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Survival differences of lung neuroendocrine tumors in California by sociodemographic, clinicopathologic, and treatment factors

Lung neuroendocrine tumors (NETs) are a rare, heterogeneous group of cancers with varying clinical behavior. Little is known about lung NET epidemiology or predictors of survival. We investigated associations between sociodemographic and disease factors and mortality for patients with lung NETs.

We conducted a population-based prospective study of mortality among individuals with an incident lung NET diagnosis (typical or atypical histology) in the California Cancer Registry (CCR) from 1992-2017. We used Kaplan-Meier time-to-event survival analysis and compared univariate survival among demographic and disease factors by the log-rank test. Multivariable Cox proportional hazard models were used to estimate associations of sociodemographic and disease-related factors with all-cause mortality.

There were 5,127 patients diagnosed with lung NETs in the CCR from 1992-2017, including 4,784 typical and 343 atypical carcinoid cases. Women were a majority of the lung NET cases (69.7%), as were non-Hispanic White Californians (74.2%). We found that several social determinants of health were independently associated with mortality. Men, unmarried Californians, cases living in low socioeconomic status neighborhoods, and those with Medicare or public insurance had higher all-cause mortality in both univariate and multivariable survival models. Non-Hispanic Black Californians also had higher mortality than non-Hispanic White Californians in univariate models, though racial differences in survival were attenuated after accounting for other prognostic factors including disease characteristics and treatment. Localized stage, typical histology, and surgical resection were also independently associated with improved survival. In contrast, rural versus urban county of residence did not impact survival.

We report novel findings that beyond disease-related factors, sociodemographic factors are independently associated with overall survival in lung NETs. We believe these results will influence future research into the pathogenesis of lung NETs and help identify opportunities for interventions to reduce disparities and improve outcomes.

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REVIEW ARTICLE

One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States

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ABSTRACT

Purpose
Neuroendocrine tumors (NETs) are considered rare tumors and can produce a variety of hormones. In this study, we examined the epidemiology of and prognostic factors for NETs, because a thorough examination of neither had previously been performed.

Methods
The Surveillance, Epidemiology, and End Results (SEER) Program registries were searched to identify NET cases from 1973 to 2004. Associated population data were used for incidence and prevalence analyses.

Results
We identified 35,618 patients with NETs. We observed a significant increase in the reported annual age-adjusted incidence of NETs from 1973 (1.09/100,000) to 2004 (5.25/100,000). Using the SEER 9 registry data, we estimated the 29-year limited-duration prevalence of NETs on January 1, 2004, to be 9,263. Also, the estimated 29-year limited-duration prevalence in the United States on that date was 103,312 cases (35/100,000). The most common primary tumor site varied by race, with the lung being the most common in white patients, and the rectum being the most common in Asian/Pacific Islander, American Indian/Alaskan Native, and African American patients. Additionally, survival duration varied by histologic grade. In multivariate analysis of patients with well-differentiated to moderately differentiated NETs, disease stage, primary tumor site, histologic grade, sex, race, age, and year of diagnosis were predictors of outcome ($P < .001$).

Conclusion
We observed increased reported incidence of NETs and increased survival durations over time, suggesting that NETs are more prevalent than previously reported. Clinicians need to be become familiar with the natural history and patterns of disease progression, which are characteristic of these tumors.

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INTRODUCTION

Neuroendocrine tumors (NETs) consist of a spectrum of malignancies that can arise from neuroendocrine cells throughout the body. These tumors are characterized by their ability to produce peptides that cause characteristic hormonal syndromes. Most are more indolent than other epithelial malignancies; however, they can be aggressive and resistant to therapy. Oberndofer[1] first described these tumors and coined the term carcinoid (or "karzinoide") in 1907.

Although authors have described the incidence of NETs and the racial, sex, and primary tumor site distributions and survival durations in patients with these tumors in the United States, the Netherlands, and the United Kingdom,[2-5] much about them remains unknown. For example, the prevalence of NETs in the general population has not been well described. Furthermore, International Classification of Diseases for Oncology (ICD-O-3) classification of NETs is complex. In particular, a significant number of NETs are not classified using the ICD-O-3 codes associated with carcinoid tumors (8240-8246 and 8249).[6] In our present study, we undertook the most complete analysis of patients with NETs reported to date. We retrospectively analyzed the epidemiology of and prognostic factors for NETs in patients identified in the Surveillance, Epidemiology, and End Results (SEER) database.

Since its inception in 1973, the SEER Program has undergone two major expansions to improve its

representative sampling of the US population. The SEER 9, 13, and 17 registries cover approximately 9.5%, 13.8%, and 26.2%, respectively, of the total US population. In our study, we obtained and analyzed the SEER data based on the November 2006 submission.[7] The data set we used contained a total of 4,926,760 neoplasms in 4,466,501 patients diagnosed from 1973 to 2004.

METHODS

ICD-O-3 histology codes were used to identify NETs. These codes correspond to the following clinical/histologic diagnoses: islet cell carcinoma (8150), insulinoma (8151), glucagonoma (8152), gastrinoma (8153), mixed islet-cell/exocrine adenocarcinoma (8154), vipoma (8155), somatostatinoma (8156), enteroglucagonoma (8157), carcinoid (8240), enterochromaffin cell carcinoid (8241), enterochromaffin-like cell tumors (8242), goblet cell carcinoid (8243), composite carcinoid (8244), adenocarcinoid (8245), neuroendocrine carcinoma (8246), and atypical carcinoid (8249). Small-cell (8002 and 8040-8045) and large-cell neuroendocrine carcinoma (8013) of the lung, pheomochromocytoma (8700), paraganglioma (8680, 8693), and medullary carcinoma of the thyroid (8510) were excluded.

Because a unified staging system for NETs is lacking, the SEER staging system was used for analysis. Tumors were classified as localized, regional, or distant. A localized NET was defined as an invasive neoplasm confined entirely to the organ of origin. A regional NET was defined as a neoplasm that (1) extended beyond the limits of the organ of origin directly into surrounding organs or tissue, (2) involved regional lymph nodes, or (3) fulfilled both of the aforementioned criteria. Finally, a distant NET was defined as a neoplasm that spread to parts of the body remote from the primary tumor.

There is no accepted uniformed grading system for malignant NETs. Pathologists in the United States typically use the terms "carcinoid tumor" or "islet-cell tumor" to denote well-differentiated NETs (G1). The term "atypical carcinoid" is frequently used to describe a moderately differentiated carcinoid and is classified as G2 tumor, poorly differentiated tumors are classified as G3 tumors, and anaplastic tumors are classified as G4 tumors. Tumors with mixed differentiation, such as adenocarcinoid and goblet-cell carcinoid tumors, are classified as having mixed histology.

Comparisons of patients, tumor characteristics, and disease extension were performed using the χ^2 test. One-way analysis of variance was used for comparison of continuous variables between groups. Survival durations were measured using the actuarial or Kaplan-Meier method and compared using the log-rank test. The statistical independence between prognostic variables was evaluated using the Cox proportional hazards model.

SEER*Stat software program (version 6.3.5; National Cancer Institute, Bethesda, MD) was used for incidence and limited-duration prevalence analysis.[7] The counting method, which estimates prevalence by counting the number of persons (first NET for patients with multiple primaries) who are known to be alive at a specific date and adjusting for those lost to follow-up, was used for prevalence analyses.[5,8,9] The expected number of cases lost to follow-up that were included in the prevalence data was calculated using conditional survival curves for cohorts by age, sex, race, year of diagnosis, and primary tumor site. All other statistical calculations were performed using SPSS (version 14.0; SPSS Inc, Chicago, IL). Comparative differences were considered statistically significant when P was less than .05.

RESULTS

Incidence and Prevalence

We identified a total of 35,825 NETs in 35,618 patients in the SEER registries. Using population files linked to the SEER database, we calculated the incidence of NETs per 100,000 per year age-adjusted to the 2000 US standard population. Because the SEER 9, 13, and 17 registries are linked to different population data sets, we computed the age-adjusted incidence for three time periods: SEER 9, 1973 to 1991; SEER 13, 1992 to 1999; and SEER 17, 2000 to 2004. We noted a significant increase in reported annual age-adjusted incidence from 1973 (1.09/100,000) to 2004 (5.25/100,000; Fig 1A). Separate time-trend analyses of the SEER 9, 13, and 17 registries showed significant increases in the reported incidence of NETs ($P < .001$ in all three analyses). Detailed incidence data for 2000 to 2004 are presented in Table 1. We also performed separate time-trend analyses by primary tumor site (Fig 1B) and disease stage at diagnosis (Fig 1C). These analyses showed statistically significant increases in the reported incidence rates over time at all primary sites ($P < .001$) and disease stages ($P < .001$).

In the SEER 9 registry, the estimated 29-year limited-duration prevalence of NETs on January 1, 2004, was 9,263. We projected this prevalence into the US standard population and matched by sex, race, and age. The resulting estimated 29-year limited-duration prevalence of NETs on January 1, 2004, in the United States was 103,312 cases or 35/100,000.

Patient Characteristics

Of the 35,618 patients with NETs identified in the SEER database, 18,614 (52%) were women and 17,004 (48%) were men. Eighty-one percent of the patients were white, 12% were African American, 5% were Asian/Pacific Islander, and 1% were American Indian/Alaskan native. The race of the remaining 1% of the patients was unknown. The median age at diagnosis was 63 years (mean, 62; standard deviation, 15).

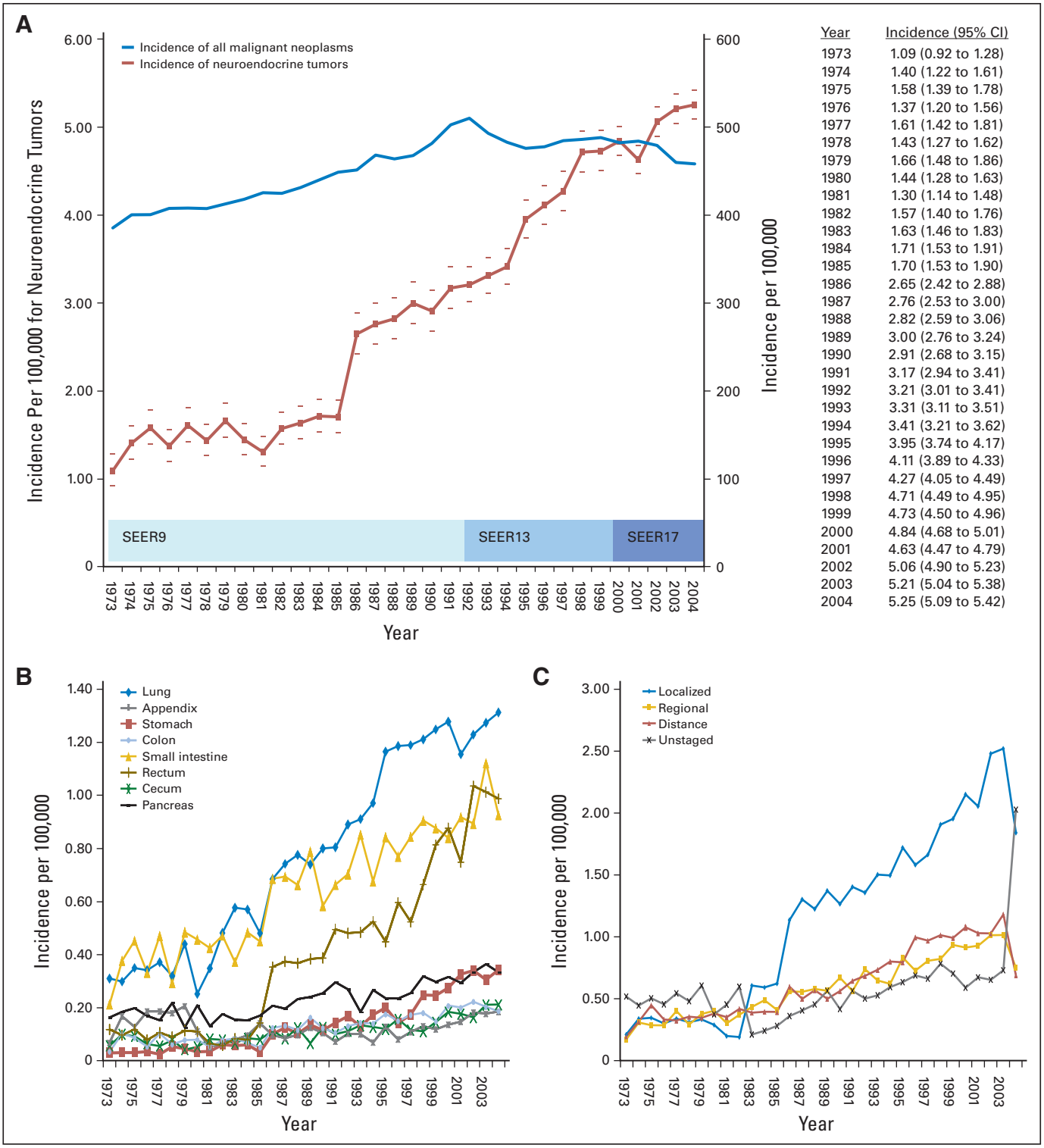
NETs are commonly classified by embryonic origin as foregut, midgut, or hindgut tumors. Of the 35,825 cases, 14,844 (41%) were foregut NETs, 9,266 (26%) were midgut, and 6,963 (19%) were hindgut; in the remaining 4,752 (13%), the primary tumor site was unknown or could not be classified using this system. The disease stage in 7,270 cases (20%) went unreported; of the remaining 28,515 cases, 14,162 (40%) were localized, 6,718 (19%) were regional, and 7,635 (21%) were distant.

