Rising Thyroid Cancer Incidence in the United States by Demographic and Tumor Characteristics, 1980-2005

Lindsey Enewold,[1] Kangmin Zhu,[1,5] Elaine Ron,[6] Aizen J. Marrogi,[1,2]
Alexander Stojadinovic,[1,3] George E. Peoples,[1,4] and Susan S. Devesa[6]

[1]United States Military Cancer Institute, [2]Department of Pathology and Area Laboratory Service, and [3]Division of Surgical Oncology, Department of Surgery, Walter Reed Army Medical Center, Washington, District of Columbia; [4]Department of Surgery, Brooke Army Medical Center, Fort Sam, Houston, Texas; and [5]Uniformed Services University and [6]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

Abstract

Thyroid cancer incidence has been rising in the United States, and this trend has often been attributed to heightened medical surveillance and the use of improved diagnostics. Thyroid cancer incidence varies by sex and race/ethnicity, and these factors also influence access to and utilization of healthcare. We therefore examined thyroid cancer incidence rates by demographic and tumor characteristics based on 48,403 thyroid cancer patients diagnosed during 1980–2005 from the Surveillance, Epidemiology and End Results program of the National Cancer Institute. The rates varied by histologic type, sex, and race/ethnicity. Papillary carcinoma was the only histologic type for which incidence rates increased consistently among all racial/ethnic groups. Subsequent analyses focused on the 39,706 papillary thyroid cancers diagnosed during this period. Papillary carcinoma rates increased most rapidly among females. Between 1992–1995 and 2003–2005, they increased nearly 100% among White non-Hispanics and Black females but only 20% to 50% among White Hispanics, Asian/Pacific Islanders, and Black males. The increases were most rapid for localized stage and small tumors; however, rates also increased for large tumors and tumors of regional and distant stage. Since 1992–1995, half the overall increase in papillary carcinoma rates was due to increasing rates of very small (≤1.0 cm) cancers, 30% to cancers 1.1 to 2 cm, and 20% to cancers >2 cm. Among White females, the rate of increase for cancers >5 cm almost equaled that for the smallest cancers. Medical surveillance and more sensitive diagnostic procedures cannot completely explain the observed increases in papillary thyroid cancer rates. Thus, other possible explanations should be explored. (Cancer Epidemiol Biomarkers Prev 2009;18(3):784–91)

Introduction

The incidence of thyroid cancer has been rising in the United States and other developed countries over the past three decades (1-8). Recently, Davies and Welch (3) analyzed data from the Surveillance, Epidemiology and End Results (SEER) program and estimated that thyroid incidence rates increased >2-fold from 1973–2002 whereas the mortality rates remained relatively constant. When the data were analyzed by histologic type and tumor size, the increase seemed predominantly among small (≤2 cm) papillary carcinomas. In a study conducted in Ontario, Canada, Kent et al. (9) reported a similar increase for differentiated cancers ≤2 cm in diameter.

The authors of both studies concluded that the observed increase in disease incidence was an artifact due to the use of better diagnostic tools, such as ultrasonography and fine-needle aspiration biopsy. Others have suggested that the data do not definitively support that conclusion and that there may be a true increase in thyroid cancer incidence (10) due to changes in other risk factors (11).

The American Cancer Society estimates that 37,340 new cases of thyroid cancer will be diagnosed in the United States during 2008 (12). About 75% of these cases are expected to occur among females, making it the sixth most common cancer among women (12). Thyroid cancer incidence rates also differ by race and ethnicity. The rates are twice as high among White as Black (13) and notably elevated among Asians, especially those from Southeast Asia (14), and the incidence patterns by Hispanic ethnicity are unclear (13, 15). Although sex and race/ethnicity are also associated with healthcare access and utilization, these characteristics were not taken into account when evaluating trends in thyroid cancer incidence during the previous analyses (3, 9).

Surgery alone, with or without adjuvant radioiodine, is the preferred treatment for differentiated thyroid cancer regardless of tumor size (16) and, although patients experience excellent 5-year survival rates (97%), treatment-related morbidity is not insignificant. Therefore, if the reported increase in thyroid cancer is

due to an upsurge in the diagnosis of subclinical tumors, maybe the clinical management of these cancers should be reconsidered. In a counter argument, Mazzaferri (17) has stressed that small, asymptomatic thyroid cancers can be metastatic, and diagnostic delays can result in higher rates of distant metastasis. If incidence patterns cannot be explained completely by better detection (e.g., if not only localized but also more advanced tumors are increasing), additional descriptive and etiologic studies will be necessary to determine the underlying cause(s) for the increase in disease incidence.

To address these issues, we conducted an in-depth analysis of SEER thyroid cancer incidence trends from 1980–2005. We focused on papillary carcinoma, the histologic type showing the largest increase in incidence over time, and then evaluated the papillary carcinoma incidence trends in terms of stage of disease and tumor size. Age-specific trends were evaluated for supporting evidence of any predominant period (improved diagnostics) or cohort (exposure) effects, and all analyses were conducted stratified by sex and race/ethnicity.

