.3)	5.05 (4.79-5.31)	479 (20.2)	0.09 (0.08-0.10)	184 (17.3)	0.03 (0.03-0.04)
Thyroid Cancer Characteristics at Diagnosis								
Histologic type								
Papillary	64 625 (83.6)	6.66 (6.61-6.71)			1063 (44.8)	0.20 (0.19-0.21)		
Follicular	8359 (10.8)	0.87 (0.85-0.89)			404 (17)	0.08 (0.07-0.08)		
Medullary	1685 (2.2)	0.18 (0.17-0.18)			189 (8)	0.04 (0.03-0.04)		
Anaplastic	975 (1.3)	0.11 (0.10-0.11)			471 (19.9)	0.09 (0.08-0.10)		
Other[f]	1632 (2.1)	0.17 (0.17-0.18)			244 (10.3)	0.05 (0.04-0.05)		
SEER Historic Stage A								
Localized	45 919 (59.4)	4.75 (4.71-4.79)	39 971 (61.9)	4.13 (4.09-4.17)	280 (11.8)	0.05 (0.05-0.06)	143 (13.5)	0.03 (0.02-0.03)
Regional	25 835 (33.4)	2.66 (2.62-2.69)	21 435 (33.2)	2.20 (2.17-2.23)	1045 (44.1)	0.19 (0.18-0.21)	566 (53.2)	0.11 (0.10-0.11)
Distant	3658 (4.7)	0.39 (0.37-0.40)	2045 (3.2)	0.21 (0.20-0.22)	922 (38.9)	0.17 (0.16-0.18)	308 (29.0)	0.06 (0.05-0.06)
Unknown	1864 (2.4)	0.19 (0.18-0.20)	1174 (1.8)	0.12 (0.11-0.13)	124 (5.2)	0.02 (0.02-0.03)	46 (4.3)	0.01 (0.01-0.01)
AJCC/TNM stage[g]								
I	25 580 (67.4)	8.91 (8.80-9.02)	23 974 (71.5)	8.34 (8.24-8.45)	17 (2.1)	0.01 (0.003-0.01)	NR[e]	NR[e]
II	2870 (7.6)	0.92 (0.89-0.96)	2091 (6.20)	0.67 (0.64-0.70)	NR[e]	NR[e]	NR[e]	NR[e]
III	4562 (12.0)	1.46 (1.42-1.50)	3821 (11.4)	1.22 (1.18-1.25)	45 (5.6)	0.02 (0.01-0.02)	24 (8.7)	0.01 (0.01-0.01)
IV	3045 (8.0)	1.01 (0.97-1.04)	2111 (6.3)	0.69 (0.66-0.72)	680 (84.4)	0.23 (0.21-0.25)	215 (77.6)	0.07 (0.06-0.08)
Unknown	1881 (5.0)	0.62 (0.59-0.65)	1541 (4.6)	0.51 (0.48-0.53)	49 (6.1)	0.02 (0.01-0.02)	19 (6.9)	0.01 (0.00-0.01)
Tumor size, cm[h]								
≤1	19 943 (28.6)	2.50 (2.47-2.54)	19 257 (32.5)	2.42 (2.38-2.45)	71 (3.1)	0.01 (0.01-0.02)	52 (5.2)	0.01 (0.01-0.01)
>1 to ≤2	18 113 (26.0)	2.26 (2.23-2.29)	16 477 (27.8)	2.05 (2.02-2.09)	188 (8.2)	0.04 (0.03-0.04)	130 (12.9)	0.02 (0.02-0.03)
>2 to ≤4	16 031 (23.0)	2.00 (1.97-2.03)	12 772 (21.6)	1.59 (1.56-1.61)	483 (21.1)	0.09 (0.08-0.10)	274 (27.2)	0.05 (0.05-0.06)
>4	6713 (9.6)	0.85 (0.83-0.87)	3973 (6.7)	0.50 (0.48-0.51)	852 (37.1)	0.16 (0.15-0.17)	277 (27.5)	0.05 (0.05-0.06)
Unknown	8879 (13.0)	1.12 (1.10-1.14)	6721 (11.4)	0.84 (0.82-0.86)	700 (30.5)	0.13 (0.12-0.14)	275 (27.3)	0.05 (0.05-0.06)

Abbreviations: AJCC/TNM, American Joint Committee on Cancer/Tumor-Node-Metastasis; NR, not reported; SEER, Surveillance, Epidemiology, and End Results.

