Ten-year Thyroid Cancer Incidence in an Integrated Healthcare Delivery System

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ABSTRACT

Introduction: The incidence of papillary thyroid cancer (PTC) has increased in recent decades, but data from community-based settings are limited. This study characterizes PTC trends in a large, integrated healthcare system over 10 years.

Methods: The annual incidence of PTC (2006-2015) was examined among Kaiser Permanente Northern California adults aged 21 to 84 years using Cancer Registry data, including tumor size and stage. Incidence estimates were age-adjusted using the 2010 US Census.

Results: Of 2990 individuals newly diagnosed with PTC (76.8% female, 52.7% non-Hispanic White), 38.5% and 61.5% were aged <45 and <55 years, respectively. At diagnosis, 60.9% had PTC tumors ≤2 cm, 9.2% had tumors >4 cm, and 66.1% had Stage I disease. The annual age-adjusted incidence of PTC increased from 9.4 (95% confidence interval [CI] = 8.1-10.7) to 14.5 (95% CI = 13.1-16.0) per 100,000 person-years and was higher for female patients than for male patients. Incidence tended to be higher in Asian/Pacific Islanders and lower in Black individuals. Increasing incidence was notable for Stage I disease (especially 2006-2012) and evident across a range of tumor sizes (3.0-4.6 for ≤1 cm, 2.5-3.5 for 1-2 cm, and 2.4-4.7 for 2-4 cm) but was modest for large tumors (0.9-1.5 for >4 cm) per 100,000 person-years.

Discussion: Increasing PTC incidence over 10 years was most evident for tumors ≤4 cm and Stage I disease. Although these findings may be attributable to greater PTC detection, the increase across a range of tumor sizes suggests that PTC burden might also have increased.

INTRODUCTION

The overall incidence of thyroid cancer has increased, especially over the last 3 decades. Based on data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER-9) Registry, thyroid cancer incidence nearly tripled from 1975 to 2009, largely attributed to an increase in the detection of papillary thyroid carcinoma (PTC), the most common histologic variant. A follow-up study using SEER data from 1983 to 2012 showed relative stabilization in the incidence of all types of thyroid cancer between 2010 and 2012, suggesting that these findings may in part reflect changes in clinical practice, including implementation of the 2009 American Thyroid Association (ATA) thyroid nodule guidelines that refined criteria for which nodules should be biopsied. Researchers in South Korea also reported large increases in thyroid cancer incidence from 1993 to 2011, whereas thyroid cancer-related mortality rates remained stable; the authors attributed the rising incidence to increased screening, including thyroid sonography, rather than an actual increase in thyroid disease. Other US studies, using data from the Veterans Affairs Health System and private and public insurance claims databases, also reported an increase in thyroid cancer incidence, accompanied by an increase in thyroid ultrasound and/or thyroid fine needle aspiration (FNA) procedures.

New considerations have arisen following recent analyses of SEER-9 data from 1974 to 2013 that demonstrated concomitant increases in the annual incidence and mortality rate of thyroid cancer for all sex, race, and age groups as well as for every stage and tumor size category at diagnosis. Notably, this included an increase in thyroid cancer incidence for advanced-stage PTC, suggesting that the rise in incidence may reflect a true increase in disease occurrence and not just overdiagnosis from greater use of ultrasound and other imaging modalities. Others have similarly reported an increased trend in the incidence of larger tumors, including data from areas of high and low socioeconomic status, which would be less likely to reflect the increased screening of asymptomatic cases. However, systematic data pertaining to thyroid cancer incidence from single community-based healthcare systems, where care delivery and case ascertainment practices are also more consistent, have not yet been reported.

For the current study, we used data from the Kaiser Permanente Northern California (KPNC) Cancer Registry to characterize recent trends in PTC incidence, overall and by tumor size, from 2006 to 2015 within a single large, integrated healthcare delivery system. The selected time window represented a period of contemporary endocrine

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Keywords: cancer, carcinoma, incidence, papillary, trends, thyroid
practice within our health system that included office-based thyroid sonography and was consistent with the clinical approach set forth in the 2009 ATA thyroid nodule guidelines. This time period allowed us to examine trends over time prior to the 2016 implementation of new evidence-based workflows for thyroid nodules and thyroid cancer within KPNC that included the revised national ATA guidelines released at the end of 2015. We hypothesized that, for the study period of 2006-2015, detection of early stage disease would contribute to rising PTC incidence, possibly attributable to identification of thyroid nodules by ultrasound that would otherwise have not been detected during routine neck examination. However, the incidence would likely plateau over time if the true burden of disease was not increased.