Materials and Methods

Data Source. Thyroid cancer incidence data were obtained from the SEER program of the National Cancer Institute, which began collecting data in the early 1970s from nine population-based registries: Connecticut, Iowa, New Mexico, Utah, Hawaii, Detroit, San Francisco-Oakland, Atlanta, and Seattle-Puget Sound (18). These SEER-9 registries include ∼10% of the U.S. population. In 1992, four registries were added: San Jose-Monterey, Los Angeles, rural Georgia, and Alaska Natives, expanding the coverage to 14% of the U.S. population. Our analysis included data available for the racial categories of White and Black since the early years of the SEER-9 registries and for Asian/Pacific Islander (API) and Hispanic ethnicity since 1992 from the SEER-13 registries. We excluded rural Georgia and Alaska Natives from the analyses because these two registries included relatively few APIs or Hispanics.

Case Definition and Tumor Characteristics. Analyses were restricted to 48,403 patients with malignant thyroid tumors that were microscopically confirmed and not diagnosed at autopsy or identified solely through death certificates; 887 (1.8%) cases were excluded based on these criteria. Since the late 1970s, histologic type has been coded according to the first International Classification of Diseases for Oncology (ICDO; ref. 19), the second edition ICDO-2 for cases diagnosed from 1992–2001 (20), and the third edition ICDO-3 for cases diagnosed since 2001 (21); all cases have been recoded with the use of the ICDO-3. To allow adequate time for all registries to convert to ICDO coding, the 1st y included for analyses was 1980. Histologic categories of papillary, follicular, medullary, anaplastic, other, and unspecified were defined according to the recommendations of the International Association of Cancer Research as used in Cancer Incidence in Five Continents, Volume IX (22). Data on stage at diagnosis (localized, regional, or distant) were determined for each case according to SEER Historic Stage A codes. Stage at diagnosis was evaluated first because this variable was available for the entire study period. Tumor size has been recorded in the SEER data for thyroid cancer cases diagnosed since 1983; however, before 1988 size was not stated for 23% of all thyroid tumors. Therefore, size was analyzed beginning in 1988 by combining two SEER variables, ''EOD 10 size'' (1988–2003) and ''CS tumor size'' (2004+), to form a single size (cm) variable.

Data Analysis. For long-term SEER-9 trend analyses among Whites, regardless of Hispanic ethnicity, and Blacks, years of diagnosis were grouped into seven calendar-year categories: 1980–1983, 1984–1987, 1988–1991, 1992–1995, 1996–1999, 2000–2002, and 2003–2005. For Whites, stratified by Hispanic ethnicity, and APIs, shorter-term trend analyses included the last four calendar-year categories 1992–1995 to 2003–2005. All incidence rates were age-adjusted to the 2000 U.S. population and expressed per 100,000 person-years with the use of the SEER*Stat version 6.4.4.[7] Disease incidence rates were reported if there were at least 10 cases in a given sex, race/ethnicity, and time category, and trend lines were plotted if at least two consecutive categories met this criterion. Temporal trends were plotted with the use of semilogarithmic scales so that slopes or rates of change could be compared; a slope of $10°$ represents a change of 1% per year (i.e., 40 y on the horizontal axis is the same length as one logarithmic cycle on the vertical axis; ref. 23). The percent changes between the first and last calendar-year categories were also calculated.

Results

The most common histologic type among all sex and racial/ethnic groups was papillary thyroid carcinoma (range, 65-88%), followed by follicular carcinoma (range, 9-23%; see Tables 1 and 2). Papillary and follicular carcinoma rates were consistently 2 to 3 times higher among females than males. Incidence rates tended to be higher among White than Black and among White non-Hispanics than White Hispanics or APIs.

Histology-Specific Time Trends. From 1980–1983, to 2003–2005, papillary carcinoma rates tripled among White and Black females and doubled among White and Black males ($P < 0.001$; see Fig. 1). From 1992–1995 to 2003–2005, papillary carcinoma rates increased among every racial/ethnic/sex group, ranging from 23% ($P = 0.07$) among API males to 104% ($P < 0.01$) among Black females.