Primary Tumor Site

The locations of the primary tumors in these patients varied significantly by sex ($P < .001$; Table 1). Female patients were more likely to have a primary NET in the lung, stomach, appendix, or cecum, whereas male patients were more likely to have a primary tumor in the thymus, duodenum, pancreas, jejunum/ileum, or rectum. The primary tumor sites also varied significantly by race ($P < .001$; Table 1). In particular, the lung was the primary NET site more often among white patients (30%) than among patients in the other racial groups ($P < .001$). Additionally, jejunal/ileal NETs were more common in white (17%) and African American (15%) patients than in Asian/Pacific Islander and American Indian/Alaskan Native patients ($P < .001$). In contrast, rectal NETs occurred at a markedly higher frequency among Asian/Pacific Islander (41%), American Indian/Alaskan Native (32%), and African American (26%) patients than among white (12%) patients ($P < .001$).

Age at Diagnosis

We next examined age at diagnosis of NET by race, sex, and primary tumor site. Overall, African American, Asian/Pacific Islander,



Year	Incidence (95% CI)
1973	1.09 (0.92 to 1.28)
1974	1.40 (1.22 to 1.61)
1975	1.58 (1.39 to 1.78)
1976	1.37 (1.20 to 1.56)
1977	1.61 (1.42 to 1.81)
1978	1.43 (1.27 to 1.62)
1979	1.66 (1.48 to 1.86)
1980	1.44 (1.28 to 1.63)
1981	1.30 (1.14 to 1.48)
1982	1.57 (1.40 to 1.76)
1983	1.63 (1.46 to 1.83)
1984	1.71 (1.53 to 1.91)
1985	1.70 (1.53 to 1.90)
1986	2.65 (2.42 to 2.88)
1987	2.76 (2.53 to 3.00)
1988	2.82 (2.59 to 3.06)
1989	3.00 (2.76 to 3.24)
1990	2.91 (2.68 to 3.15)
1991	3.17 (2.94 to 3.41)
1992	3.21 (3.01 to 3.41)
1993	3.31 (3.11 to 3.51)
1994	3.41 (3.21 to 3.62)
1995	3.95 (3.74 to 4.17)
1996	4.11 (3.89 to 4.33)
1997	4.27 (4.05 to 4.49)
1998	4.71 (4.49 to 4.95)
1999	4.73 (4.50 to 4.96)
2000	4.84 (4.68 to 5.01)
2001	4.63 (4.47 to 4.79)
2002	5.06 (4.90 to 5.23)
2003	5.21 (5.04 to 5.38)
2004	5.25 (5.09 to 5.42)

Fig 1. These graphs show the incidence of neuroendocrine tumors (NETs) over time, by site and by disease stage. (A) Annual age-adjusted incidence of NETs by year (1973 to 2004). The incidence is presented as the number of tumors per 100,000 (with 95% CIs) age-adjusted for the 2000 US standard population. Cases were selected from the Surveillance, Epidemiology, and End Results database (1973 to 2004) using International Classification of Diseases for Oncology histology codes 8150 to 8157, 8240 to 8246, and 8249. (B) Time-trend analyses of the incidence of NETs by primary tumor site (1973 to 2004). Statistically significant increases in incidence at all sites are shown ($P < .001$). (C) The incidence of NETs by disease stage at diagnosis. Statistically significant increases in incidence at all stages are shown ($P < .001$).

Table 1. Incidence and Distribution of NETs by Sex and Race in the SEER 17 Registry (2000-2004)

	Incidence*							Fraction Within Sex and Racial Groups (%)					
		Sex		Race				Sex		Race			
Distribution	All Cases	Male	Female	White	African American	Asian/P Islander	AI/AN	Male	Female	White	African American	Asian/P Islander	AI/AN
All cases	5.00	5.35	4.76	4.92	6.82	3.19	3.07						
Disease stage													
Localized	2.01	2.00	2.05	1.86	3.24	1.68	1.66	47	52	47	57	65	61
Regional	0.88	0.99	0.79	0.90	1.06	0.38	0.52	24	23	25	21	15	19
Distant	1.03	1.18	0.92	1.08	1.17	0.49	0.48	29	25	28	22	20	20
Unstaged	1.08	1.18	1.01	1.08	1.36	0.53	0.53						
Primary tumor site													
Lung	1.35	1.30	1.40	1.45	1.17	0.50	0.70	24	30	30	18	15	22
Thymus	0.02	0.02	0.01	0.02	0.01	0.04	0.00	1	0.2	0.4	0.1	1	1
Stomach	0.30	0.29	0.31	0.29	0.39	0.23	0.35	4	6	5	5	6	9
Duodenum	0.19	0.24	0.16	0.15	0.64	0.18	0.03	4	3	2	7	4	2
Jejunum/ileum	0.67	0.80	0.57	0.71	0.88	0.09	0.09	18	14	17	15	4	5
Cecum	0.16	0.16	0.17	0.17	0.21	0.04	0.09	3	4	4	3	1	1
Appendix	0.15	0.14	0.16	0.16	0.14	0.03	0.02	3	4	4	3	2	1
Colon	0.20	0.23	0.17	0.18	0.38	0.12	0.22	4	4	4	5	4	6
Rectum	0.86	0.92	0.81	0.66	1.80	1.25	1.00	16	14	12	26	41	32
Pancreas	0.32	0.38	0.27	0.32	0.36	0.25	0.20	8	6	7	6	8	10
Liver	0.04	0.03	0.04	0.04	0.05	0.01	0.07	1	1	1	1	0.4	1
Other/unknown	0.74	0.84	0.69	0.77	0.79	0.45	0.30	14	14	15	12	12	11

Abbreviations: SEER, Surveillance, Epidemiology, and End Results database; NETs, neuroendocrine tumors; P Islander, Pacific Islander; AI/AN, American Indian/Alaskan native.
*Age-adjusted annual incidence per 100,000 to the 2000 US standard population.

and American Indian/Alaskan Native patients were younger at diagnosis than white patients were ($P < .001$). We observed no difference in age at diagnosis by sex ($P = .44$). The ages at diagnosis did varied significantly by primary tumor site ($P < .001$). Details regarding age at diagnosis are presented in Table 2.

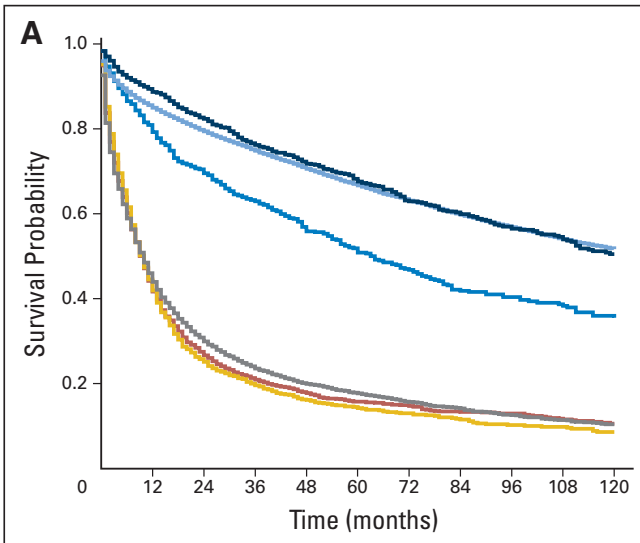
Tumor Stage

Next, we examined factors associated with extent of disease and observed a strong correlation between primary tumor site and disease stage, among the 28,515 cases where stage information was available (Table 2; $P < .001$). We also found that histologic grade was strongly

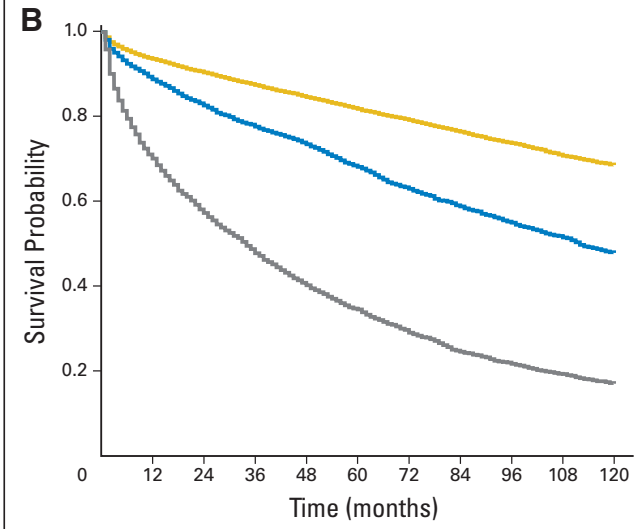
Table 2. Age and Disease Stage at Diagnosis of NETs by Race, Sex, and Primary Tumor Site

	Age at Diagnosis (years)			Disease Stage (%)		
Characteristic	Median	Mean	Standard Deviation	Localized	Regional	Distant
Race						
White	64	62	15	47	25	28
Black	59	59	14	57	21	22
Asian/P Islander	59	59	14	65	15	20
AI/AN	58	57	16	61	19	20
Sex						
Male	63	62	14	47	24	29
Female	63	62	15	52	23	25
Primary tumor site						
Lung	64	62	15	49	23	28
Thymus	59	56	16	28	41	31
Stomach	65	64	15	76	9	15
Duodenum	67	65	14	81	10	9
Jejunum/ileum	66	65	13	29	41	30
Cecum	68	66	14	14	42	44
Appendix	47	48	18	60	28	12
Colon	65	64	14	45	23	32
Rectum	56	57	13	92	4	5
Pancreas	60	59	15	14	22	64
Liver	67	64	15	45	27	28

NOTE. Cases selected from the SEER Program database (1973-2004) using ICD-O-3 histology codes 8150-8157, 8240-8246, and 8249.
Abbreviations: NETs, neuroendocrine tumors; P Islander, Pacific Islander; AI/AN, American Indian/Alaskan native.

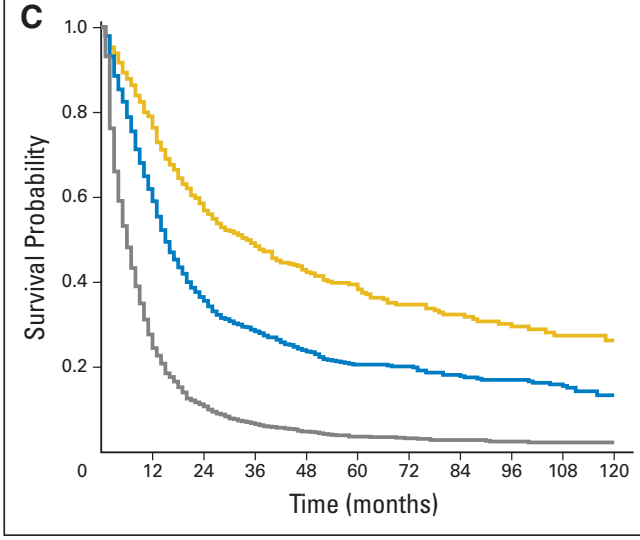


	Median Survival	
	Months	95%CI
Carcinoid/islet cell: well-differentiated	124	101 to 147
Carcinoid/islet cell: unspecified grade	129	124 to 134
Carcinoid/islet cell: moderately differentiated	64	56 to 72
Neuroendocrine: poorly differentiated	10	9 to 11
Neuroendocrine: anaplastic	10	9 to 11
Neuroendocrine: unspecified grade	10	9 to 11



	Median Survival	
	Months	95%CI
Localized	223	208 to 238
Regional	111	104 to 118
Distant	33	31 to 35

	Survival probability		
Year	Localized	Regional	Distant
1	.94	.89	.70
2	.90	.83	.57
3	.87	.78	.48
4	.85	.73	.40
5	.82	.68	.35
6	.79	.63	.29
7	.76	.59	.25
8	.74	.55	.22
9	.71	.51	.19
10	.69	.48	.17



	Median Survival	
	Months	95%CI
Localized	34	27 to 41
Regional	14	13 to 15
Distant	5	4.5 to 5.5

	Survival probability		
Year	Localized	Regional	Distant
1	.76	.59	.25
2	.57	.36	.11
3	.48	.28	.07
4	.42	.24	.05
5	.38	.21	.04
6	.35	.20	.03
7	.32	.18	.03
8	.30	.17	.03
9	.28	.15	.02
10	.27	.13	.02

Fig 2. Survival duration by (A) histology (B) well- and moderately differentiated histology, and (C) poorly differentiated histology. Neuroendocrine tumor cases identified at autopsy or solely on the basis of death certificates were excluded. Median survival durations are presented in months (with 95% CIs).

linked with disease stage ($P < .001$). Among patients with NETs with explicitly stated tumor histologic grades, 21% of those with well-differentiated (G1) tumors and 30% of those with moderately differentiated (G2) tumors had synchronous distant metastasis at diagnosis, whereas 50% of those with poorly differentiated (G3) tumors or undifferentiated (G4) tumors had synchronous distant metastasis at diagnosis.

Other factors associated with disease stage included race and sex (Table 2). White patients were the most likely to present with advanced disease ($P < .001$), with 28% having synchronous distant metastasis at diagnosis. Also, male patients were more likely to have metastasis at presentation than female patients were (29% *v* 25%; $P < .001$).

Survival

For survival analyses, we excluded 521 cases that were identified at autopsy or solely on the basis of death certificates. The median overall survival duration in the remaining 35,097 cases was 75 months. When we examined survival by histologic grade (Fig 2A), we found that the median survival duration in patients with G1 and G2 NETs was 124 and 64 months, respectively. Patients with G3 and G4 tumors had identical survival curves; the median survival duration in these patients was 10 months. Among cases where histologic grade was not explicitly stated, those with ICD-O-3–designated neuroendocrine histology and those with G3 or G4 tumors had identical survival curves; the median survival duration in these patients was 10 months. The survival curves for those with ICD-O-3–designated carcinoid or islet cell histology but an unspecified tumor grade were similar to those for patients with G1 tumors; the median survival duration in these patients was 129 months. The difference in survival duration between the patients with G1, G2, and G3/G4 NETs was statistically significant ($P < .001$).