[a] Cases included first primary tumors that matched the selection criteria, were microscopically confirmed, and were not identified only from autopsy records or death certificates.

[b] Rates were calculated as number of cases or deaths per 100 000 person-years and age adjusted to the 2000 US standard population.

[c] No. (%) of deaths were based on cases diagnosed during 1974-2013.

[d] Includes American Indian/Alaskan Native and Asian/Pacific Islander.

[e] Statistic suppressed because of fewer than 16 cases or deaths in the time interval.

[f] Includes other specified, poorly differentiated, and other types of thyroid cancers.

[g] AJCC/TNM stage is based on cases diagnosed during 2004-2013 and deaths during 2004-2013.

[h] Tumor size is based on cases diagnosed during 1983-2013 and deaths during 1994-2013.

Table 2. Trends in Thyroid Cancer Incidence Rates (1974-2013): The SEER-9 Registry Database[a]

	Overall (1974-2013)		Trend[b]														
			1			2			3			4			5		
	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value
Overall	3.6 (3.2 to 3.9)	<.001	1974-1977	5.5 (1.4 to 9.8)	.01	1977-1980	−5.9 (−13.1 to 1.9)	.10	1980-1997	2.6 (2.3 to 2.9)	<.001	1997-2009	6.7 (6.1 to 7.2)	<.001	2009-2013	1.8 (−0.7 to 4.4)	.20
Sex																	
Male	3.1 (2.7 to 3.5)	<.001	1974-1980	−2.9 (−5.9 to 0.2)	.07	1980-1998	2.5 (1.8 to 3.2)	<.001	1998-2013	5.6 (4.7 to 6.4)	<.001						
Female	3.7 (3.3 to 4.1)	<.001	1974-1977	5.8 (0.7 to 11.2)	.03	1977-1980	−5.3 (−14.2 to 4.6)	.30	1980-1996	2.6 (2.2 to 3.0)	<.001	1996-2009	6.7 (6.1 to 7.4)	<.001	2009-2013	1.6 (−1.5 to 4.8)	.30
Race																	
White	3.8 (3.4 to 4.2)	<.001	1974-1977	6.2 (2.2 to 10.4)	<.001	1977-1980	−5.9 (−12.9 to 1.6)	.10	1980-1997	2.9 (2.6 to 3.2)	<.001	1997-2009	7.0 (6.5 to 7.6)	<.001	2009-2013	1.4 (−1.1 to 3.9)	.30
Black	3.4 (2.8 to 4.0)	<.001	1974-1988	−1.3 (−2.8 to 0.3)	.10	1988-2013	5.4 (4.7 to 6.1)	<.001									
Other[c]	1.5 (1.1 to 1.9)	<.001	1974-1996	−0.2 (−0.9 to 0.4)	.50	1996-2013	3.9 (2.9 to 5.0)	<.001									
Age at diagnosis, y																	
<20	1.9 (1.3 to 2.4)	<.001	1974-2006	1.1 (0.5 to 1.7)	<.001	2006-2013	9.8 (3.4 to 16.7)	.003									
20-39	3.0 (2.6 to 3.3)	<.001	1974-1982	−1.4 (−3.1 to 0.3)	.10	1982-1993	1.8 (0.6 to 3.1)	.005	1993-2013	4.7 (4.3 to 5.2)	<.001						
40-59	3.9 (3.5 to 4.3)	<.001	1974-1981	−1.2 (−3.9 to 1.5)	.40	1981-1995	2.8 (1.7 to 3.9)	<.001	1995-2013	6.2 (5.5 to 6.9)	<.001						
60-79	4.2 (3.8 to 4.6)	<.001	1974-1996	2.2 (1.8 to 2.7)	<.001	1996-2009	7.7 (6.5 to 8.9)	<.001	2009-2013	0.8 (−5.2 to 7.2)	.80						
≥80	2.3 (1.8 to 2.7)	.002	1974-1996	1.0 (0.1 to 2.0)	.03	1996-2013	4.1 (2.7 to 5.5)	<.001									
Thyroid cancer histologic type																	
Papillary	4.4 (4.0 to 4.7)	<.001	1974-1977	6.9 (1.5 to 12.6)	.01	1977-1980	−5.9 (−15.2 to 4.4)	.20	1980-1997	3.6 (3.2 to 4.0)	<.001	1997-2009	7.3 (6.6 to 8.1)	<.001	2009-2013	2.6 (−0.7 to 6.1)	.10
Follicular	0.6 (0.2 to 0.8)	<.001	1974-2000	−0.2 (−0.7 to 0.2)	.30	2000-2006	6.0 (0.8 to 11.4)	.03	2006-2013	−3.0 (−5.9 to −0.1)	.05						
Medullary	0.7 (0.2 to 1.1)	.005															
Anaplastic	−0.1 (−0.7 to 0.6)	.80															
Other[d]	−0.6 (−1.3 to 0)	.06	1974-1994	−3.0 (−4.6 to −1.7)	<.001	1994-2013	1.9 (0.2 to 3.7)	.03									