The trends for the other histologic types were more variable. Follicular carcinoma rates increased only modestly among White ($P < 0.01$) and Black ($P > 0.40$). Medullary carcinoma seemed to increase dramatically among White Hispanic males (144%; $P = 0.13$), but the rates were based on small numbers. Anaplastic carcinoma rates were low and did not show consistent trends. The rates for other specified and unspecified histologic types were not plotted because

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[7] http://seer.cancer.gov/seerstat/

Table 1. Incidence rates of thyroid cancer by race, sex, and histology, 1980-2005, SEER-9 registries

Histology	Whites				Blacks			
	Female		Male		Female		Male	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Overall	24,764	9.59	8,557	3.59*	1,743	5.28[†]	458	1.84*,[†]
Papillary	20,559	8.00	6,532	2.70*	1,276	3.80[†]	299	1.16*,[†]
Follicular	2,872	1.10	1,217	0.53*	353	1.10	106	0.47*
Medullary	533	0.20	349	0.15*	33	0.10[†]	24	0.09[†]
Anaplastic	303	0.11	189	0.09	18	0.07	11	0.05
Other specified	206	0.08	141	0.06	16	0.06[†]	9	—
Unspecified	291	0.11	129	0.06*	47	0.15[†]	9	—

NOTE: Age-adjusted (2000 U.S. standard population) rates per 100,000 person-years. Rates were not calculated when counts were <10.
*$P < 0.01$ in comparison with same-race females.
[†]$P < 0.05$ in comparison with same-sex Whites.

they were low and could not provide an explanation of the trends for the more common histologic types.

Stage-Specific Time Trends in Papillary Carcinomas. All subsequent analyses focused on papillary carcinoma because this histologic type was increasing the most rapidly and was by far the most frequent, allowing for stratification by other variables. The most common stage of disease at time of diagnosis was localized for all racial/ethnic groups except White Hispanic and API males, for whom regional stage was the most frequent (Fig. 2). The proportion of tumors that were localized was higher among females than males (62% versus 50%), among Black than White (66% versus 61%), and among White non-Hispanics (63%) compared with White Hispanics (51%) or APIs (54%; all $P < 0.01$).

Papillary thyroid cancer incidence rates increased for tumors of each stage, but the increases for localized stage tumors were the most consistent among all the racial/ethnic groups. Among White and Black, localized tumor rates increased about 200% (range, 186-232%) since 1980–1983, and 100% (range, 97-155%) since 1992–1995 until 2003–2005. Among APIs, localized papillary cancer rates increased moderately (females, 39%; males, 57%) since 1992–1995. All reported increases were significant ($P \leq 0.01$).

Rates for regional and distant stage tumors also increased. In the >20-year period from 1980–1983 to 2003–2005, regional tumor rates increased 171% and

156% among White females and males, respectively, and 290% and 33% among Black females and males, respectively. Since 1992–1995, regional tumor rates increased 49% to 76% among White non-Hispanics, 32% among White Hispanic females, and 25% among API females. Regional tumor rates were stable among White Hispanic and API males. Distant stage tumor rates more than doubled among White since 1980–1983 and among APIs since 1992–1995. All reported increases were significant ($P < 0.01$) except for regional tumors among Black males ($P > 0.40$). The rates for unstaged tumors were low, and decreases could not explain the observed trends for tumors of known stage.

Tumor-Size Specific Time Trends in Papillary Carcinomas. Disease incidence rates increased for tumors of all sizes, but the increases were most rapid for the smaller size tumors (Fig. 3). Among White females since 1988–1991 (earliest years that tumor size were adequately recorded), rates increased 248% for tumors ≤1 cm, 106% for those 1.1–2 cm, 113% for those 2.1–5 cm, and 222% for those >5 cm (all $P < 0.01$). Size-specific increases in disease incidence among White males and Black females were similar. During the years studied, the rates for most tumor sizes also increased among White Hispanics, APIs, and Black males. About 50% of the overall increase in papillary carcinomas since 1992–1995 was due to increasing rates of very small cancers (≤1.0 cm), 30% to cancers 1.1 to 2 cm, and 20% to

Table 2. Incidence rates of thyroid cancer by race/ethnicity, sex, and histology, 1992-2005, SEER-11 registries

Histology	White non-Hispanics				White Hispanics				Asian/Pacific Islanders			
	Female		Male		Female		Male		Female		Male	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Overall	19,243	11.54	6,927	4.33*	4,057	10.94[†]	935	3.09*,[†]	3,652	12.08[†]	931	3.72*,[†]
Papillary	16,450	9.94	5,444	3.38*	3,549	9.34[†]	772	2.48*,[†]	3,204	10.53[†]	775	3.04*,[†]
Follicular	1,935	1.13	890	0.56*	352	1.05	88	0.31*,[†]	315	1.06[†]	94	0.40*,[†]
Medullary	358	0.21	261	0.16*	67	0.21	44	0.16	40	0.13[†]	23	0.09[†]
Anaplastic	205	0.10	146	0.10	40	0.18[†]	8	—	38	0.15[†]	22	0.11
Other specified	141	0.08	104	0.07	24	0.09	16	0.07	37	0.13[†]	6	—
Unspecified	154	0.08	82	0.05*	25	0.09	7	—	18	0.07	11	0.06