Survival for G1/G2 tumors. We found several factors, including disease stage ($P < .001$), to be predictors of outcome. The median survival durations in patients with G1/G2 NETs who had localized, regional, and distant disease was 223 months, 111 months, and 33 months, respectively (Fig 2B). We then examined potential prognostic factors for survival duration stratified by disease stage and found the primary tumor site to be a powerful predictor of survival duration ($P < .001$). The median survival durations among patients with localized NETs varied from greater than 360 months (appendiceal tumors) to 111 months (jejunal/ileal tumors) to 50 months (liver tumors). Among patients with regional NETs, the median survival durations varied from 360 months (appendiceal tumors) to 36 months (colon tumors [excluding cecal and rectal tumors]) to 14 months (liver tumors). In addition, among patients with metastasis, the median survival durations varied from 56 months (jejunal/ileal tumors) to 5 months (colon tumors [excluding cecal and rectal tumors]). Details regarding the results of these analyses by primary tumor site are presented in Figure 3A.

Another significant predictor of outcome was histopathology. In addition to tumor grade, the presence of adenocarcinoma features in mixed-histology NETs has been thought to portend a poor prognosis. We compared the survival durations in patients with G1, G2, and mixed-histology NETs stratified by disease stage. Those with G1 tumors had the best outcomes in all stage groups ($P < .001$; Fig 3B). Interestingly, patients with local/regional mixed-histology tumors had better outcomes than did those with G2 NETs. However, among patients with metastatic disease, those with mixed-histology tumors had worse outcomes than did those with G2 NETs.

Age at diagnosis ($P < .001$; Fig 3C), sex ($P < .001$; Fig 3D), and race ($P < .001$; Fig 3E) were also prognostic of survival. Women had better survival durations than men did in all stage categories. Also, Asian/Pacific Islander and American Indian/Alaskan Native patients had the best survival durations among patients with localized disease (median survival duration not reached), whereas white patients had the best survival durations among patients with metastatic disease. We also examined the effect of age at diagnosis on survival by separating the patients into three groups (≤ 30, 31 to 60, and > 60 years). We found age to be a strong predictor of survival duration ($P < .001$; Fig 3C).

Next, we sought to determine whether the survival durations improved in patients with NETs over time. Because the somatostatin analog octreotide was the only new drug introduced for use against NETs during this period (in 1987), we compared the survival durations in patients who received diagnoses from 1973 to 1987 with those who received diagnoses from 1988 to 2004 (Fig 3G). Although the survival durations did not improve significantly among patients with localized NETs (hazard ratio [HR] = 0.96; 95% CI, 0.87 to 1.06; $P = .43$) or regional NETs (HR = 0.91; 95% CI, 0.82 to 1.01; $P = .08$), they improved dramatically among patients with metastatic disease (HR = 0.67; 95% CI, 0.62 to 0.73; $P < .001$).

Finally, we performed multivariate survival analysis of G1/G2 NETs using the Cox proportional hazards model. We included potentially prognostic parameters such as disease stage, primary tumor site, histology, age, sex, race, and period of diagnosis (1973 to 1987 and 1988 to 2004) in this model. We found that all of the parameters that were significant in the univariate analysis were also significant in the multivariate analysis (Table 3).

Survival for G3/G4 tumors. Poorly differentiated NETs, which are also known as high-grade NETs, are aggressive and associated with poor survival. We analyzed the survival of 4,054 patients with G3/G4 NETs in the SEER registries (1973 to 2004). The median survival durations in patients with localized, regional, and distant disease were 34 months (95% CI, 27 to 41 months), 14 months (95% CI, 13 to 15 months), and 5 months (95% CI, 4.5 to 5.5 months), respectively (Fig 2C).

DISCUSSION

In this study, we took advantage of the vast amount of data collected by the SEER Program to examine the largest series of NET cases reported to date with a focus on incidence, prevalence, and prognostic factors. Similar to those of previous reports,[3] our results indicated a significant increase in the reported incidence of NETs over time. This increase was likely caused in part by improvements in classification of these tumors. Also, widespread use of endoscopy for cancer screening likely contributed to the increase in reported incidence of rectal carcinoid NETs. Whether changes in dietary habits, environmental factors, and use of certain medications such as proton pump inhibitors resulted in increased reported incidence of NETs of various types is unknown.

Prevalence of a disease is defined as the number of people alive on a certain date in a population who have never had a diagnosis of that disease. In our study, we used the counting method[8-10] to estimate prevalence from incidence and follow-up data. Complete prevalence can be determined using this method with registries containing data obtained over long periods of time. Given the long survival durations

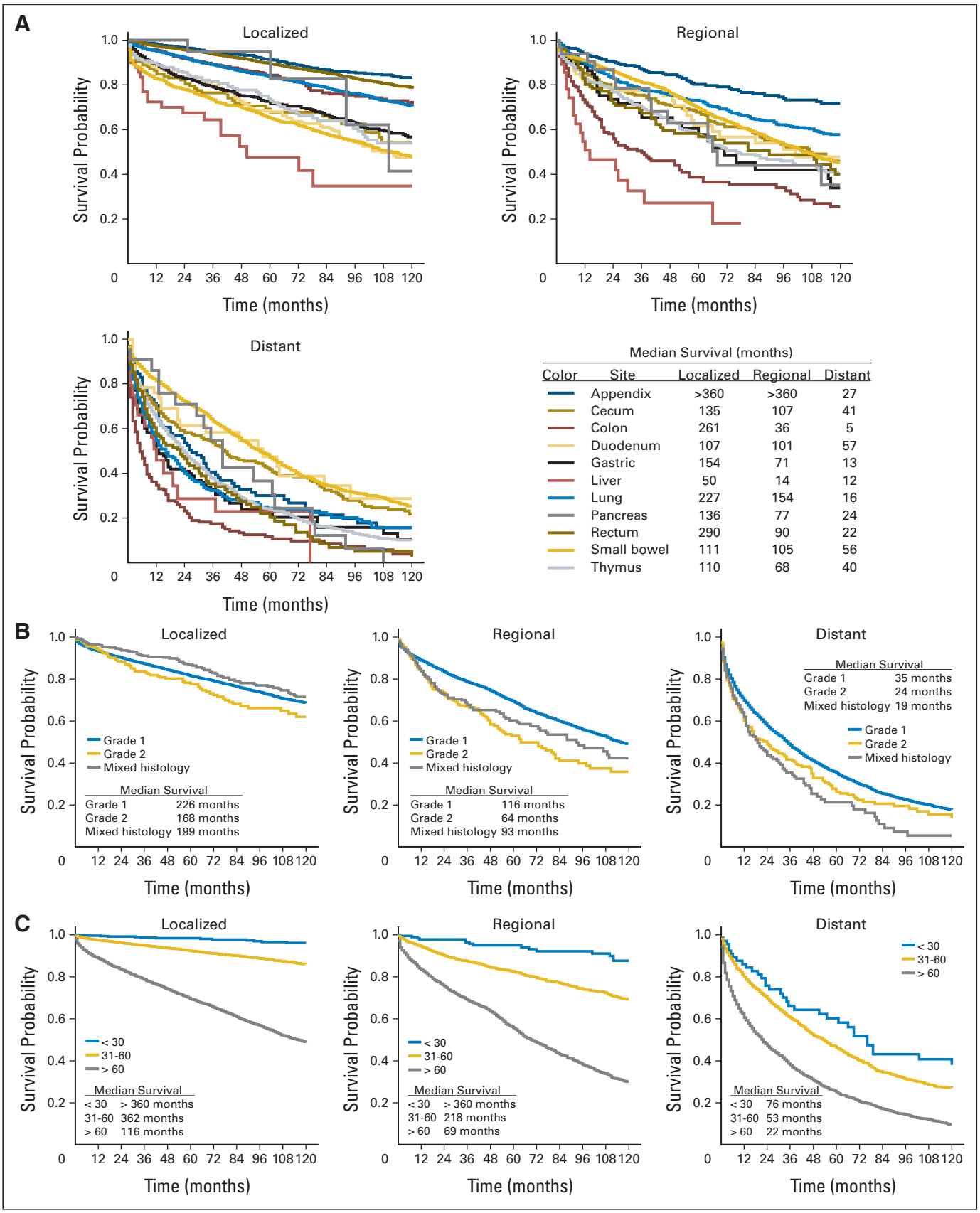


Fig 3. (A) Survival duration by primary tumor site. Neuroendocrine tumor cases identified at autopsy or solely on the basis of death certificates were excluded, as were those with missing site and/or stage data. Median survival durations are presented in months. (B) Survival duration by histology. G1 tumors had the best outcome in all staging groups ($P < .001$).

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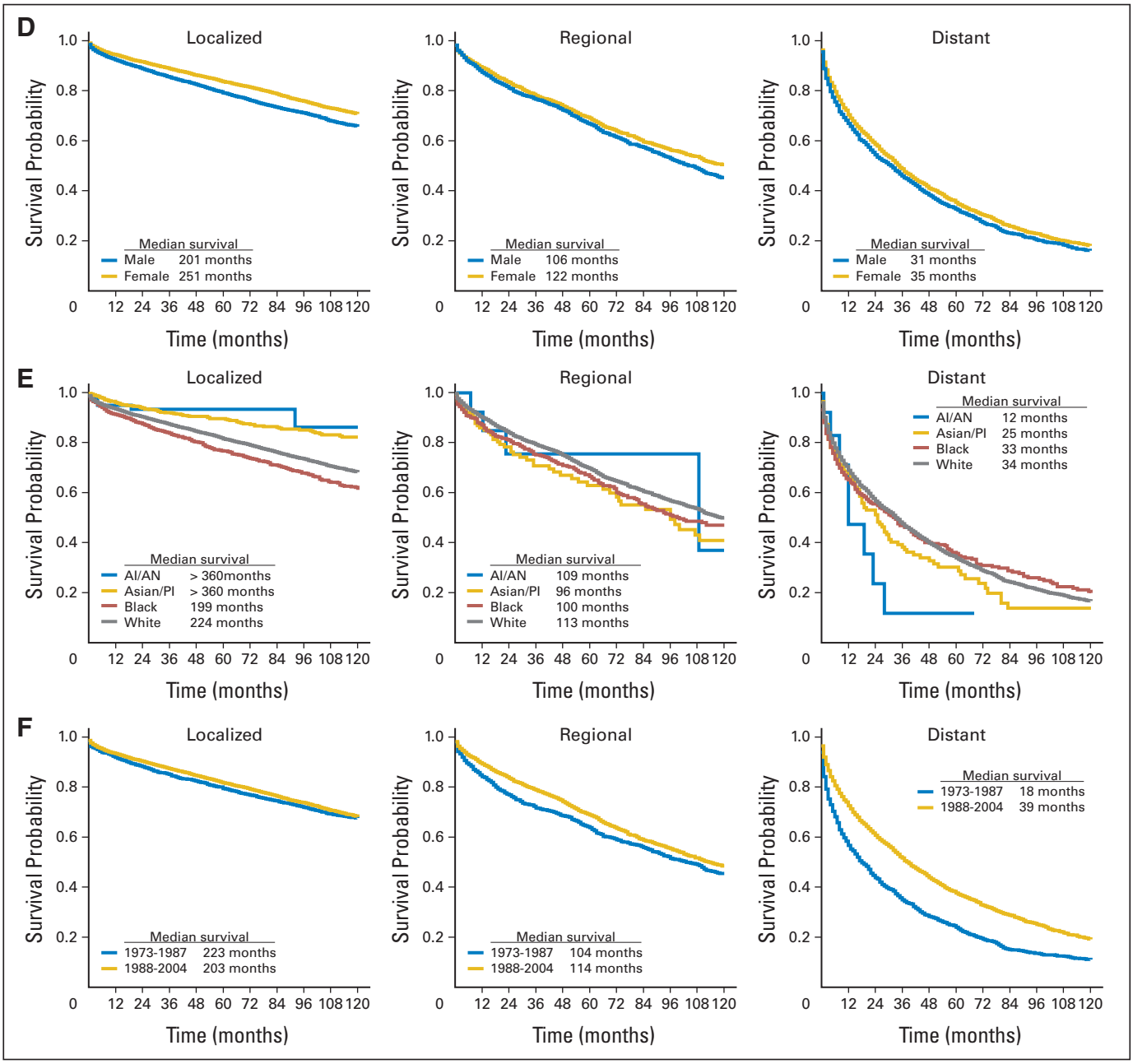

Fig 3 (Continued). (C) Survival duration by age at diagnosis. Patients were separated into three groups according to their age at diagnosis (≤ 30, 31 to 60, and > 60 years). Age was found to be a strong predictor of outcome ($P < .001$). (D) Survival duration by sex. Women had statistically significantly longer survival durations over all three categories histologies ($P < .001$). (E) Survival duration by race. Patients were separated into four categories on the basis of race (American Indian/Alaskan Native [AI/AN], Asian/Pacific Islander [Asian/PI], African American, and white). American Indian/Alaskan Native and Asian/Pacific Islander patients had the longest survival durations for localized tumors, whereas white patients had the longest survival durations for metastatic disease. (F) Survival duration by period of diagnosis. Patients were separated into two groups by year of diagnosis (1973 to 1987 and 1988 to 2004). Patients with metastatic disease had an improvement in median survival duration ($P < .001$; from 8 to 39 months). There were no significant improvements in survival duration among patients with localized or regional disease. Each set of three graphs shows localized, regional, and distant survival from left to right.