METHODS

Study Population and Setting

KPNC is a large, integrated healthcare delivery system providing care to more than 4 million members. The membership population is racially and ethnically diverse, with demographic and health-associated characteristics similar to those of the general northern California population. Each of the 21 KPNC medical centers is staffed by clinical endocrinologists, head and neck surgeons, and/or general surgeons with expertise in the medical and surgical management of differentiated thyroid carcinoma.

Incident cases of PTC diagnosed from 2006 to 2015 in adults aged 21 to 84 years were identified using the KPNC Cancer Registry. Following SEER Program standards, the KPNC Cancer Registry includes data on all patients diagnosed or treated with any primary cancer (except non-melanoma skin cancer) at its medical centers since 1988. Histologic types of thyroid cancer were defined using morphology codes as proposed by Lim et al: PTC (8050, 8260, 8340-8344, 8350, 8450-8460), follicular thyroid cancer (8290, 8330-8335), medullary thyroid cancer (8345, 8510-8513), and anaplastic thyroid cancer (8020-8035). Identified PTC cases were characterized in the Cancer Registry with respect to tumor size and stage, the latter informed by tumor size, evidence of extrathyroidal extension (metastatic disease), and the extent and level of lymph node involvement. Tumor stage at diagnosis was classified following the American Joint Commission on Cancer (AJCC) Tumor-Node-Metastasis Staging System (sixth edition for tumors diagnosed from 2006 to 2009 and seventh edition for tumors diagnosed from 2010 to 2015). No major changes in staging for PTC occurred between the sixth and seventh editions that would have affected classification in this study. Consistent with the AJCC/TMN criteria for staging of thyroid cancer, we used an age threshold of 45 years to compare subgroups. We note that the AJCC PTC staging guidelines changed in 2018 with the eighth edition, raising the age cutoff from 45 to 55 years for Stage I-II in younger patients, but this change does not affect the time period of our study.

For population denominators used to calculate disease incidence, we obtained KPNC membership data for adults aged 21 to 84 years using membership counts at the midpoint (ie, July 1) of each calendar year of the study. Race/ethnicity was determined using administrative data and classified as non-Hispanic White, Black, Hispanic, Asian/Pacific Islander, and other or unknown race/ethnicity. The study was approved by the KPNC Institutional Review Board, and a waiver of consent was obtained due to the nature of the study.

Statistical Analyses

The annual incidence of PTC with 95% confidence intervals (CI) was calculated overall, by sex, and by race/ethnicity using KPNC health plan membership denominators, with age-adjusted rates standardized to the 2010 US Census. Subgroup-specific rates based on tumor size and cancer stage were also examined. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Among the adult population aged 21 to 84 years, we identified 2990 new cases of PTC diagnosed during the 10-year period from 2006 to 2015. Two-thirds of PTC cases (66.1%) were classified as Stage I disease based on AJCC sixth and seventh edition criteria. The average age (± standard deviation) at PTC diagnosis was 49.6 ± 14.5 years, and 61.5% and 38.5% of diagnosed individuals were aged < 55 and < 45 years, respectively, at diagnosis. Overall, 52.7% individuals were non-Hispanic; 76.8% of patients were female. Moreover, 60.9% and 9.2% of individuals with PTC had tumor sizes ≤ 2 and > 4 cm, respectively. Demographic and tumor characteristics of incident PTC cases, overall and stratified by age at diagnosis, are shown in Table 1.

The overall age-adjusted incidence of PTC increased by 54.3% from 9.4 (95% CI = 8.1-10.7) to 14.5 (95% CI = 13.1-16.0) per 100,000 person-years between 2006 and 2015 (Figure 1A). Age-adjusted incidence was higher for female patients, increasing by 60.9% from 12.8 (95% CI = 10.9-15.1) to 20.6 (95% CI = 18.3-23.2) per 100,000 person-years over the 10-year period. Incidence in female patients reached a peak of 21.8 (95% CI = 19.3-24.1) in 2012 and stabilized over the subsequent 3 years, with an incidence of 20.6 (95% CI = 18.3-23.2) per 100,000 person-years in 2015. The age-adjusted incidence in male patients was 7.9 (95% CI = 6.5-9.6) per 100,000 person-years in 2015. Figure 1B shows the variation in PTC incidence by race/ethnicity over time. The incidence of PTC tended to be slightly higher in Asian/Pacific Islander than
in non-Hispanic White and Hispanic individuals for most years and lower among Black individuals.