NOTE: The SEER-11 registries consist of the SEER-13 registries excluding the Alaska Natives and rural Georgia registries. Age-adjusted (2000 U.S. standard population) rates per 100,000 person-years. Rates were not calculated when counts were <10.
*$P < 0.01$ in comparison with same-race/ethnicity females.
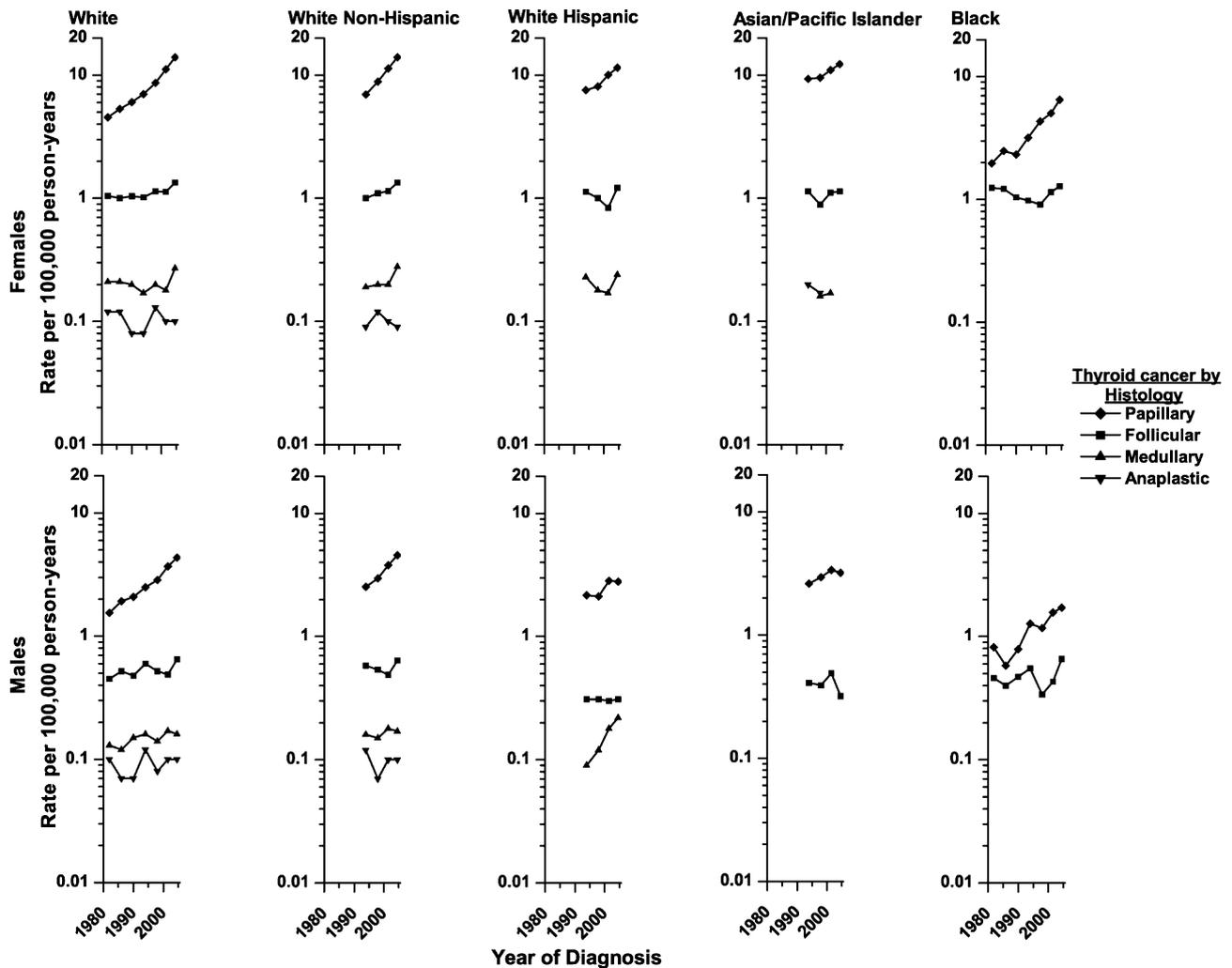[†]$P < 0.05$ in comparison with same-sex White non-Hispanics.

Figure 1. Histology-specific trends in thyroid cancer incidence in SEER diagnosed from 1980–1983 to 2003–2005 by sex and race/ethnicity. Rates are age-adjusted (2000 U.S. standard population), and each point represents 3 or 4 y. Nine regions were included for White and Black, and 11 for White non-Hispanics, White Hispanics, and Asian/Pacific Islanders.

cancers >2 cm. The rates for tumors of unknown size decreased, most consistently among White Hispanic females, but the declines could not account for the observed trends for tumors of known size.

Age-Specific Time Trends in Papillary Carcinomas. Except for the youngest (<20 years) and oldest (80+ years) age groups, which each accounted for only 2% to 3% of the papillary carcinomas within each racial/ethnic group, consistently increasing time trends were apparent across all age, sex, and racial/ethnic groups (Fig. 4). Among females, the highest rates occurred among individuals ages 40 to 59 years, but the steepest increases were observed among those ages 60 to 79 years whereas, among males, both the highest rates and the largest increases over time tended to be among older individuals.