often experienced by patients with NETs, we report here only 29-year limited-duration prevalence, which estimates the number of people alive on January 1, 2004, who were diagnosed with NET during the preceding 29 years. Clearly, however, NETs are more common than generally believed. For example, when compared with other GI neoplasms, the estimated 29-year limited-duration prevalence of NETs of 103,312 in 2004 makes these tumors significantly more common than esophageal cancer (28,664), gastric cancer (65,836), pancreatic cancer (32,353), and hepatobiliary cancer (21,427) in the United States.[11]

Using multivariate survival analysis, we found that disease stage, primary tumor site, histology, age, sex, race, and period of diagnosis (1973 to 1987 and 1988 to 2004) were important predictors of outcome. We found the primary tumor site to be perhaps the most useful

Table 3. Survival Analysis of Patients with Well-Differentiated to Moderately Differentiated NETs: Univariate and Multivariate Cox Proportional Hazards Analysis of G1/G2 NETs Diagnosed From 1973 to 2004

Parameter	Median Survival (months)	Univariate		Multivariate		Multivariate *P*
		Hazard Ratio	95% CI	Hazard Ratio	95% CI	
Disease stage						
Localized	223	1*	—	1*	—	< .001
Regional	111	1.89	1.79 to 2.01	1.60	1.50 to 1.71	
Distant	33	4.93	4.68 to 5.21	3.85	3.60 to 4.11	
Primary tumor site						
Jejunum/ileum	88	1*	—	1*	—	< .001
Lung	193	0.53	0.50 to 0.57	1.01	0.93 to 1.08	
Thymus	77	1.12	0.82 to 1.53	1.47	1.06 to 2.03	
Stomach	124	0.83	0.75 to 0.91	1.54	1.38 to 1.73	
Duodenum	99	0.89	0.78 to 0.99	1.42	1.24 to 1.62	
Cecum	83	1.16	1.05 to 1.29	1.06	0.96 to 1.18	
Appendix	NR	0.33	0.29 to 0.37	0.66	0.57 to 0.76	
Colon	121	0.93	0.84 to 1.03	1.54	1.38 to 1.71	
Rectum	240	0.32	0.29 to 0.34	0.74	0.67 to 0.82	
Pancreas	42	1.65	1.53 to 1.78	1.65	1.53 to 1.79	
Liver	23	2.20	1.76 to 2.75	2.92	2.25 to 3.79	
Histology						
Well-differentiated	134	1*	—	1*	—	< .001
Moderately differentiated	64	1.67	1.53 to 1.82	1.26	1.15 to 1.40	
Mixed	135	1.02	0.92 to 1.14	1.65	1.45 to 1.88	
Sex						
Female	145	1*	—	1*	—	< .001
Male	114	1.21	1.16 to 1.26	1.20	1.14 to 1.25	
Race						
White	126	1*	—	1*	—	< .001
AI/AN	NR	0.56	0.36 to 0.87	0.79	0.50 to 1.26	
Asian/P Islander	204	0.65	0.58 to 0.72	0.94 (0.83 to 1.07)		
African American	117	1.04	0.98 to 1.10	1.28	1.19 to 1.37	
Age, years						
≤ 30	NR	1*	—	1*	—	< .001
31-60	247	3.31	2.74 to 4.00	3.03	2.41 to 3.81	
≥ 61	71	10.08	8.36 to 12.15	9.23	7.34 to 11.61	
Year of diagnosis						
1973-1987	95	1*	—	1*	—	< .001
1988-2004	138	0.75	0.72 to 0.79	0.73	0.69 to 0.77	

Abbreviations: NET, neuroendocrine tumor; NR, not reached; AI/AN, American Indian/Alaskan Native; P Islander, Pacific Islander.
*Referent.

predictor of outcome in patients with NETs. Using the primary tumor site as a prognostic marker, we were better able to separate outcomes into categories. We therefore included a table of survival duration by primary tumor site and disease stage for patients who received diagnoses from 1988 to 2004 as a practical guide for clinicians in Table 4.

In our analyses, we did not observe a statistically significant difference in survival duration among patients with local and regional NETs over time. However, we observed a dramatic improvement in survival duration among patients with metastatic NETs diagnosed in the later period (1988 to 2004). One possible explanation is that the introduction of octreotide in 1987 improved the control of carcinoid syndrome and changed the natural history of NETs. For example, carcinoid crisis with severe flushing, diarrhea, and hemodynamic instability, which was a major cause of morbidity and mortality in the past, now occurs rarely. Organ failure, which tends to occur later in the course of illness, is now the major cause of mortality. Whereas many researchers have speculated that octreotide has a disease-stabilizing effect in patients with NETs,[12-14] conclusive data from randomized human studies are lacking.

We acknowledge that our analysis of data obtained from the SEER registries likely underestimated the total number of patients with NETs. Only patients with malignant NETs are included in the SEER registries. Thus, data on many small, benign-appearing tumors (ie, appendiceal tumors) likely are excluded from the registries. Whereas histologic evidence of invasion of a basement membrane defines malignant behavior for most epithelial malignancies, the definition of malignant behavior for NETs is more complex. In the absence of obvious malignant behavior, such as direct invasion of adjacent organs and metastasis to regional lymph nodes or distant sites, classifying a NET as benign or malignant may be difficult. Thus, whereas SEER registry data provide important information about malignant NETs, the extent to which these data underestimate the frequency of small, benign-appearing NETs is unknown.

Table 4. Survival Analysis of Patients with Well-Differentiated to Moderately Differentiated NETs: Actuarial Survival by Disease Stage and Primary Tumor Site in Patients With G1/G2 NETs Diagnosed From 1988 to 2004

Primary Tumor Site	Localized				Regional				Distant			
	Median Survival (months)	Survival Rate (%)			Median Survival (months)	Survival Rate (%)			Median Survival (months)	Survival Rate (%)		
		3-Year	5-Year	10-Year		3-Year	5-Year	10-Year		3-Year	5-Year	10-Year
Thymus	92	93	93	52	68	78	65	49	40	62	32	0
Lung	NR	89	84	70	151	77	72	56	17	34	27	15
Pancreas	NR	83	79	58	111	73	62	46	27	42	27	11
Liver	47	64	43	—	14	32	27	—	12	34	26	0
Gastric	163	80	73	56	76	75	65	43	13	33	25	9
Duodenum	112	80	68	48	69	75	55	44	57	60	46	27
Jejunum/ileum	115	73	65	49	107	83	71	46	65	70	54	30
Cecum	135	74	68	55	107	78	71	44	55	61	48	23
Colon	NR	90	85	74	52	60	46	33	7	20	14	6
Rectum	NR	94	90	80	90	74	62	47	26	37	24	3
Appendix	NR	93	88	72	NR	86	78	67	31	42	25	11

Abbreviations: NET, neuroendocrine tumor; NR, not reached.

At present, surgery is the only curative treatment for NETs, and is recommended for most patients for whom cross-sectional imaging suggests that complete resection is possible.[15,16] Although NETs generally have a better prognosis than adenocarcinomas at the same site, NETs are incurable once they advance to unresectable metastatic disease. New therapeutic approaches for NETs, such as peptide receptor radiotherapy and systemic agents targeting vascular endothelial growth factor and mammalian target of rapamycin, are under development.[17]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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JAMA Oncology | Original Investigation

Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States

Arvind Dasari, MD, MS; Chan Shen, PhD; Daniel Halperin, MD; Bo Zhao, MS; Shouhao Zhou, PhD; Ying Xu, MD; Tina Shih, PhD; James C. Yao, MD

IMPORTANCE The incidence and prevalence of neuroendocrine tumors (NETs) are thought to be rising, but updated epidemiologic data are lacking.

OBJECTIVE To explore the evolving epidemiology and investigate the effect of therapeutic advances on survival of patients with NETs.

DESIGN, SETTING, AND PARTICIPANTS A retrospective, population-based study using nationally representative data from the Surveillance, Epidemiology, and End Results (SEER) program was conducted to evaluate 64 971 patients with NETs from 1973 to 2012. Associated population data were used to determine annual age-adjusted incidence, limited-duration prevalence, and 5-year overall survival (OS) rates. Trends in survival from 2000 to 2012 were evaluated for the entire cohort as well as specific subgroups, including distant-stage gastrointestinal NETs and pancreatic NETs. Analyses were conducted between December 2015, and February 2017.

MAIN OUTCOMES AND MEASURES Neuroendocrine tumor incidence, prevalence, and OS rates.

RESULTS Of the 64 971 cases of NETs, 34 233 (52.7%) were women. The age-adjusted incidence rate increased 6.4-fold from 1973 (1.09 per 100 000) to 2012 (6.98 per 100 000). This increase occurred across all sites, stages, and grades. In the SEER 18 registry grouping (2000-2012), the highest incidence rates were 1.49 per 100 000 in the lung, 3.56 per 100 000 in gastroenteropancreatic sites, and 0.84 per 100 000 in NETs with an unknown primary site. The estimated 20-year limited-duration prevalence of NETs in the United States on January 1, 2014, was 171 321. On multivariable analyses, the median 5-year OS rate varied significantly by stage, grade, age at diagnosis, primary site, and time period of diagnosis. The OS rate for all NETs improved from the 2000-2004 period to the 2009-2012 period (hazard ratio [HR], 0.79; 95% CI, 0.73-0.85). Even larger increases in OS between these periods were noted in distant-stage gastrointestinal NETs (HR, 0.71; 95% CI, 0.62-0.81) and distant-stage pancreatic NETs (HR, 0.56; 95% CI, 0.44-0.70).

CONCLUSIONS AND RELEVANCE The incidence and prevalence of NETs are steadily rising, possibly owing to detection of early-stage disease and stage migration. Survival for all NETs has improved over time, especially for distant-stage gastrointestinal NETs and pancreatic NETs in particular, reflecting improvement in therapies. These data will help to prioritize future research directions.

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Invited Commentary
page 1343

Author Audio Interview

Supplemental content

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Given the rarity and indolent clinical course of neuroendocrine tumors (NETs), the epidemiology of these tumors is best studied in large, population-based registries with considerable longitudinal follow-up.[1-3] The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program is a comprehensive source of population-based information initiated in 1973 that is updated annually.[4,5] Previously, the most comprehensive population-based study of NETs in the United States had been performed by our group using the November 2006 submission of SEER data with cases diagnosed up to 2004 that showed increasing incidence.[1] Since then, the SEER Program has expanded and the current (SEER 18) registry grouping now includes approximately 30% of the US population. Diagnostic techniques for NETs, such as computed tomography and endoscopy, have improved and have likely increased NET diagnosis rates and accuracy of staging.[6-8] In addition, updated staging and grading classifications for NETs have been proposed and more universally adopted, possibly further increasing the recognition of NETs and improving their pathologic classification.[9-11] Based on these observations, we hypothesized that the increased incidence of NETs is associated mainly with the rise in detection of early-stage disease.

The somatostatin analogue octreotide acetate was initially introduced in 1987 and as a long-acting release form in 1998 for management of carcinoid syndrome given their ability to inhibit hormone secretion by NETs.[12] With the lack of adequate treatment options for NETs until recently, these agents were likely used for tumor control even before the completion of randomized trials (octreotide long-acting release in midgut NETs in 2008 and lanreotide acetate for gastroenteropancreatic NETs in 2011) establishing their efficacy.[1,13-15] In addition, for pancreatic NETs, the alkylating agent streptozocin was the first drug approved in 1982; further research in the mid-2000s showed that another alkylating agent, temozolomide, also had antitumor activity.[16,17] Given the rise in early-stage disease and improvements in systemic therapies, we also hypothesized that the limited-duration prevalence (the proportion of patients alive on a certain day and diagnosed within a limited duration prior to that date) would also be increasing. Therefore, in the present study, we attempted to comprehensively evaluate the demographic, clinical, and prognostic features of NETs using data from the SEER Program.

Key Points

Question Has the epidemiology of neuroendocrine tumors changed over time?

Findings In this population-based study that included 64 971 patients with neuroendocrine tumors, age-adjusted incidence rates increased 6.4-fold between 1973 and 2012, mostly for early-stage tumors. Survival for all neuroendocrine tumors has improved, especially for distant-stage gastrointestinal and pancreatic neuroendocrine tumors.

Meaning Neuroendocrine tumors are increasing in incidence and prevalence owing to increased diagnosis of early-stage tumors. Survival of patients with distant-stage tumors has improved, reflecting improvements in therapies.

Methods

Data Source

The SEER database on the November 2014 submissions was used for our study.[4] The SEER Program is a coordinated system of population-based state cancer registries collecting incidence and survival data on cases reported from the target geographic areas. Since its inception in 1973 (SEER 9 registry), the program has undergone 2 major expansions to include additional areas (SEER 13 in 1992 and SEER 18 in 2000) and currently includes 20 geographic areas with demographics representative of the entire US population. The pertinent population data are obtained from the US Census Bureau and mortality data are obtained from the US National Center for Health Statistics. Strict quality control is maintained by the SEER Quality Improvement program that establishes standards for cancer registries and maintains them through continual monitoring, assessment, and education.[5] We used histologic codes from the *International Classification of Diseases for Oncology, 3rd Edition*, to identify patients with NETs, as detailed in a prior publication.[1] Per policy of The University of Texas MD Anderson Cancer Center, no institutional review board approval was required for the study. Data analysis was conducted between December 2015, and February 2017.

NET Classification

We used SEER histologic grade information to classify cases as grade (G) 1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; and G4, undifferentiated or anaplastic. G3 and G4 were combined into 1 category for all analyses.

Statistical Analysis

Given that there are 3 SEER registry groupings, to maximize the representativeness of our study, we calculated the 1973-2012 incidences using SEER 9, the 1992-1999 incidences using SEER 13, and the 2000-2012 incidences using SEER 18 databases. Limited-duration prevalence rates were calculated for 10 and 20 years. We examined the 15-year survival by site and stage using the Kaplan-Meier method and log-rank test. Furthermore, we provided the median overall survival (OS) by site, stage, and grade with a maximum follow-up time of 30 years using data from the SEER 9 registry. Finally, we provided the most recent median, 3-year, and 5-year survival rates for distant-stage G1 and G2 NETs from the SEER 18 cohort. Time of follow-up for all analyses was from the date of diagnosis until death, date of last contact, or end of study period.