Figure 1C illustrates the incidence of PTC by tumor size each year. The annual age-adjusted incidence of PTC increased for tumors ≤ 4 cm between 2006 and 2015. For tumors ≤ 1 cm, incidence increased from 3.0 (95% CI = 2.3-3.8) to 4.6 (95% CI = 3.8-5.5) during the period studied, with a peak of 5.2 (95% CI = 4.3-6.2) per 100,000 person-years in 2012. The incidence of tumors 1.1 to 2.0 cm increased from 2.5 (95% CI = 1.9-3.2) to 3.5 (95% CI = 2.8-4.3), with a peak of 4.8 (95% CI = 3.9-5.8) per 100,000 person-years in 2011. For tumors 2.1 to 4.0 cm, incidence increased from 2.4 (95% CI = 1.8-3.1) to 4.7 (95% CI = 3.9-5.6) per 100,000 person-years in 2006-2015. In contrast, for tumors > 4.0 cm, changes in incidence were more modest, increasing from 0.9 (95% CI = 0.5-1.4) to 1.5 (95% CI = 1.1-2.0) per 100,000 person-years. Approximately 4% of cases had tumor size undefined in the KPNC Cancer Registry across all years, and the proportion with undefined sizes declined over the observation period.

Figure 1D shows annual age-adjusted incidence of PTC by tumor stage, which was most notable for Stage 1 tumors, which increased from 6.4 (95% CI = 5.4-7.6) in 2006 to a peak of 10.7 (95% CI = 9.4-12.2) per 100,000 person-years in 2012 and then decreased to 9.1 (95% CI = 8.0-10.3) per 100,000 person-years in 2015. Changes in PTC incidence for higher stage tumors were modest and variable. A small decline in the number of cases with undefined tumor stage in the KPNC Cancer Registry was also observed, especially in the latter years.

**DISCUSSION**

Within our integrated healthcare system, we found an overall increase in PTC incidence from 2006 to 2015. This period was characterized by relatively consistent clinical practice pertaining to thyroid cancer screening and management in our organization, during which thyroid sonography (including the availability of office-based thyroid sonography) increased. Others have also observed national increases in PTC incidence using data from SEER, including data from KPNC that have contributed to the larger SEER-91-3,8 and SEER-1315 datasets. Although the SEER program uses race/ethnicity- and sex-specific population denominators based on county population estimates that have been aggregated,16 an important contribution of our study is the examination of findings from a single integrated healthcare delivery system serving a diverse northern California patient population, with population denominators derived from the same health plan membership from which the PTC cases were identified.

A national study of the US Veterans Affairs Health Care System found that thyroid cancer incidence doubled from

| Table 1. Baseline demographic and clinical characteristics of adults with papillary thyroid cancer, 2006-2015 |
|--------------------------------------------------------|-----------------|-----------------|
| Total population (N = 2990)                            | Age < 45 y (n = 1150) | Age 45-84 y (n = 1840) |
| Age in years, mean ± SD                                | 49.6 ± 14.5       | 34.6 ± 6.4       | 59.0 ± 9.4       |
| Female sex, %                                          | 76.8             | 80.9             | 74.2             |
| Race/ethnicity, %                                      |                 |                 |                 |
| Non-Hispanic White                                     | 52.7             | 46.4             | 56.7             |
| Black                                                  | 4.7              | 4.2              | 5.1              |
| Hispanic                                               | 17.4             | 22.5             | 14.1             |
| Asian/Pacific Islander                                 | 22.7             | 25.0             | 21.3             |
| Multiple/other/unknown                                  | 2.5              | 1.9              | 2.8              |
| Tumor size, %                                          |                 |                 |                 |
| 0.1-1.0 cm                                             | 33.0             | 26.2             | 37.3             |
| 1.1-2.0 cm                                             | 27.9             | 29.0             | 27.2             |
| 2.1-4.0 cm                                             | 26.1             | 31.0             | 22.9             |
| ≥ 4.1 cm                                               | 9.2              | 10.7             | 8.2              |
| Unknown                                                | 3.9              | 3.0              | 4.4              |
| AJCC/TNM stage, %                                      |                 |                 |                 |
| I                                                      | 66.1             | 97.9             | 46.2             |
| II                                                     | 8.2              | 1.6              | 12.4             |
| III                                                    | 11.8             | 0                | 19.2             |
| IV                                                     | 9.1              | 0                | 14.8             |
| Unknown                                                | 4.8              | 0.5              | 7.4              |