(continued)

Table 2. Trends in Thyroid Cancer Incidence Rates (1974-2013): The SEER-9 Registry Database[a] (continued)

	Overall (1974-2013)		Trend[b]														
			1			2			3			4			5		
	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value	Year	APC (95% CI)	*P* Value
Papillary Thyroid Cancer																	
SEER Historic Stage A at diagnosis																	
Localized	4.6 (4.1 to 5.1)	<.001	1974-1977	8.2 (0 to 17.2)	.05	1977-1980	−7.3 (−20.9 to 8.7)	.30	1980-1993	2.6 (1.6 to 3.5)	<.001	1993-2009	7.8 (7.1 to 8.5)	<.001	2009-2013	1.1 (−3.8 to 6.3)	.70
Regional	4.3 (4.0 to 4.6)	<.001	1974-1977	8.4 (1.4 to 15.9)	.02	1977-1981	−3.3 (−9.5 to 3.4)	.30	1981-1984	11.7 (−2.2 to 27.5)	.10	1984-1999	2.8 (2.1 to 3.4)	<.001	1999-2013	6.7 (6.0 to 7.4)	<.001
Distant	2.4 (1.7 to 3.2)	<.001	1974-1981	−7.7 (−15.0 to 0.3)	.06	1981-2013	3.5 (2.6 to 4.4)	<.001									
Unknown	1.8 (0.9 to 2.7)	<.001	1974-1978	−18.2 (−33.2 to 0.1)	.05	1978-1995	7.7 (5.1 to 10.4)	<.001	1995-2001	−11.8 (−23.6 to 1.7)	.08	2001-2013	5.6 (1.7 to 9.6)	<.001			
AJCC/TNM stage at diagnosis[e]																	
I	5.8 (4.5 to 7.1)	<.001	2004-2009	8.2 (5.7 to 10.7)	<.001	2009-2013	2.6 (−0.7 to 6.1)	.10									
II	3.9 (0.6 to 7.3)	.03															
III	9.2 (6.6 to 11.9)	<.001	2004-2006	26.0 (7.8 to 47.3)	.01	2006-2013	6.5 (4.3 to 8.7)	<.001									
IV	5.2 (3.3 to 7.2)	<.001															
Unknown	−3.9 (−6.4 to −1.3)	.009															
Tumor size at diagnosis, cm[f]																	
≤1	9.3 (8.8 to 9.8)	<.001	1983-1988	2.6 (−1.0 to 6.3)	.15	1988-1998	9.0 (7.4 to 10.6)	<.001	1998-2008	12.2 (10.6 to 13.8)	<.001	2008-2013	3.1 (−0.5 to 6.9)	.09			
>1 to ≤2	5.4 4.9 to 5.9)	<.001	1983-1999	3.1 (2.6 to 3.7)	<.001	1999-2009	9.1 (7.6 to 10.6)	<.001	2009-2013	2.2 (−2.5 to 7.2)	.40						
>2 to ≤4	4.5 (4.2 to 4.9)	<.001	1983-1995	2.5 (1.4 to 3.6)	<.001	1995-2013	5.7 (5.1 to 6.3)	<.001									
>4	6.1 (5.4 to 6.7)	<.001	1983-1988	−2.8 (−9.7 to 4.6)	.40	1988-2013	6.9 (6.2 to 7.6)	<.001									
Unknown	−1.8 (−2.6 to −1.0)	<.001	1983-2000	1.4 (0.4 to 2.4)	.005	2000-2013	−6.4 (−7.7 to −5.1)	<.001									

Abbreviations: AJCC/TNM, American Joint Committee on Cancer/Tumor-Node-Metastasis; APC, annual percent change; SEER, Surveillance, Epidemiology, and End Results.