To evaluate the most recent trends in survival, we conducted multivariable survival analyses of the SEER 18 data (2000-2012). Three cohorts were identified for multivariable survival analyses: the total SEER 18 NET cohort, which comprised all patients with NETs in SEER 18; the distant-stage gastrointestinal NET cohort (liver was excluded since it had a high probability of being a metastatic rather than primary site); and the distant-stage pancreatic NET cohort. The latter 2 cohorts

were chosen to evaluate the effect of advances in systemic therapies for these sites on survival. Distant-stage pancreatic NETs were analyzed separately given the unique biology and clinical behavior of this subgroup. Five-year OS and the Cox proportional hazards model were used in the multivariable analysis, with censoring applied at 5 years.[18] Covariates for this analysis included factors known to influence prognosis of NETs, including grade, race, age, stage, site, and time interval from diagnosis.[1,2] The overall model was significant at $P < .001$.

Incidence (including annual percentage change) and limited-duration prevalence rates (10-year and 20-year) were calculated using SEER*Stat software, version 8.2.1 (Surveillance Research Program, National Cancer Institute). In this software, annual percentage change is calculated by fitting a least-squares regression to the natural logarithm of the rates, using the calendar year as a regressor variable, and age-adjusted incidence rates are computed using weighted proportions of corresponding age groups in the 2000 US standard population. The projected prevalence of NETs in the US population on January 1, 2014, matched by age, sex, and race, was calculated using ProjPrev, version 1.0.4 (Data Modeling Branch, National Cancer Institute).

All other statistical analyses were performed using SAS, version 9.3 (SAS Institute). Comparative differences were considered significant at $P < .05$.

Results

The data set that we used contained a total of 64 971 patients, including 7294, 10 631, and 64 971 in SEER 9, 13, and 18 registries, respectively. Of these patients, 34 233 (52.7%) were women. The annual number of NET cases and the numbers at risk are detailed in eTable 1 in the Supplement. Of 45 318 NETs with a known grade, 23 126 were G1, 7416 were G2, and 14 766 were G3 and G4. Of 53 465 NETs with a known stage, 28 031 were localized, 10 777 were regional, and 14 657 were distant at the time of diagnosis.

Annual Incidence

The annual age-adjusted incidence of NETs was 1.09 per 100 000 persons in 1973 and increased to 6.98 per 100 000 persons by 2012 as shown in **Figure 1**A (and contrasted with annual age-adjusted incidence of all malignant neoplasms). Age-specific incidence rates were calculated for 3 age groups: younger than 50 years, 50 to 64 years, and 65 years or older. The most dramatic rise in incidence was noted in patients 65 years or older with a more than 8-fold rise to 25.3 per 100 000 persons and, in those 50 to 64 years, to 14.3 per 100 000 persons; those younger than 50 years had a more modest 3-fold rise to 1.75 per 100 000 persons (eTable 1 in the Supplement). The annual percentage change for age-adjusted incidence from 2000 to 2012 in SEER 18 was 3.2 per 100 000 persons ($P < .001$).

The increase in the incidence of NETs from 1973 to 2012 occurred across all sites, stages, and grades. The increases in incidence for various sites ranged from 15-fold in the stomach to 2-fold in the cecum (Figure 1B). Among stage groups, the incidence increased the most in localized NETs, from 0.21 per 100 000 persons in 1973 to 3.15 per 100 000 persons in 2012 ($P < .001$) (Figure 1C). Among grade groups, incidence increased the most in G1 NETs, from 0.01 per 100 000 persons in 1973 to 2.53 per 100 000 persons in 2012 ($P < .001$) (Figure 1C). In SEER 18 (2000-2012), the highest incidences were 1.49 per 100 000 persons in the lung, 3.56 per 100 000 persons in gastroenteropancreatic sites (including 1.05 per 100 000 persons in the small intestine, 1.04 per 100 000 persons in the rectum, and 0.48 per 100 000 persons in the pancreas), and 0.84 per 100 000 persons in NETs with an unknown primary site of origin.

Prevalence

Reflecting the rising incidence and indolent nature of NETs, the 20-year limited-duration prevalence increased substantially, from 0.006% in 1993 to 0.048% in 2012 ($P < .001$) (**Figure 2**A). Ten-year limited-duration prevalence and absolute counts for both time periods are detailed in eTable 2 in the Supplement. Among grade groups, prevalence increased the most in G1 NETs and, among sites, prevalence was highest in the rectum, followed by the lung and small intestine (Figure 2). The projected prevalence of NETs in the US population on January 1, 2014, matched by age, sex, and race, was 171 321 per 100 000 persons.

Survival

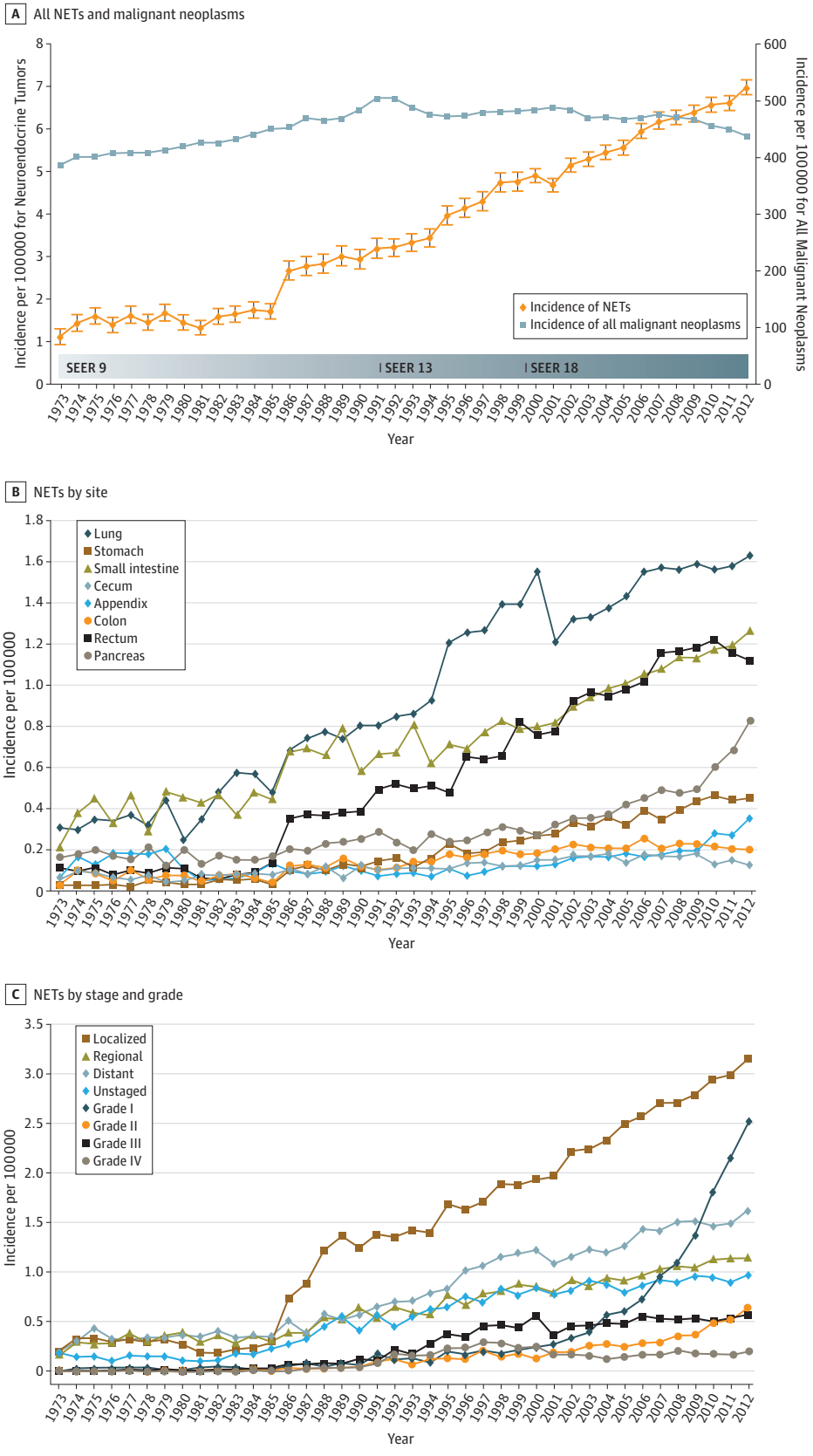
The median OS time for all patients was 9.3 years (112 months). Localized NETs had better median OS (>30 years) compared with regional NETs (10.2 years) and distant NETs (12 months) ($P < .001$). Of those with known grades, G1 NETs had the highest median OS (16.2 years) among grade groups, G2 NETs had the worse OS (8.3 years), and G3 and G4 NETs had the worst OS (10 months). NETs in the rectum (24.6 years) and appendix (>30.0 years) had the best median OS among site groups, while NETs in the pancreas (3.6 years) and lung (5.5 years) had the worst median OS. All these differences in survival were significant (log-rank $P < .001$).

We then evaluated survival patterns according to site and stage (**Figure 3**). In localized NETs, median OS ranged from 14 years in the small intestine to more than 30 years in the appendix. In regional NETs, median OS ranged from 33 months for NETs with an unknown primary to more than 30 years in the appendix. For distant NETs, those in the small intestine had the best median OS (5.83 years); NETs in the lung (6 months) and colon (4 months) had the worst median OS. All of these differences in OS were significant (log-rank $P < .001$).

Next, we evaluated OS according to site and grade. Patients with G1 or G2 appendiceal NETs or G1 rectal NETs had the longest median OS (>30 years). Irrespective of site, patients with G3 and G4 NETs had poor OS, ranging from 30 to 33 months for the small intestine and appendix, respectively, to 8 months for the cecum and colon ($P < .001$) (Figure 3).

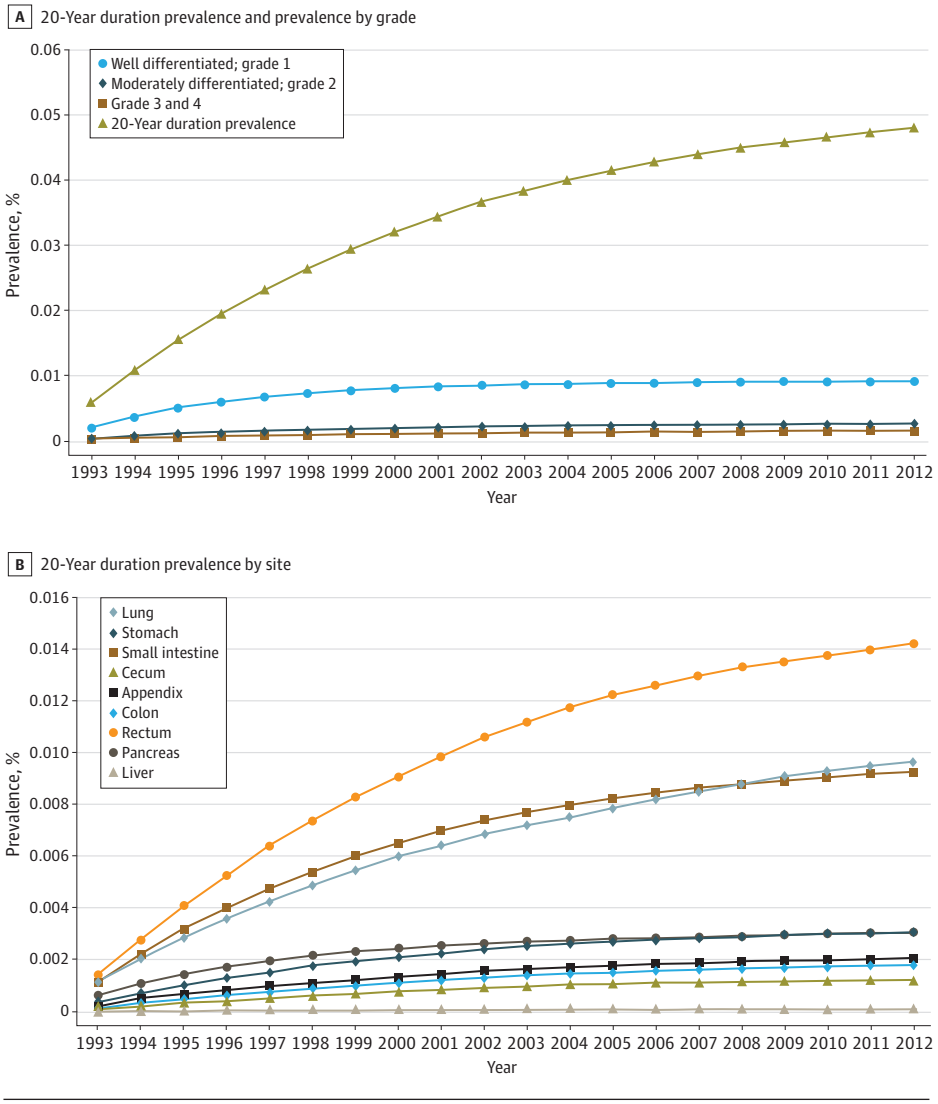
Finally, we evaluated the median, 3-year, and 5-year survival rates for well-differentiated to moderately differentiated distant stage NETs in the SEER 18 cohort (2000-2012) since we believed that this information would be most helpful for practicing clinicians (eTable 3 in the Supplement).

Figure 1. Incidence Trends of Neuroendocrine Tumors (NETs) From 1973 to 2012



A, Annual age-adjusted incidence of all neuroendocrine tumors and all malignant neoplasms. B, Annual age-adjusted incidence of NETs by site. C, Annual age-adjusted incidence of NETs by stage and grade.