AJCC = American Joint Commission on Cancer; TNM = tumor node metastasis.
2000 to 2012, corresponding to a 4.6-fold increase in thyroid ultrasound use and a 6.6-fold increase in thyroid FNA procedures. Data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample, the Thomson Reuters MarketScan Outpatient database, and the American Cancer Society similarly indicated that the incidence of thyroid cancer increased by 59% from 2006 to 2011, accompanied by more than double the number of thyroid FNAs performed and a 31% increase in number of thyroid nodule-related operations. Our results support the increase in thyroid cancer trend reported by others, with additional observations about tumor size, stage, and demographic factors that complement existing reports.

Investigation of thyroid cancer incidence by race/ethnicity using SEER-13 data from 1992 to 2010 found an increase in observed thyroid cancer incidence in non-Hispanic compared with Hispanic adults and in White adults compared with Asian/Pacific Islander adults, with the highest overall incidence in White adults. In contrast, we observed a slightly higher incidence of PTC among Asian/Pacific Islander, followed by non-Hispanic White and Hispanic adults, with a generally lower incidence of PTC among Black adults except for 2011-2012, when the incidence was similar between Black and non-Hispanic White adults. In comparison to national observations, our study population reflects the diversity of the northern California population and contributes a larger proportion of Asian/Pacific Islanders and immigrants than other regions of the US. Furthermore, all KPNC health plan members have access to healthcare and preventive exams, which may explain the relatively high incidence of PTC among those of non-White race/ethnicity. Also consistent with published SEER-9 results from 1974 to 2013 by Lim et al, the rise in new cases of PTC over the 10-year observation period was reflected across most tumor sizes ≤ 4 cm, although large increases in incidence were seen primarily for Stage I disease. The findings from SEER-9 also demonstrated an increase in identification of localized PTC disease.

We postulate that the rising incidence of PTC is largely attributable to higher rates of PTC detection but similar to others, we cannot exclude the possibility that PTC burden has also increased due to other contributing factors. The availability of thyroid sonography, integration of office-based thyroid sonography in current endocrine practice, and greater incidental thyroid screening would be expected to contribute to greater detection of thyroid nodules and subsequent thyroid FNA biopsies, as demonstrated in multiple

Figure 1. Incidence of papillary thyroid cancer, 2006-2015. (A) Age-adjusted incidence overall and by sex. (B) Age-adjusted incidence by race/ethnicity. (C) Age-adjusted incidence by tumor size. (D) Age-adjusted incidence by stage at diagnosis.
prior published reports.6,7 These clinical management factors likely explain the increased detection of early-stage thyroid cancer and small tumors, with peak incidence evident in 2012, after which the detection of small tumors appears to have declined. In analyses of more than 77,000 patients with thyroid cancer, Lim et al8 observed that the increase in thyroid cancer incidence is accompanied by a concomitant increase in thyroid cancer mortality, possibly reflecting an actual increase in thyroid disease burden, and cited risk factors such as the increasing burden of obesity, exposure to ionizing radiation, and endocrine-disrupting chemicals as potential contributors. Indeed, recent data regarding environmental exposures report a potential association of endocrine disruptors and PTC risk.17 Individuals with increased exposure to selected flame-retardant chemicals previously shown to be associated with thyroid disease in women18 were twice as likely to develop PTC, and specific types of flame retardants have also been associated with tumor size and severity.17

Although the burden of newly identified PTC cases has clearly increased, the revised 2015 ATA guidelines currently support a less aggressive surgical approach and surveillance for low-risk PTC and allow for safe monitoring of small, incidentally detected thyroid nodules with low-risk imaging phenotypes.10 Several recent studies demonstrate that active surveillance of low-risk papillary microcarcinoma for selected patients appears to be feasible and may even become the standard of care in certain countries.19 Data from Japan suggest that active surveillance of these select tumors (without thyroidectomy) could be a safe and cost-effective alternative in health systems where patients are able to be carefully monitored.19 Future studies should be conducted to examine trends in PTC incidence and healthcare expenditures as practice patterns shift toward less aggressive intervention for low risk thyroid nodules, especially PTC tumors ≤ 1 cm in size.