Discussion

Papillary thyroid carcinoma was the only histology for which rates increased consistently among both sexes and all racial/ethnic groups; however, significant variations in the rate of increase were observed. For papillary carcinoma, increases in disease incidence tended to be more rapid among females than males and, over the same time period, were more rapid among White, especially non-Hispanic Whites, and Blacks than among APIs. Within each sex and racial/ethnic group, the largest increases were for localized and smaller tumors; however, we also found that rates increased for the more advanced and larger tumors.

If all of the increase in thyroid cancer incidence was due to improved disease detection, one would expect more rapid increases in small early-stage tumors than large late-stage tumors; subsequently, rates for larger, more advanced tumors should decline. One would also expect increases across all specified histologies except anaplastic. However, the observed trends in disease incidence do not completely support this hypothesis. Consistent increases were observed for papillary cancer only and, although the greatest increases were observed

among smaller early-stage tumors, we did not observe declines in larger, more advanced tumors. Instead, we found that tumors of all sizes increased over time. For example, rates for the smallest tumors (≤1 cm) increased 248% and those for the largest tumors (>5 cm) increased 222% among White females since 1988–1991. Furthermore, rates for all stages of disease at time of diagnosis increased. Among White males and females, localized stage disease rates increased >220%, regional stage rates increased at least 150%, and distant stage rates >130% since 1980–1983. In agreement with previous national and regional studies (15, 24), the proportion of tumors that were localized was highest among Blacks, which is surprising given the racial disparities in access to and utilization of healthcare in the United States. These findings are in contrast to an ecologic analysis (25) in Wisconsin that observed the strongest correlation ($r = 0.41$) between thyroid cancer incidence rates and percent of residents with health insurance when assessing other community-level socioeconomic status and healthcare access variables. Although this study

gives some support to the notion that the thyroid cancer "epidemic" is related to the growth in diagnostic imaging, methodologic problems associated with ecologic studies (26) limit the interpretation of these results. Analyzing data from Australia, Burgess (27) estimated that no more than 50% of the increase in thyroid cancer could be attributed to technological advances in diagnosis and case ascertainment. Since 1992–1995 we calculated that half the overall increase in papillary carcinoma rates in SEER was due to increasing rates of very small (≤1.0 cm) cancers, 30% to cancers 1.1 to 2 cm, and 20% to cancers >2 cm. Therefore, if we assume that all the increases in the very small tumors and none of the increases in tumors >1 cm were related to improved early detection, then we also would estimate that about 50% of the observed increase in papillary carcinomas may be attributed to advances in diagnostic accuracy. If, however, changes in potential risk factors are related to the increasing thyroid cancer incidence, then the estimate for the role of early detection would be lower.
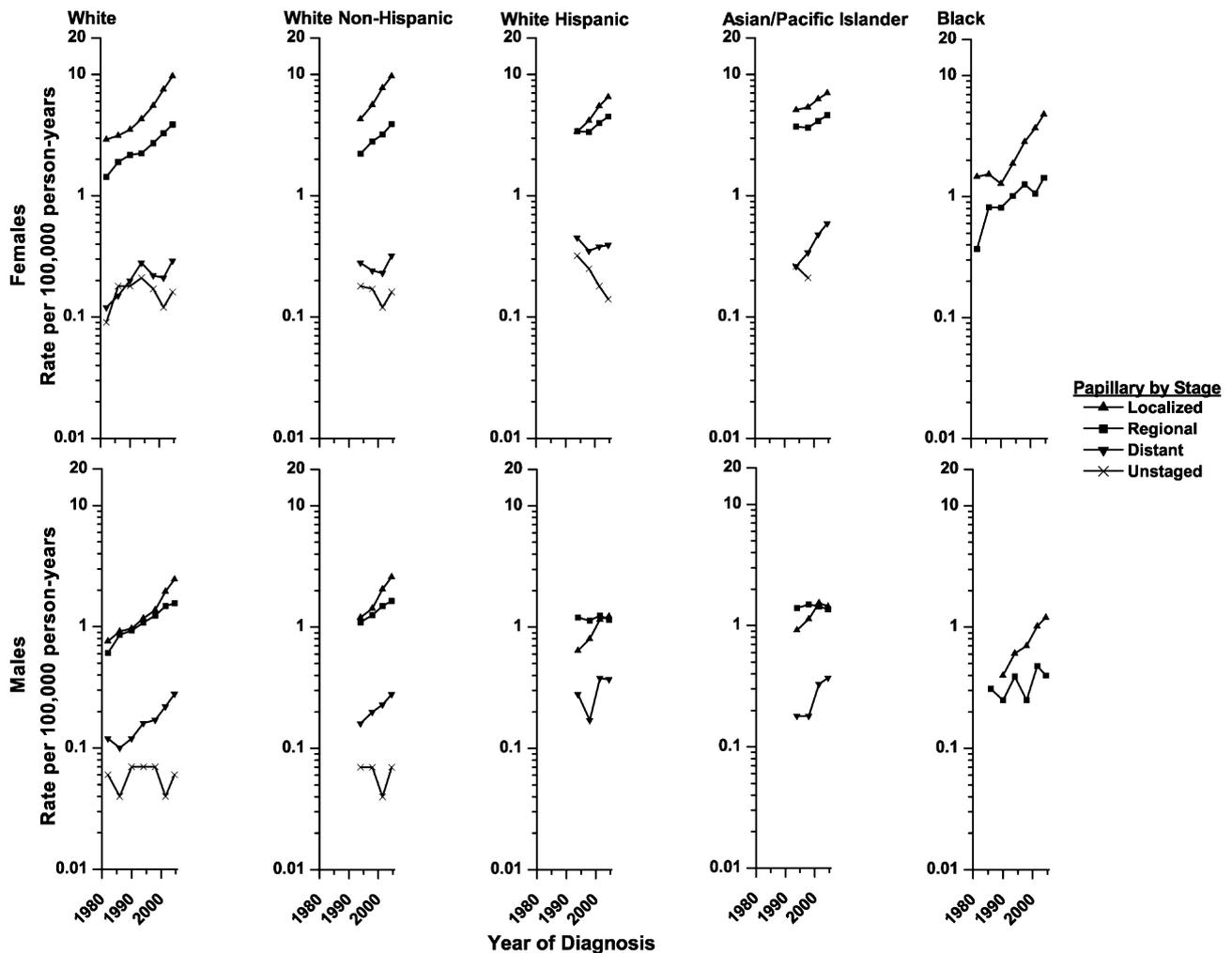