[a] Rates were calculated as number of cases per 100 000 person-years and age adjusted to the 2000 US standard population.

[b] The calendar period of each segment was defined based on the identification of calendar years when a statistically significant change in the APC occurred (ie, the joinpoint).

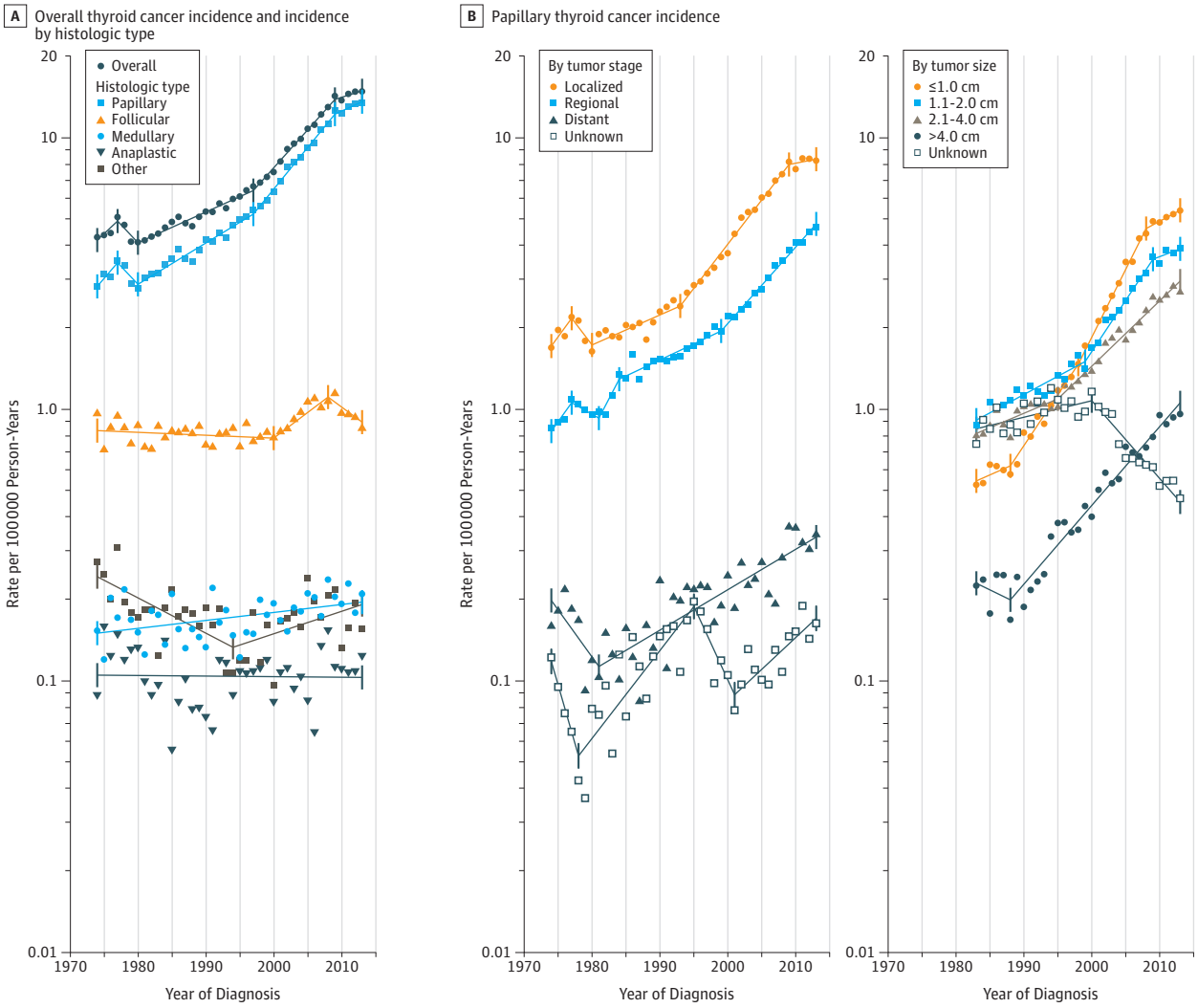
[c] American Indian/Alaskan Native and Asian/Pacific Islander.