Our study has several limitations to consider. First, we report data on a population of northern California adults who have access to healthcare, which may limit the generalizability of our findings; however, the large size and consistency of practice within our region allows for a more specific examination of incidence trends not influenced by practice variation and access to care, as would be the case with national data. Second, we did not examine the concomitant frequency of thyroid sonography and FNA biopsy and are thus unable to determine the extent to which our findings are due to increased diagnostic activity, an important speculation. During the latter part of the observation period, the proportion of PTC cases with unknown tumor size/stage in the KPNC Cancer Registry declined, potentially contributing to a slightly greater incidence of PTC by tumor size and stage, although this would not explain the large increase in prevalence of Stage I disease before 2012. Finally, the number of PTC cases identified within KPNC was relatively small compared with large epidemiologic reports based on data from multiple SEER regions; therefore, we did not attempt to calculate the annual percentage change by tumor size or stage for comparison.

The primary goal of this study was to examine population-level PTC trends within a single health system, where the strengths of our data include use of a comprehensive cancer registry coupled with known health plan population denominators to calculate disease incidence, as opposed to determining population denominators from US Census data at the local or county level (as implemented for SEER Registry-based studies). Additionally, we conducted our study in a single integrated healthcare delivery system over a period of relatively consistent clinical practice related to thyroid cancer screening, whereas most previous studies focused primarily on data from multiple health systems with variable practices. Furthermore, the KPNC population was large and racially and ethnically diverse, allowing for comparisons across ethnic subgroups.

CONCLUSIONS

In summary, we found an overall increase in PTC incidence from 2006 to 2015 within our large, integrated healthcare delivery system, supporting findings from other studies. The increase in PTC incidence was reflected largely for tumors ≤ 4 cm. At diagnosis, the majority of PTC cases had tumors ≤ 2 cm and Stage I disease and, relevant to the age thresholds used in the 2018 AJCC staging criteria, occurred among adults aged < 55 years. Although these findings may be attributable to higher rates of PTC detection, the modest increases observed in the incidence of larger tumors raise the possibility that the true burden of PTC may also have increased. Additionally, higher PTC incidence was noted in Asian/Pacific Islander adults, compared with non-Hispanic White, Hispanic, and Black adults. This study provides an important benchmark for future studies following implementation of the revised 2015 ATA guidelines for the management of thyroid nodules and differentiated thyroid cancer.10

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

The authors thank Jennifer Green for editorial assistance.

Authors’ Contributions

Stephanie Kim, MD, MPH; Joan C Lo, MD; Hasmik Arzumanyan, MD; Jeanne A Darbinian, MPH; Megan Durr, MD; and Lori C Sakoda, PhD, conceived the study. Charles Meltzer, MD; Kevin Wang, MD; Jonathan Lin, MD; and Deepak Gurushanthaiah MD, provided input on the design. Jeanne A Darbinian, MPH; led the acquisition and analysis of data. Stephanie Kim, MPH, drafted the
manuscript in collaboration with Joan C Lo, MD; Jeanne A Darbiniian, MPH; Lori C Sakoda, PhD; Hassmin Arzumanyan, MD; Charles Melzer, MD; and Megan Durr, MD. All authors provided important input, revised the manuscript for important intellectual content, and approved the final manuscript for submission.

Funding
This study was supported by Kaiser Permanente Northern California Graduate Medical Education, funded by the KPNC Community Benefit Program. The sponsor had no role in the study design, data collection, analysis, and interpretation; writing of the report; and the decision to submit for publication.

Abbreviations
AJCC, American Joint Commission on Cancer; ATA, American Thyroid Association; CI, Confidence intervals; FNA, Fine-needle aspiration; KPNC, Kaiser Permanente Northern California; PTC, Papillary thyroid cancer; SEER-9, Surveillance, Epidemiology and End Results; TNM, Tumor-node-metastasis

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