Figure 2. Limited Duration Prevalence of Neuroendocrine Tumors (NETs)



A, 20-Year limited duration prevalence of all neuroendocrine tumors and according to grade. B, 20-Year limited duration prevalence of neuroendocrine tumors by site.

Multivariable Analysis of OS

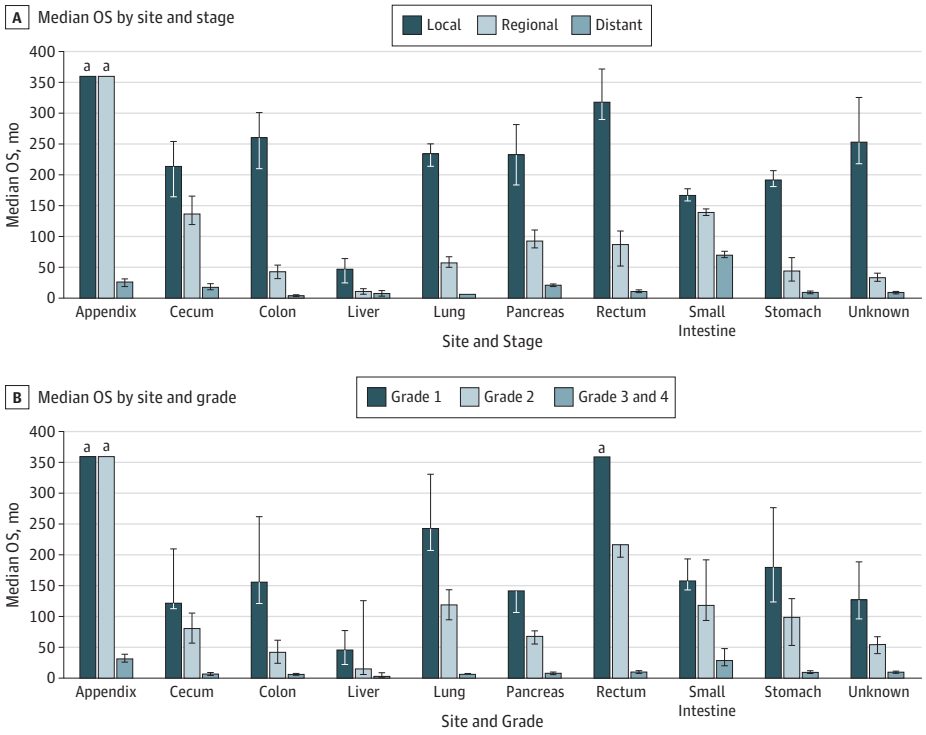
We next performed multivariable analysis with hazard ratios (HRs) calculated for 5-year mortality hazard rates (**Table**). We found that patients with G2 NETs (HR, 1.76; 95% CI, 1.59-1.94) and G3 and G4 NETs (HR, 5.26; 95% CI, 4.85-5.71) had worse OS than did those with G1 NETs. Race, age, stage, and site were all found to have significant correlation with survival. Overall survival was worse in regional NETs (HR, 1.73; 95% CI, 1.57-1.90) and distant NETs (HR, 5.05; 95% CI, 4.64-5.50) than in localized NETs after adjustment for other covariates. NETs in the liver had the worst OS (HR, 1.85; 95% CI, 1.46-2.36) and NETs in the stomach had the second-worst OS (HR, 1.20; 95% CI, 1.07-1.34) compared with NETs in the lung.

We then focused on the SEER 18 cohort to evaluate the most recent trends in OS over 3 time periods: 2000-2004, 2005-2008, and 2009-2012. In the overall SEER 18 cohort, compared with 2000-2004, patients who received the NET diagnosis between 2005 and 2008 had a 17.1% lower risk of death (HR, 0.83; 95% CI, 0.78-0.89) and those diagnosed in 2009-2012 had a 21.3% lower risk of death (HR, 0.79; 95% CI, 0.74-0.85). In these 2 subcohorts, we also found better survival in recent years compared with previous years. The improvement in survival over the same time intervals was more pronounced in the subgroup with distant GI NETs (HR, 0.76; 95% CI, 0.67-0.86 for 2005-2008 and HR, 0.71; 95% CI, 0.63-0.82 for 2009-2012 compared with 2000-2004). The subgroup with distant pancreatic NET saw the biggest improvements. Compared with patients who received the NET diagnosis in 2000-2004, those diagnosed in 2005-2008 had a 24% reduction in risk of death (HR, 0.76; 95% CI, 0.61-0.96) and those diagnosed in 2009-2012 had a 44% reduction in risk of death (HR, 0.56; 95% CI, 0.44-0.71). All of the above comparisons were significant at $P < .001$.

Discussion

In this population-based study, we found that the age-adjusted annual incidence of NETs increased from 1.09 per

Figure 3. Median Overall Survival (OS) of Neuroendocrine Tumors



A, Median OS of all patients included in study according to stage. B, Median OS of all patients included in study according to grade. Error bars indicate 95% CI.

[a] Maximum follow-up time was 360 months.

100 000 in 1973 to 6.98 per 100 000 in 2012, a 6.4-fold increase. Survival of patients with NET has improved over time, and this increase was especially pronounced in distant gastrointestinal NETs and in distant pancreatic NETs, reflecting improvements in therapies for those sites.

Although prior studies done across the world have also shown a rise in the incidence of NETs, this elevation has been most marked in North American studies. Whether these differences are due to underlying biologic factors, environmental factors, health care patterns, and/or data capture by registries is unknown.[1-3] Although the increase in incidence occurred across all sites and all stages during this period, it was markedly greater for the localized stage, possibly due to an increased diagnosis of asymptomatic, early-stage disease. This finding is supported by a Canadian population-based study that showed that, despite the overall increase in the incidence of NETs, the proportion of patients with metastatic disease has remained constant over time.[3] In the present study, we provide extensive details regarding the trends at each site during a much longer time period and show that the rise in incidence was greatest in the stomach (15-fold) and rectum (9-fold). The trends at these sites may be associated with the increased use of endoscopic procedures. The steady rise in the incidence of NETs at other common sites, including the lung and small intestine, is probably related to increased use of imaging procedures in clinical practice. Similarly, the steep rise in G1 NETs is possibly related to increased recognition and widespread adoption of the formalization of the nomenclature, grading, and staging of these tumors.[11] To highlight the burden of NETs, we evaluated the rising prevalence in the form of 20-year and 10-year limited-duration prevalence rates. Since these prevalence rates include patients irrespective of whether they are under treatment or considered cured, they are a composite of the incidence and survival rates. The age-, sex-, and race-adjusted 20-year limited duration prevalence for the US population for January 1, 2014, was estimated to be 171 321, which is significantly higher than the previously reported prevalence of 103 312 in 2004.[1]

Survival analyses using SEER 18 confirmed prior findings of the prognostic significance of age, sex, histologic grade, primary site, and stage at diagnosis.[1,2] Most cases that were coded as liver likely represented metastatic disease from other primary sites, thus making for a very heterogeneous group but with poor outcomes overall. The improvements in survival for the entire cohort over time were likely driven largely by factors pertaining to nonmetastatic disease and may be due in part to the changes in the incidence discussed above, including a higher proportion of relatively more indolent NETs, such as gastric and rectal carcinoids, being discovered that would have otherwise gone undetected. Stage migration (also known as the "Will Rogers phenomenon") also may have occurred affecting survival owing to improvements in general radiology techniques, such as more sensitive computed tomography and magnetic resonance imaging. Improvements in the management of NETs, including development of octreoscans in the late 1980s, and the adoption of standardized staging and pathology guidelines may also have contributed.[19]

To evaluate the effect of the evolution of systemic therapies on survival, we evaluated OS trends of distant-stage NETs in the SEER 18 registry grouping, with subgroup analyses in distant gastrointestinal NETs and distant pancreatic NETs. We found improvements in OS in all distant NETs in SEER 18 over

Table. Multivariable Survival Analysis of Patients With NETs Diagnosed From 2000 to 2012

Covariate	HR (95% CI)		
	Total SEER 18 NET Cohort (n = 14 757)	Distant GI NET (n = 2681)	Distant Pancreatic NET (n = 850)
Year			
2000-2004	1 [Reference]	1 [Reference]	1 [Reference]
2005-2008	0.83 (0.78-0.89)	0.76 (0.67-0.86)	0.76 (0.61-0.96)
2009-2012	0.79 (0.73-0.85)	0.71 (0.62-0.81)	0.56 (0.44-0.70)
Grade			
1: Well differentiated	1 [Reference]	1 [Reference]	1 [Reference]
2: Moderately differentiated	1.76 (1.59-1.94)	1.81 (1.52-2.14)	1.36 (1.04-1.77)
3 and 4: Poorly differentiated and undifferentiated; anaplastic	5.26 (4.85-5.71)	6.72 (5.89-7.67)	4.81 (3.85-6.02)
Race			
White	1 [Reference]	1 [Reference]	1 [Reference]
American Indian/Alaska Native	1.45 (1.00-2.11)	1.73 (0.86-3.47)	2.07 (0.66-6.50)
Asian or Pacific Islander	1.03 (0.91-1.17)	1.40 (1.11-1.76)	1.00 (0.69-1.46)
Black	1.23 (1.13-1.34)	1.31 (1.12-1.52)	1.28 (0.98-1.68)
Age, y			
≤30	0.23 (0.17-0.33)	0.46 (0.28-0.76)	0.44 (0.23-0.86)
31-60	0.54 (0.51-0.57)	0.62 (0.56-0.69)	0.58 (0.48-0.70)
≥61	1 [Reference]	1 [Reference]	1 [Reference]
Stage		NA	NA
Localized	1 [Reference]		
Regional	1.73 (1.57-1.90)		
Distant	5.05 (4.64-5.50)		
Site		NA	NA
Lung	[Reference]		
Appendix	0.53 (0.43-0.65)		
Cecum	0.81 (0.72-0.91)		
Colon	0.99 (0.88-1.12)		
Liver	1.85 (1.46-2.36)		
Pancreas	0.86 (0.78-0.94)		
Rectum	0.71 (0.62-0.82)		
Small intestine	0.53 (0.48-0.59)		
Stomach	1.20 (1.07-1.34)		

Abbreviations: HR, hazard ratio; NA, not applicable; NET, neuroendocrine tumor; SEER, Surveillance, Epidemiology, and End Results.

time, with pronounced improvements in OS in distant gastrointestinal NETs and distant pancreatic NETs. It is likely that these trends are an underestimation of the true impact of recent advances in systemic therapies for these subtypes, given the data's inability to account for more recent drug approvals.[15,20-22] Furthermore, these favorable trends in the survival of patients with metastatic NETs will likely continue as data on newer agents, such as peptide receptor radionuclide therapy, become integrated into routine clinical care.[23] A large volume of retrospective data from Europe supports the efficacy of peptide receptor radionuclide therapy in well-differentiated NETs that show adequate expression of somatostatin receptors as demonstrated by activity on somatostatin receptor scintigraphy.[24] The recently completed phase 3 Neuroendocrine Tumors Therapy-1 trial, although limited to small-bowel NETs, provides the first randomized data and firmly establishes the activity of this modality.[23] It is likely that peptide receptor radionuclide therapy and other peptide radionuclide conjugate therapies targeted toward somatostatin receptors currently in development will have a significant effect on the natural history of NETs arising at sites other than the small bowel.

Limitations

Our study has several limitations. First, given that NETs may not have been reported to cancer registries unless considered malignant, it is likely that we have underestimated their true incidence and prevalence. Second, several known prognostic indicators are not captured by the SEER database. In addition, the database does not provide information regarding the functional status of the NETs that may also affect treatment decisions and survival. Finally, treatment factors, such as quality of surgery, time to diagnosis, and systemic therapy, were unavailable and may have confounded the results. Such drawbacks are inherent to any retrospective, population-based study and may raise concerns about the generalizability of the findings. However, the size of the present study, which we believe to be the largest to date, and the long duration of follow up compensate to a great extent and provide a comprehensive epidemiologic picture of NETs.

Conclusions

The incidence and prevalence of NETs have continued to rise in the United States, owing to the increased diagnosis of early-stage disease and possibly stage migration. The survival of patients with NETs has improved, and this improvement has been greater for those with distant gastrointestinal NETs and, in particular, distant pancreatic NETs.

ARTICLE INFORMATION

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Study concept and design: Dasari, Shen, Halperin, Yao.
Acquisition, analysis, or interpretation of data: Dasari, Shen, Zhao, Zhou, Xu, Shih, Yao.
Drafting of the manuscript: Dasari, Shen, Zhao.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Dasari, Shen, Zhao, Zhou, Yao.
Obtained funding: Yao.
Administrative, technical, or material support: Halperin, Yao.
Supervision: Dasari, Xu, Shih, Yao.

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RESEARCH ARTICLE Open Access

Incidence and prevalence of neuroendocrine tumors of the lung: analysis of a US commercial insurance claims database

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Abstract

Background: As reported in Surveillance, Epidemiology, and End Results (SEER) data, US incidence and prevalence of neuroendocrine tumors (NET) has increased over recent years. The study objective was to update incidence and prevalence information for lung NET using administrative claims.

Methods: This descriptive epidemiological study used 2009–2014 data from 2 US claims databases: MarketScan and PharMetrics. Patients (18–64 years old) had ≥1 inpatient or ≥ 2 outpatient claims with NET of bronchus or lung, identified by International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes. Prevalence was number of lung NET patients divided by number of enrollees/year. Incidence was number of patients with a first observed NET diagnosis who were disease-free for 2 years prior, divided by number of enrollees. Age and gender adjustments performed.