Figure 2. Stage-specific trends in papillary thyroid cancer incidence in SEER diagnosed from 1980–1983 to 2003–2005 by sex and race/ethnicity. Rates are age-adjusted (2000 U.S. standard population), and each point represents 3 or 4 y. Nine regions were included for White and Black, and 11 for White non-Hispanics, White Hispanics, and Asian/Pacific Islanders.

Figure 3. Size-specific trends in papillary thyroid cancer incidence in SEER diagnosed from 1988–1991 to 2003–2005 by sex and race/ethnicity. Rates are age-adjusted (2000 U.S. standard population), and each point represents 3 or 4 y. Nine regions were included for White and Black, and 11 for White non-Hispanics, White Hispanics, and Asian/Pacific Islanders.
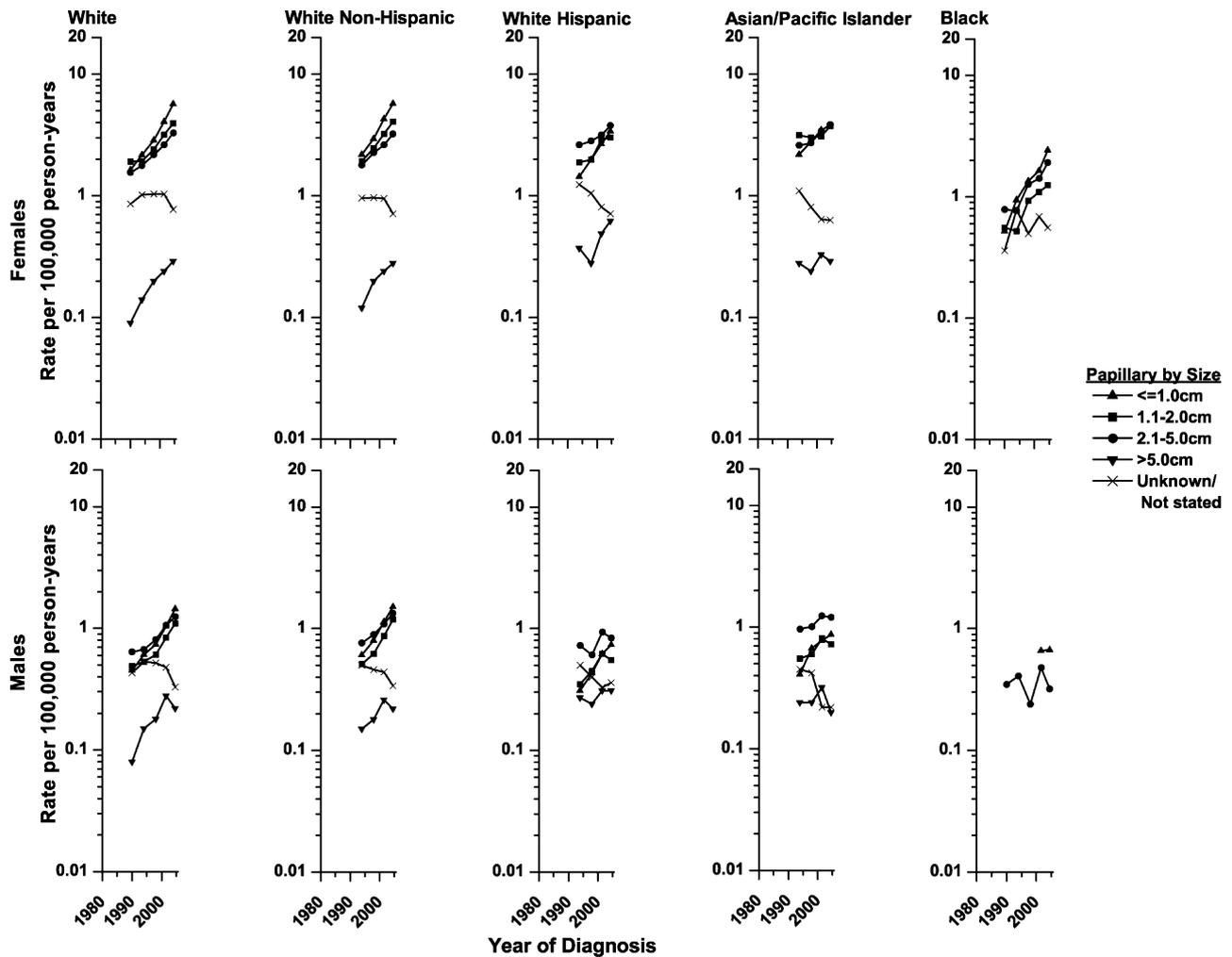
The significant increase in incidence of papillary carcinomas may also have been partially affected by a change in diagnostic criteria. In 1988, a new WHO classification system (28) was introduced, which recommended reclassifying tumors with follicular architecture but nuclear features characteristic of papillary carcinoma as papillary carcinomas. The change in classification may have artificially inflated papillary thyroid cancer incidence rates but, at the same time, may have masked a real increase in follicular carcinoma rates. This reclassification cannot entirely account for the increase in papillary carcinomas. Although the rate for the papillary follicular variant (morphology code 8340) increased more rapidly than for papillary carcinomas overall (235% versus 191% from 1980–1983 to 2003–2005; data not shown) among White and Black combined, this increase accounted for only one third of the overall increase in papillary carcinoma rates. During this time period, the papillary follicular variant comprised 20% to 30% of all papillary carcinomas. Another possible explanation is that information on tumor histology and stage has