[d] Includes other specified, poorly differentiated, and other types of thyroid cancers.

[e] AJCC/TNM stage is based on cases diagnosed during 2004-2013.

[f] Tumor size is based on cases diagnosed during 1983-2013.

Figure 1. Trends in Annual Thyroid Cancer Incidence Rates



Data markers represent the observed incidence rates (cases per 100 000 person-years). The slope of the lines represents the annual percent change (APC); vertical tics on these lines denote the joinpoints. Rates are age-adjusted to the 2000 US standard population. A, Shows thyroid cancer incidence, overall and by histologic type (1974-2013). B, Shows papillary thyroid cancer incidence by SEER Historic Stage A at diagnosis (1974-2013) and by tumor size at diagnosis (1983-2013). Tumor size was not recorded for cases diagnosed during 1974-1982.

Figure 2). Positive APCs occurred for PTCs of all known sizes, with significant increases for tumors smaller than or equal to 2 cm and tumors that were greater than 2 cm to less than or equal to 4 cm (Table 3; Figure 2).

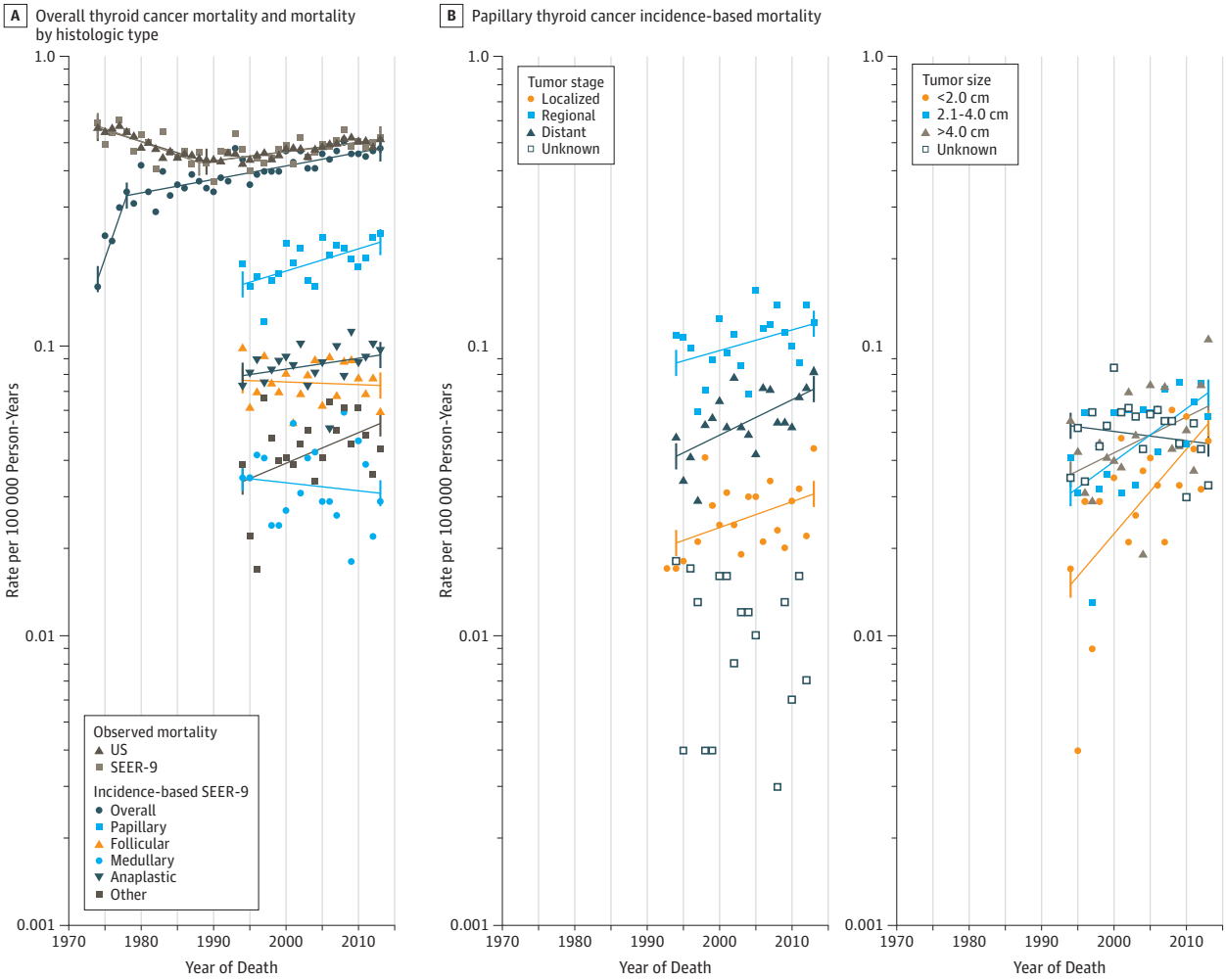
Rate differences were calculated for PTCs by known and unknown values of SEER stage and tumor size (eTables 3 and 4 in the Supplement). The incidence rate for unstaged PTC increased by 0.07 (95% CI, 0.04 to 0.10) from 1974-1977 to 2010-2013, indicating that the observed increase in PTC with known SEER stage was underestimated by this amount. PTC with unknown tumor size declined by 0.57 (95% CI, 0.49 to 0.65) from 1994-1997 to 2010-2013, which may have overestimated the observed increase in PTC with known tumor size by this amount; however, apart from PTCs greater than 4 cm, the observed increases for PTCs with known tumor sizes were much larger. The unstaged PTC mortality rate declined by −0.01 (95% CI, −0.01 to 0.01) from 1994-1997 to 2010-2013, indicating that the increase in mortality for PTCs with known SEER stage was overestimated by this amount. The mortality rate for PTCs with unknown tumor size decreased by 0.02 (95% CI, 0.00 to 0.04) since 1998-2001, which may have overestimated mortality rates for PTC with known tumor size by this amount.