Results: The annual number of patients with lung NET identified from 2009 to 2014 ranged from 435 to 796 (MarketScan) and 419–648 (PharMetrics). In MarketScan, there was a 7.4% (95%CI 2.1–13.0; $p = 0.027$) annual percent change (APC) in the age-adjusted incidence for males and 6.8% (− 0.2–14.3; 0.052) for females. In PharMetrics, APC was − 2.9% (− 13.8–9.4; 0.395) for males; 14.7% (− 12.9–51.2; 0.165) for females. In MarketScan, APC in age-adjusted prevalence for males was 9.9% (4.7–15.3; 0.006); 16.2% (11.4-21.1; <.001) for females. For PharMetrics, APCs were 9.5% (2.3–17.2; 0.021) for males; 16.3% (9.6–23.5; 0.002) for females.

Conclusions: From 2009 to 2014 there was a statistically significant increase in age-adjusted lung NET incidence for males in MarketScan, and a statistically significant increase in age-adjusted prevalence for both genders in PharMetrics. Incidence and prevalence changes, to the extent they exist, may be due to better diagnostic methods, increased awareness of NET among clinicians and pathologists, and/or an actual increase in US disease occurrence. Differences in rates across databases are difficult to explain. These results suggest the need for awareness of the clinically effective and safe treatment options available for lung NET patients among healthcare providers.

Keywords: Lung neuroendocrine tumors, Epidemiology, Prevalence, Incidence, Insurance claims

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Background

Neuroendocrine tumors (NET) comprise a broad family of rare and often slow growing malignancies. NET can develop anywhere in the body and arise from neuroendocrine cells throughout the endocrine system [1, 2]. Approximately one-quarter to one-third of NET occur in the lung [3, 4]. NET secrete peptides and neuroamines that may cause distinct syndromes (e.g., carcinoid syndrome, glucagonoma), in which case they are referred to as "functional" tumors. Clinical presentation depends on the site of the primary tumor and whether or not they are functional. Research on risk factors for lung NET is limited, although the authors of a recent meta-analysis concluded, "family history of cancer is the most relevant risk factor for [NET] development at all investigated sites, followed by BMI and diabetes. Cigarette smoking and alcohol consumption are potential risk factors for selected anatomical sites" [5]. Surgery may be curative in the early stages, but delayed diagnosis is typical.

While rare, the incidence and prevalence of NET appear to be increasing worldwide [4–10]. In a 2008 study using the US Surveillance, Epidemiology, and End Results (SEER) database, the incidence of NET in the US increased from 10.9 cases per million person-years (PMPY) in 1973 to 52.5 PMPY in 2004 [4] and in a 2017 study to 69.8 PMPY in 2012 [10]. Overall NET prevalence was 350 per 1 million in 2004 [4] and 480 per 1 million in 2012 [10]. Only patients with malignant cancers are included in the SEER registries, and the separation of NET into clear-cut benign and malignant categories is not as straightforward as it is for most epithelial malignancies [11]. NET that have not invaded adjacent organs or metastasized may not be immediately labeled as malignant. Thus, many small, benign-appearing tumors may not get included in SEER [4].

The objective of this study was to update incidence and prevalence information for lung NET with non-registry-based data, specifically insurance claims, using additional data beyond what had previously been reported.

Methods

Design and data source

This was a descriptive epidemiological study using insurance claims data from January 1, 2009 to December 31, 2014. The data were from two large US commercial claims databases: Truven Health MarketScan Commercial Claims and Encounters Database, and IMS Health PharMetrics. The MarketScan database has information from more than 100 payers of private health insurance for employees and their dependents, covering more than 25 million lives annually. The PharMetrics database is a nonpayer owned integrated claims database of commercial insurers that includes medical and pharmacy claims for more than 70 million unique individuals across the US. Both databases contain de-identified adjudicated medical claims (e.g., inpatient and outpatient services) and pharmacy claims (e.g., outpatient prescriptions).

Payments to providers, healthcare facilities, and pharmacies for the 66% of the US population with commercial insurance are contingent on submission of claims for services [12]. These insurance claims contain information about diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis codes) and procedures (Current Procedural Terminology 4 [CPT-4] and ICD-9-CM procedure codes). Information on each physician visit, medical procedure, hospitalization, drug dispensed, date of service, number of days of medication supplied, test performed, as well as complete payment information, is available for covered individuals from their insurance claims. Available patient demographic information is limited to age, gender, and broad geographic region. An "enrollment" file provides information on each individuals' dates of coverage—the dates for which we can find their insurance claims. No information is available about individuals for dates outside their dates of enrollment. Information about death, including date or cause, is not available. Privacy restrictions make it impossible to contact patients or review their detailed medical records to obtain additional clinical or demographic information such as health behaviors, tumor size/stage, or race/ethnicity. In the US, individuals may change their insurance coverage over time, and thus the number of individuals enrolled in a given plan changes from year to year. For this study, we were provided the total number of individuals in each database each year, broken down by age and gender. Both databases contain a limited number of individuals ≥65 years old. US individuals ≥65 who have commercial insurance are not representative of the broader age group, a large majority of whom are insured through the Federal Medicare program. Therefore, the analysis was restricted to individuals < 65. Analyses were performed separately using each database and results were compared to check consistency. As the data were de-identified, this study was considered exempt from approval by the Institutional Review Board.

Cohort selection

Individuals at least 18 years of age were identified as having lung NET if, during a single calendar year, they had at least 1 claim from a hospital setting, or at least 2 claims from the outpatient setting, that included an ICD-9-CM diagnosis code for lung NET (that is, either 209.21 malignant carcinoid tumor of bronchus and lung, or 209.61 benign carcinoid tumor of bronchus and lung). Coding of inpatient claims in the US is usually performed by professional coders and is thus more reliable than claims from the outpatient setting, which may be

recorded by a variety of staff with limited clinical training. A limitation of using claims data to estimate disease incidence is the inability to know with certainty that the first diagnosis seen in the data represents the first clinical diagnosis of the condition. Therefore, for incident cases, we required individuals to have been continuously enrolled for 3 years: the specific calendar year of diagnosis and 2 years prior, with no evidence of disease in the prior 2 years. For example, a cohort of individuals identified with lung NET in 2011 must have been enrolled during the entire 2009 to 2011 period, with their lung NET diagnosis in 2011.

Statistical analysis

For each calendar year, we reported the distribution of patient demographics, summarizing continuous variables with means, and categorical variables with patient counts and percentages. Incidence rate was calculated as the number of individuals with lung NET in a particular year divided by the number of all individuals who were continuously enrolled (that is, for whom we had data for the entire year) across the three-year period (year of diagnosis and 2 prior disease-free years) and reported as per million person-years (PMPY). Prevalence was calculated as the number of lung NET patients in a particular year divided by the total number of individuals continuously enrolled for that calendar year and reported as patients per million. For both incidence and prevalence, rates were reported overall and by sex and age categories (18–24, 25–34, 35–44, 45–54, and 55–64 years). To allow comparisons within genders and between databases over time, we calculated adjusted (gender-specific) rates by standardizing the age distribution for each gender based on the distribution of ages (in those same 4 age categories) from both databases in 2014. Similarly, we calculated overall adjusted rates by standardizing to the age and gender distribution from both databases in 2014. The enrollment requirements for inclusion in the incidence and prevalence denominators differed (3 years of enrollment for incidence and a single calendar year for prevalence), and the denominator drops substantially when the continuous enrollment criteria is added. We believe the underlying US commercially insured population is more similar to the one used for calculating prevalence; therefore, to calculate standardized rates for both incidence and prevalence, we used the age and gender distribution from the prevalent population in 2014.

We used annual percent change (APC) to study trends over time [13, 14]. APC was calculated by least-squares linear regression on a log-linear model to characterize trends in rates over calendar year. With this approach, each rate is assumed to change at a constant percentage of the previous year's rate. Because each database had a different denominator, results are reported separately by database. All data transformations and statistical analysis were performed using SAS® version 9.4 (SAS Institute, Cary, NC).

Results

On average, in each year from 2009 to 2014, 631 patients were identified as having lung NET in the MarketScan database. The annual number ranged from 435 in 2009 to low of 435 in 2009 to a high of 796 in 2012. In the PharMetrics database, the range was 419 in 2009 to 648 in 2014, with a mean of 559. In the MarketScan and PharMetrics databases, 65.2 and 64.0% of cases were female, respectively (ranging from 59.8 to 69.4%). More than half of the cases (53.0 to 61.7%) were patients between 55 and 64 years old (Table 1).

Generally, in every year and for both databases, unadjusted incidence was higher for each successive age group. Incidence was highest in the two oldest groups: 12.2–27.8 PMPY (depending on year and gender) in individuals aged 45–54, compared to 25.7–53.6 PMPY in individuals aged 55–64 in MarketScan; and 8.2–19.5 PMPY in individuals 45–54 compared to 20.6–55.4 in 55–64 year olds in PharMetrics (Tables 2 and 3).

After adjustment for age and gender, in the MarketScan database combined (males and females) incidence increased from 14.4 PMPY in 2011 and to 17.5 in 2014, an annual percent change (APC) (95% CI; *P* value) of 7.0% (4.3–9.8; 0.008). The gender-specific incidence (adjusted for age) showed a statistically significant change for males: 7.4% (2.1–13.0; 0.027); and a similar (but not statistically significant) change for females: 6.8% (− 0.2–14.3; 0.052). In the PharMetrics database, the overall age and gender-adjusted incidence was 11.7 PMPY in 2011, 13.8 in 2012, 15.2 in 2013 and 14.6 in 2014, an APC of 7.8% (− 5.7–23.4; 0.137) (Fig. 1, Tables 2 and 3). The APC was not statistically significant for males (− 2.9% [− 13.8–9.4; 0.395]) or females (14.7% [− 12.9–51.2; 0.165]) individually. When data from MarketScan and PharMetrics were combined and adjusted to the age-gender distribution for 2014, incidence rose from 13.0 PMPY in 2011 to 16.2 PMPY in 2014, an overall APC of 7.7% (1.3–14.4; 0.035). However, the combined result masks differences in results across the 2 databases, as described above.

With few exceptions, in each year and for both databases, unadjusted prevalence was higher for each successive age group. Prevalence was highest in 55–64 year olds (between 25.1 and 102.3 per million, depending on year, gender, and database). With few exceptions, unadjusted prevalence was higher in females than in males in every age category (Tables 4 and 5). After age and gender adjustment, prevalence for males and females combined rose from 16.0 per million in 2009 to 30.7 in 2014 in the MarketScan database, an APC of 14.0% (10.2–17.9; <.001). The age-adjusted APC in

Table 1 Patients with lung NET, N[a]

	MarketScan						PharMetrics					
	2009	2010	2011	2012	2013	2014	2009	2010	2011	2012	2013	2014
N	435	521	681	796	667	687	419	510	563	598	616	648
Age, year, no. (%)												
18–24	9 (2.1)	6 (1.2)	9 (1.3)	9 (1.1)	7 (1.0)	2 (0.3)	7 (1.7)	5 (1.0)	10 (1.8)	10 (1.7)	7 (1.1)	9 (1.4)
25–34	16 (3.7)	27 (5.2)	26 (3.8)	37 (4.6)	26 (3.9)	30 (4.4)	29 (6.9)	18 (3.5)	23 (4.1)	19 (3.2)	27 (4.4)	17 (2.6)
35–44	44 (10.1)	57 (10.9)	67 (9.8)	75 (9.4)	68 (10.2)	79 (11.5)	38 (9.1)	59 (11.6)	46 (8.2)	61 (10.2)	65 (10.6)	60 (9.3)
45–54	117 (26.9)	152 (29.2)	205 (30.1)	217 (27.3)	182 (27.3)	198 (28.8)	123 (29.4)	136 (26.7)	156 (27.7)	166 (27.8)	165 (26.8)	162 (25.0)
55–64	249 (57.2)	279 (53.6)	374 (54.9)	458 (57.5)	384 (57.6)	378 (55.0)	222 (53.0)	292 (57.3)	328 (58.3)	342 (57.2)	352 (57.1)	400 (61.7)
Female	260 (59.8)	340 (65.3)	445 (65.3)	515 (64.7)	463 (69.4)	459 (66.8)	258 (61.6)	315 (61.8)	352 (62.5)	392 (65.6)	403 (65.4)	435 (67.1)

[a] Adult patients (age 18 years or older) with ≥1 inpatient or ≥ 2 outpatient claims for lung NET in a calendar year. Patients may have been identified in multiple calendar years. Continuous enrollment not required

Table 2 MarketScan Database: Lung NET Incidence Rate, Cases per Million Person-Years[a]