become more accurate and complete, resulting in reduced frequencies in the unspecified/unknown tumor categories. Although some decreases in the unspecified/unknown tumor categories were observed, these changes were too small to explain the increases in the specified categories. With respect to timeliness of case ascertainment and reporting of thyroid cancers overall, delay adjustment of rates resulted in minimal increases in recent SEER thyroid cancer incidence rates (13), indicating that case ascertainment has been high for many years, and our results, if anything, underestimate the true increases.

Radiation exposure is the major known risk factor for thyroid cancer (14). It was used from about the 1930s–1960s to treat several benign conditions of the head and neck, and follow-up of several of these irradiated populations showed a strong radiation dose-response relationship with thyroid cancer, especially papillary carcinoma (29). Persons treated as young children have particularly high risk, and many of them would be in the age range to develop radiation-related thyroid cancer during the study period (30). This may at least partially
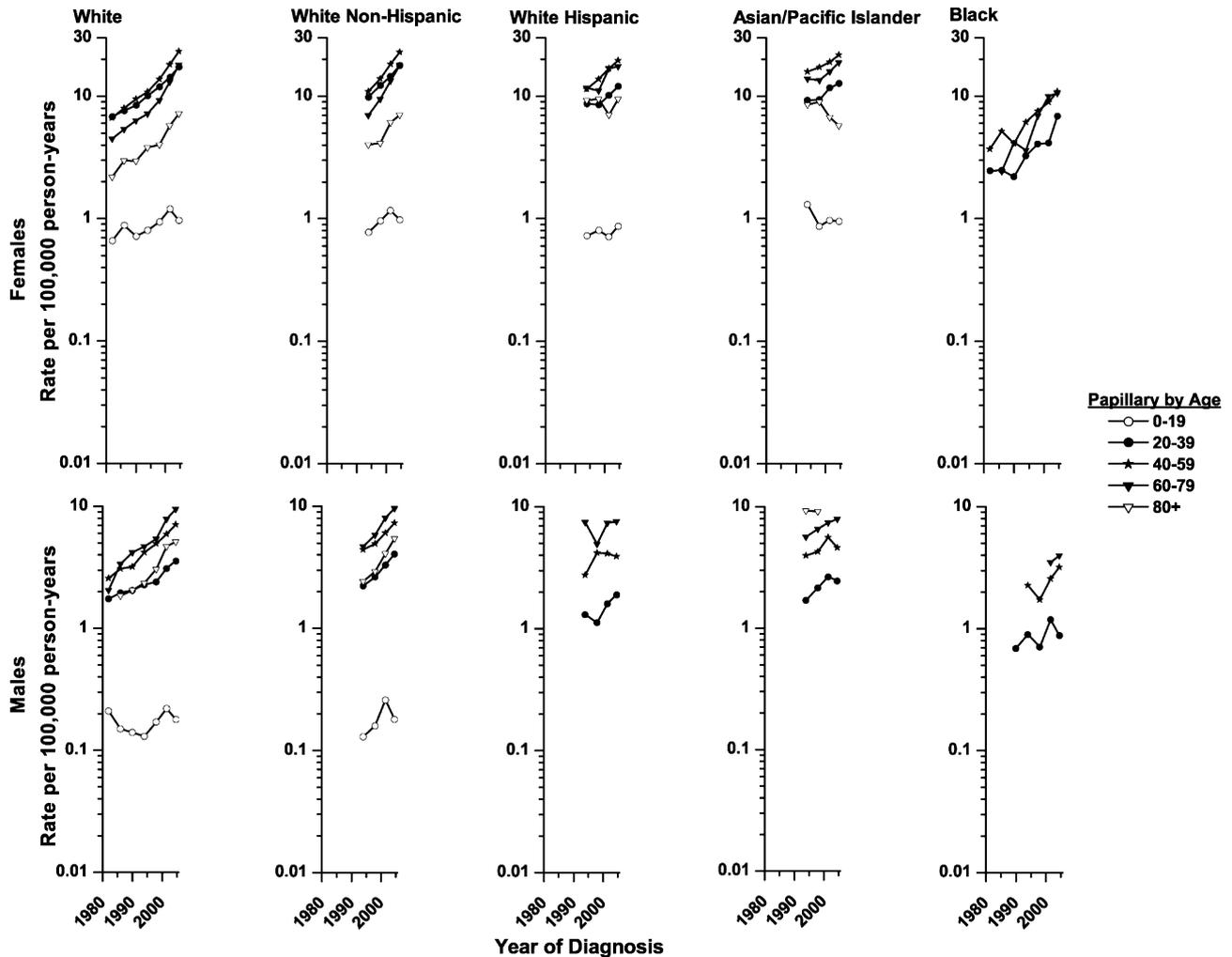
Figure 4. Age-specific trends in papillary thyroid cancer incidence in SEER diagnosed from 1980–1983 to 2003–2005 by sex and race/ethnicity. Rates are age-adjusted (2000 U.S. standard population), and each point represents 3 or 4 y. Nine regions were included for White and Black, and 11 for White non-Hispanics, White Hispanics, and Asian/Pacific Islanders.

explain why the steepest trends among both sexes were among individuals older than 40 years, which is suggestive of a cohort effect. It is difficult to sort out the relative roles of period and cohort effects, however, as there are no clear changes in the age-specific trends. Furthermore, over the last few decades there have been significant increases in the use of medical diagnostic radiation, especially computed tomography scans, which have gone from ~3 million done in the United States in 1980–1967 million in 2006 (31, 32). The young thyroid gland is very sensitive to radiation, leading some authors to speculate that the greater use of pediatric computed tomography scanning could be accounting for a part of the thyroid cancer increase later in life (11, 33).