The annual numbers of cases or deaths and incidence and incidence-based mortality rates used in this analysis are provided in eTables 5-16 in the Supplement.

Discussion

To our knowledge, the current study is the first to describe US trends in thyroid cancer mortality by demographic and tumor

Figure 2. Trends in Annual Thyroid Cancer Mortality Rates



Data markers represent the observed mortality rates (deaths per 100 000 person-years). Rates are age-adjusted to the 2000 US standard population. The slope of the lines represents the annual percent change (APC); vertical tics on these lines denote the joinpoints. APCs were not calculated if 0 deaths occurred in 1 or more years. A, Shows observed total US thyroid cancer mortality (1974-2013), observed SEER-9 thyroid cancer mortality (1974-2013), and thyroid cancer incidence-based mortality overall (1974-2013) and by histologic type (1994-2013) based on cases diagnosed during 1974-2013. B, Shows thyroid cancer incidence-based mortality by SEER Historic Stage A at diagnosis (1994-2013), based on papillary thyroid cancer cases diagnosed during 1974-2013 and by tumor size at diagnosis (1994-2013) based on papillary thyroid cancer cases diagnosed during 1983-2013. Tumor size was not recorded for cases diagnosed 1974-1982.

characteristics at diagnosis and to systematically compare trends in thyroid cancer incidence and mortality rates by these characteristics. The main finding from this study was the significant increase in thyroid cancer incidence-based mortality from 1994 to 2013 (approximately 1.1% per year) for thyroid cancer patients overall and for those who were diagnosed with advanced-stage PTC (2.9% per year). This finding appears to be associated with the increasing incidence of advanced-stage PTC (3.5% per year since 1981).

The results of this study challenge the prevailing notion that all of the increase in PTC incidence in the United States is related to overdiagnosis,[2,4,19] resulting from the introduction and increasing widespread use of diagnostic ultrasound and other imaging modalities and fine-needle aspiration biopsies that have allowed for incidental detection and diagnosis of mostly indolent localized cancers, small (<2 cm) cancers, or both.[20] Such changes could account for the rapid increases in the incidence rates for localized and small PTCs that have been previously observed.[2,4,6,19,21] Likewise, the deceleration in rates for localized but not advanced PTC incidence rates since 2009, as observed previously,[19,21] may be explained by less-aggressive diagnostic workup of small thyroid tumors in recent years due to rising awareness of problems associated with overtreatment of low-risk thyroid cancers.[15,19,22] However, the significant, albeit less-rapid increase in advanced-stage and larger PTC incidence rates and increasing thyroid cancer mortality rates among patients diagnosed with advanced-stage PTC is not consistent with the notion that overdiagnosis is solely responsible for the changing trends in PTC incidence. Thus, trends in PTC