As reviewed by Boas et al. (34), environmental chemicals, such as polychlorinated biphenyls and dioxins, have been positively correlated with thyroid-stimulating hormone levels. Thyroid-stimulating hormone is the principal hormone responsible for regulating the growth and function of the thyroid gland, and higher levels are associated with increased proliferation (35),

resulting potentially in an increased opportunity for mutations and the development of cancer. Results from the National Health and Nutrition Examination Survey III study indicate that White non-Hispanics have higher thyroid-stimulating hormone levels than Black non-Hispanics and Mexican-Americans have intermediate levels (36), which is consistent with the observed incidence rates of thyroid cancer. Thyroid-stimulating hormone levels also vary by sex, with females tending to have higher levels (36), especially during pregnancy (37).

Other risk factors suspected in the increase in thyroid cancer incidence include the increase in body mass index and height (38, 39), use of fertility drugs (40), changes in reproductive patterns (41, 42), immigration from high-incidence countries (43), and, possibly, insulin resistance syndrome (44).

Conclusion

Through the examination of the SEER database and its racially/ethnically diverse national sample, we were able

to provide a more complete epidemiologic portrait of thyroid cancer according to common demographic and tumor-specific characteristics. Our findings indicate that the implementation of more sensitive diagnostic procedures cannot completely explain the observed increases in papillary thyroid cancer incidence. Further investigation of the relationship between environmental chemicals known to interfere with thyroid function as well as other potential risk factors for the development of thyroid cancer is therefore warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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