Table 3. Trends in Observed Thyroid Cancer Mortality Rates (Total United States and SEER-9) and Thyroid Cancer Incidence-Based Mortality Rates (1994-2013): The SEER-9 Registry Database[a]

Characteristic	Overall (1994-2013) Annual Percent Change (95% CI)	*P* Value
US total thyroid cancer deaths	0.9 (0.7 to 1.5)	<.001
SEER-9 total thyroid cancer deaths	1.0 (0.4 to 1.5)	<.001
Incidence-Based SEER-9 Thyroid Cancer Deaths[b]		
Overall	1.1 (0.6 to 1.6)	<.001
Sex		
Male	1.0 (−0.1 to 2.1)	.10
Female	1.2 (0.4 to 2.0)	.01
Race		
White	0.9 (0.3 to 1.6)	.01
Black	3.8 (0.2 to 7.6)	.04
Other[c]	−0.2 (−2.4 to 2.2)	.90
Age at diagnosis, y		
<20	NR[d]	NR[d]
20-39	NR[d]	NR[d]
40-59	1.4 (0.0 to 2.8)	.05
60-79	0.8 (−0.2 to 1.8)	.10
≥80	1.3 (0.5 to 2.1)	.002
Thyroid cancer histologic type		
Papillary	1.7 (0.6 to 2.9)	.01
Follicular	−0.2 (−1.6 to 1.2)	.80
Medullary	−0.7 (−3.2 to 1.9)	.60
Anaplastic	0.9 (−0.4 to 2.2)	.20
Other[e]	2.4 (−0.1 to 5.1)	.06
Papillary Thyroid Cancer		
SEER Historic Stage A at diagnosis[b]		
Localized	2.1 (−0.1 to 4.2)	.06
Regional	1.7 (−0.3 to 3.6)	.09
Distant	2.9 (1.1 to 4.7)	.003
Unknown	NR[d]	NR[d]
AJCC/TNM stage at diagnosis[f]		
I	NR[d]	NR[d]
II	NR[d]	NR[d]
III[g]	14.5 (−6.1 to 39.7)	.20
IV[g]	12.9 (7.2 to 19.0)	<.001
Unknown[g]	16.5 (−3.4 to 40.4)	.09
Tumor size at diagnosis, cm[h]		
≤2	6.8 (2.4 to 11.4)	.004
>2 to ≤4	4.3 (1.3 to 7.3)	.01
>4	2.8 (−0.1 to 5.9)	.06
Unknown	−0.6 (−2.7 to 1.5)	.50

Abbreviations: AJCC/TNM, American Joint Committee on Cancer/Tumor-Node-Metastasis; NR, not reported; SEER, Surveillance, Epidemiology, and End Results.

[a] Rates for observed thyroid cancer mortality and for thyroid cancer incidence-based mortality were calculated as number of deaths per 100 000 person-years and age adjusted to the 2000 US standard population.

[b] Based on deaths during 1994-2013 and cases diagnosed during 1974-2013.

[c] American Indian/Alaskan Native and Asian/Pacific Islander.

[d] APC could not be calculated because there were 0 deaths in 1 or more years.

[e] Includes other specified, poorly specified, and other types of thyroid cancers.

[f] Based on deaths during 2004-2013 and cases diagnosed during 2004-2013.

[g] Calculations include 2005-2013 because there were 0 deaths in 2004.

[h] Based on deaths during 1994-2013 and cases diagnosed during 1983-2013.

incidence may be explained by 2 underlying processes: the dominant one is overdiagnosis, and the other is a small but actual increase in PTC incidence, possibly resulting from changes in exposure to environmental risk factors.[7]

Additional epidemiological research is needed to identify the specific environmental factors that have contributed to increasing rates of PTC, namely, those with greater aggressive potential. Ionizing radiation exposure in childhood is the most established risk factor for PTC,[23] and exposure has increased in the US general population in recent decades primarily because of more widespread use of diagnostic medical examinations.[24] However, studies of changes in radiation-related somatic mutations have shown declines in the proportion of PTCs with radiation signatures, such as *RET/PTC* rearrangements over time; whereas point mutations, such as *BRAF* or *RAS,* which are more likely to have a nonradiation etiology, have increased.[25-28]

There is growing evidence suggesting that changes in obesity and smoking prevalence have contributed to increasing thyroid cancer rates.[7] Paralleling trends in thyroid cancer incidence, obesity prevalence has increased 3-fold among US adults between 1960 and 2012, with the fastest rate of increase between 1980 and 2010.[29] In contrast, the prevalence of daily cigarette smoking has significantly decreased in the United States since 1980.[30] Epidemiological studies have consistently found positive associations between excess adiposity in childhood and adulthood and subsequent risk of thyroid cancer, including PTC,[31,32] whereas current smoking consistently has been associated with a 30% to 40% reduction in thyroid cancer risk, independent of obesity and other risk factors.[33] Obesity and smoking could influence thyroid cancer development via insulin resistance, thyroid hormone, and estrogen-related pathways.[34,35] Together, these factors have been estimated to be related to more than 40% of all new cases of thyroid cancer annually in the United States.[7]

Endocrine-disrupting chemicals (eg, pesticides, bisphenol A) also have been suspected to contribute to thyroid cancer incidence trends through their effects on thyroid hormone metabolism.[36] However, evidence in support of a causal association between environmental chemicals and thyroid cancer risk is currently lacking, largely due to the challenges in studying exposures that are ubiquitous and for which long-term exposure is extremely difficult to measure accurately.

The increasing mortality rates among patients with advanced-stage PTC suggest that for patients with these high-risk tumors, there should be renewed focus on aggressive transdisciplinary management that includes surgery, adjuvant radioactive iodine, and, when indicated for the 5% to 10% of patients who develop progressive disease, systemic therapy. Although there is continued debate about the appropriate extent of surgery for low-risk tumors, recent clinical guidelines suggest that total thyroidectomy and adjuvant radioactive iodine are indicated for high-risk disease.[15] Thorough preoperative imaging should be used to evaluate the neck for nodal metastases to inform whether simultaneous lymphadenectomy is necessary, and prophylactic central neck dissection should be considered for large and advanced tumors. Sorafenib and lenvatinib are approved for the management of

advanced, iodine-resistant differentiated thyroid cancer including PTC, but neither has been shown yet to afford a survival advantage, likely due to the indolent natural history of the disease.[37,38] Clinical trials to optimize the development and use of novel systemic therapies are necessary.

This study has several important limitations. Due to the descriptive nature of this study, it is only possible to speculate about potential explanations for the observed thyroid cancer trends. Individual-level environmental exposures and lifestyle-related factors were not captured by registries, nor were methods of thyroid cancer detection. Although changes in mortality and incidence-based mortality rates capture secular trends in detection, diagnosis, case ascertainment, and treatment and associated survival, the current study did not evaluate the influence of treatment on these trends. Analyses relying on tumor size and AJCC/TNM stage data were restricted to the years in which the information was reported to the registries. APC estimates for incidence-based mortality by tumor size and AJCC/TNM stage may be artificially inflated because this information was only available for cases diagnosed during 1983-2013 and 2004-2013, leaving a shorter latency period between diagnosis and death; however, the results generally agree with estimates by SEER stage. The results of an analysis evaluating the relationship of unknown data on tumor stage and size during the study period with the observed trends suggest that the increasing incidence rates of PTC with unknown SEER stage information underestimated, rather than overestimated, the true increase in PTC incidence for known SEER stages. Unknown SEER stage data could only explain, at most, approximately one-third of the observed increase in mortality due to advanced-stage PTC. Because specimens have been cut more finely and smaller tumors that are incidental findings have become better documented, the reduction in unknown size data over time most likely overestimated the observed trends for the smallest rather than largest PTCs. Additionally, some results were based on small numbers of cases or deaths. It will be important to continue monitoring thyroid cancer incidence and mortality rates over time to see if the observed trends persist.

Conclusions

Among patients in the United States diagnosed with thyroid cancer from 1974-2013, the overall incidence of thyroid cancer increased 3% annually, with increases in the incidence rate and thyroid cancer mortality rate for advanced-stage PTC. These findings are consistent with a true increase in the occurrence of thyroid cancer in the United States.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Lim, Devesa, Check.
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Supervision: Devesa, Sosa, Kitahara.

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