		No. Of Cases Per Million Person-Years (Numerator/Denominator)											
		2011			2012			2013			2014		
Gender	Age												
Female	18–24	0.0	(0	/629,902)	2.6	(2	/761,959)	2.5	(2	/806,972)	0.0	(0	/791,556)
	25–34	5.8	(5	/857,782)	4.4	(4	/905,705)	2.7	(2	/751,148)	1.4	(1	/711,916)
	35–44	10.3	(14	/1,361,165)	7.5	(11	/1,460,802)	12.7	(16	/1,264,584)	11.6	(14	/1,203,355)
	45–54	15.8	(28	/1,767,104)	23.3	(44	/1,889,625)	26.7	(44	/1,645,900)	27.8	(43	/1,547,477)
	55–64	49.2	(76	/1,545,517)	44.5	(75	/1,687,254)	49.0	(75	/1,531,896)	53.6	(78	/1,454,099)
	All Female	20.0	(123	/6,161,470)	20.3	(136	/6,705,345)	23.2	(139	/6,000,500)	23.8	(136	/5,708,403)
Male	18–24	1.6	(1	/632,342)	0.0	(0	/768,240)	0.0	(0	/829,650)	0.0	(0	/813,048)
	25–34	1.3	(1	/741,337)	2.6	(2	/775,911)	6.2	(4	/648,646)	1.6	(1	/626,307)
	35–44	5.7	(7	/1,221,845)	6.2	(8	/1,294,055)	5.4	(6	/1,120,973)	7.5	(8	/1,066,055)
	45–54	12.2	(19	/1,562,471)	13.9	(23	/1,656,616)	14.5	(21	/1,446,886)	16.8	(23	/1,365,158)
	55–64	25.7	(35	/1,363,927)	28.8	(42	/1,458,077)	27.2	(36	/1,323,391)	31.8	(40	/1,256,884)
	All Male	11.4	(63	/5,521,922)	12.6	(75	/5,952,899)	12.5	(67	/5,369,546)	14.0	(72	/5,127,452)
All Gender	18–24	0.8	(1	/1,262,244)	1.3	(2	/1,530,199)	1.2	(2	/1,636,622)	0.0	(0	/1,604,604)
	25–34	3.8	(6	/1,599,119)	3.6	(6	/1,681,616)	4.3	(6	/1,399,794)	1.5	(2	/1,338,223)
	35–44	8.1	(21	/2,583,010)	6.9	(19	/2,754,857)	9.2	(22	/2,385,557)	9.7	(22	/2,269,410)
	45–54	14.1	(47	/3,329,575)	18.9	(67	/3,546,241)	21.0	(65	/3,092,786)	22.7	(66	/2,912,635)
	55–64	38.2	(111	/2,909,444)	37.2	(117	/3,145,331)	38.9	(111	/2,855,287)	43.5	(118	/2,710,983)
	All Patients	15.9	(186	/11,683,392)	16.7	(211	/12,658,244)	18.1	(206	/11,370,046)	19.2	(208	/10,835,855)
		Adjusted Rate (No. Of Cases Per Million Person-Years)[b]											
All Female[c]		18.3			18.6			21.3			21.8		
All Male[d]		10.3			11.4			11.7			12.9		
All Patients[e]		14.4			15.2			16.6			17.5		

[a] Cases (adults with ≥1 inpatient or ≥ 2 outpatient claims for lung NET in listed year and continuous enrollment in year listed and two years prior) ÷ number of members with continuous enrollment in same period

[b] APC (95% CI; P value): female 6.8% (−0.2–14.3; 0.052); male 7.4% (2.1–13.0; 0.027); all patients 7.0% (4.3–9.8; 0.008)

[c] Adjusted based on distribution of age among male from both databases in 2014

[d] Adjusted based on distribution of age among female from both databases in 2014

[e] Adjusted based on combined distribution of age among male from both databases in 2014

Table 3 PharMetrics Database: Lung NET Incidence Rate, Cases per Million Person-Years[a]

		No. Of Cases Per Million Person-Years (Numerator/Denominator)											
		2011			2012			2013			2014		
Gender	Age												
Female	18–24	2.5	(2	/809,900)	1.2	(1	/803,203)	0.0	(0	/844,220)	1.5	(1	/670,429)
	25–34	5.5	(5	/915,829)	4.7	(4	/846,136)	3.5	(3	/851,694)	1.5	(1	/659,964)
	35–44	2.2	(3	/1,387,525)	7.0	(9	/1,280,702)	12.8	(16	/1,249,676)	10.3	(10	/972,515)
	45–54	10.0	(19	/1,902,036)	18.9	(33	/1,747,518)	18.9	(32	/1,688,747)	19.5	(25	/1,282,436)
	55–64	37.6	(68	/1,809,406)	47.4	(81	/1,708,362)	55.4	(94	/1,697,399)	51.9	(67	/1,290,342)
	All Female	14.2	(97	/6,824,696)	20.0	(128	/6,385,921)	22.9	(145	/6,331,736)	21.3	(104	/4,875,686)
Male	18–24	1.2	(1	/828,261)	3.6	(3	/823,432)	2.3	(2	/875,326)	1.4	(1	/698,342)
	25–34	2.4	(2	/839,247)	1.2	(1	/800,680)	0.0	(0	/818,984)	1.5	(1	/662,957)
	35–44	5.5	(7	/1,266,850)	5.1	(6	/1,185,774)	3.4	(4	/1,164,816)	6.4	(6	/935,200)
	45–54	10.5	(18	/1,713,588)	11.9	(19	/1,599,135)	12.8	(20	/1,556,840)	8.2	(10	/1,218,043)
	55–64	28.7	(47	/1,637,294)	20.6	(32	/1,552,538)	23.2	(36	/1,551,338)	26.3	(32	/1,216,691)
	All Male	11.9	(75	/6,285,240)	10.2	(61	/5,961,559)	10.4	(62	/5,967,304)	10.6	(50	/4,731,233)
All Gender	18–24	1.8	(3	/1,638,161)	2.5	(4	/1,626,635)	1.2	(2	/1,719,546)	1.5	(2	/1,368,771)
	25–34	4.0	(7	/1,755,076)	3.0	(5	/1,646,816)	1.8	(3	/1,670,678)	1.5	(2	/1,322,921)
	35–44	3.8	(10	/2,654,375)	6.1	(15	/2,466,476)	8.3	(20	/2,414,492)	8.4	(16	/1,907,715)
	45–54	10.2	(37	/3,615,624)	15.5	(52	/3,346,653)	16.0	(52	/3,245,587)	14.0	(35	/2,500,479)
	55–64	33.4	(115	/3,446,700)	34.7	(113	/3,260,900)	40.0	(130	/3,248,737)	39.5	(99	/2,507,033)
	All Patients	13.1	(172	/13,109,936)	15.3	(189	/12,347,480)	16.8	(207	/12,299,040)	16.0	(154	/9,606,919)
		Adjusted Rate (No. Of Cases Per Million Person-Years)[b]											
All Female[c]		12.8			18.0			20.6			19.3		
All Male[d]		10.6			9.3			9.3			9.6		
All Patients[e]		11.7			13.8			15.2			14.6		

[a] Cases (adults with ≥1 inpatient or ≥ 2 outpatient claims for lung NET in listed year and continuous enrollment in year listed and two years prior) ÷ number of members with continuous enrollment in same period
[b]APC (95% CI; P value): female 14.7% (−12.9–51.2; 0.165); male −2.9% (−13.8–9.4; 0.395); all patients 7.8% (−5.7–23.4; 0.137)
[c]Adjusted based on distribution of age among male from both databases in 2014
[d]Adjusted based on distribution of age among female from both databases in 2014
[e]Adjusted based on combined distribution of age among male from both databases in 2014

prevalence for females was 16.2% (11.4–21.1; <.001) and for males was 9.9% (4.7–15.3; 0.006). The age- and gender-adjusted APC in the PharMetrics database was 13.9% (7.4–20.9; 0.004); 16.3% (9.6–23.5; 0.002) for females and 9.5% (2.3–17.2; 0.021) for males. (Fig. 2, Tables 4 and 5). When both datasets were combined and adjusted for age and gender, prevalence rose from 14.6 cases per million in 2009 to 28.5 per million in 2014, an APC of 14.2% (9.5–19.0; <.001) overall (16.5% [10.9–22.3; 0.001] for females and 9.9% (5.6–14.3; 0.003) for males.

Discussion

From 2009 to 2014 there was a statistically significant increase in age-adjusted lung NET incidence for males in the MarketScan database. Incidence increased at an annual age and gender-adjusted rate of 7.0% per year, reaching an overall 17.5 PMPY by 2014. In the same database, prevalence rose at an annual age- and gender-adjusted rate of 14.0% per year, reaching 30.7 cases per million per year. The number of cases identified, incidence, and prevalence were all higher in the MarketScan database than in the PharMetrics database. In the PharMetrics database, incidence increased 7.8% per year, but this change was not statistically significant, while age- and gender-adjusted prevalence increased 13.9% per year ($p < .001$). A study using older data recently reported the incidence of NET in the US increased from 3 cases PMPY in 1973 to 16 PMPY in 2012 [10]. The preponderance of female cases has been observed in prior studies using these and other data sources [4, 9, 15].

There are many possible reasons for the observed changes in incidence and prevalence, although determining which reason or reasons are most important was beyond the scope of this study. First, more tumors may be found incidentally over time. Rates of both CT and MRI use in the general population have been steadily

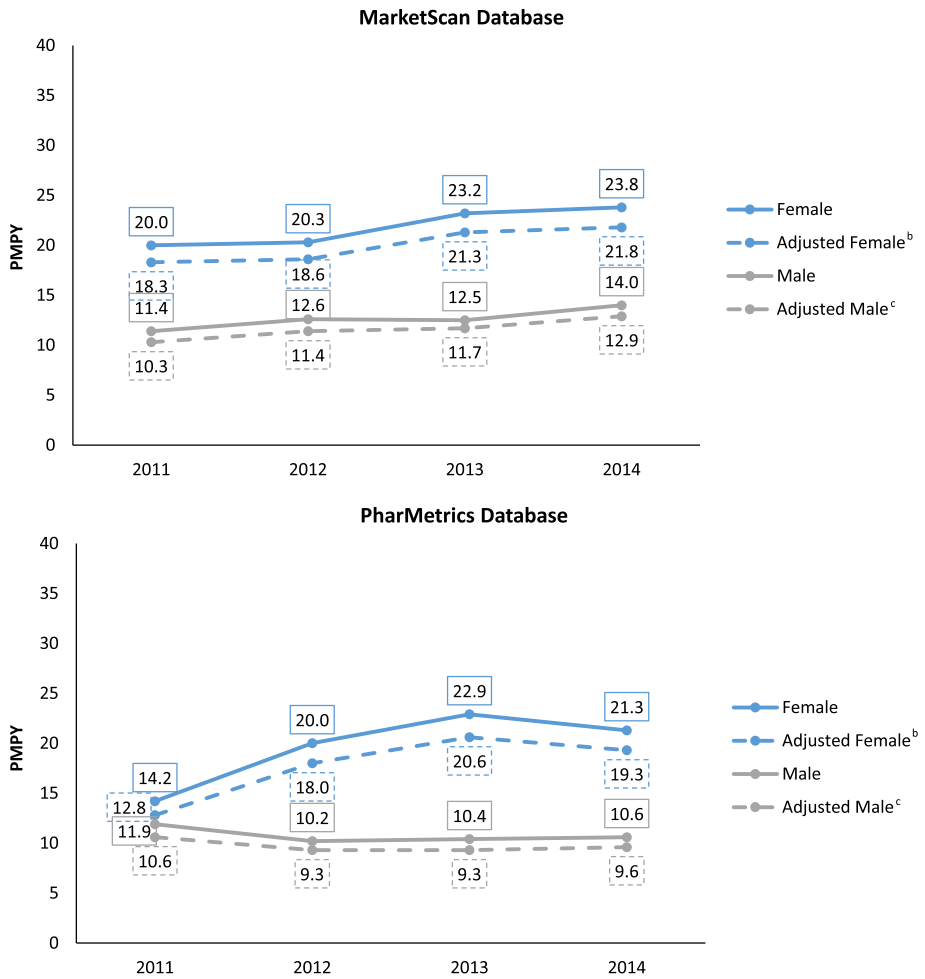

Fig. 1 Lung NET Incidence Rate, Cases per Million Person-Years[a]. [a] In the combined database (adjusted for age and gender) the no. of cases per million person-years was 13.0 (2011), 14.5 (2012), 15.9 (2013), and 16.2 (2014) for all patients. [b] Adjusted based on distribution of age among males from both databases in 2014. [c] Adjusted based on distribution of age among females from both databases in 2014

increasing, as has the accuracy of these tests [16]. Some patients may have their tumors detected simply because they have a chest imaging study for another reason. Second, screening for lung cancer appears to be rising [17]. As screening rates increase, more lung NET may be detected. Third, in the last decade, high sensitivity assays for 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A, both markers for certain NET, have come into more common use. Increased use of these tests may have improved identification of previously undetected tumors [18]. Fourth, pathologists may be improving their ability to identify NET. Finally, the underlying rate of the development of NET may be increasing. The increased prevalence would be expected from the combination of increasing incidence [4, 10] and improved survival [19, 20]. Incidental identification of lung NET might also partially explain the finding that prevalence increased more than incidence during the period studied. If earlier tumors were being identified, survival would appear to increase, which in turn would increase prevalence. We could not test this theory in the current study, as data on disease stage is lacking. A recent analysis of pancreatic NET using the SEER database found increases in both incidence and survival and concluded that stage migration, or an increased detection of localized disease, explained at least part of these observations [21]. In the current study, although the adjusted annual percent change differed between the PharMetrics and MarketScan databases, these between-database differences were not statistically significant (e.g., the 95% CI overlapped) and the estimate from the combined databases was consistent with the individual ones. Both databases are derived from wide geographic regions, encompass diverse practice types, and represent multiple insurance plan types, between-database differences on any of these individual factors may explain why the estimates are numerically different between PharMetrics and MarketScan.

Table 4 MarketScan Database: Lung NET Prevalence, Cases per Million per Year[a]

		No. Of Cases Per Million Per Year (Numerator/Denominator)																	
		2009			2010			2011			2012			2013			2014		
Gender	Age																		
Female	18–24	1.7	(2	/1,200,214)	1.7	(2	/1,179,801)	0.7	(1	/1,535,683)	3.0	(5	/1,668,409)	3.6	(5	/1,404,034)	0.7	(1	/1,342,845)
	25–34	4.9	(10	/2,032,535)	8.2	(16	/1,962,108)	5.8	(12	/2,052,889)	10.5	(22	/2,089,096)	9.8	(16	/1,640,542)	8.3	(13	/1,562,298)
	35–44	7.6	(20	/2,616,976)	9.9	(25	/2,533,283)	12.9	(34	/2,643,239)	14.7	(39	/2,660,474)	18.8	(40	/2,123,456)	21.0	(42	/1,996,743)
	45–54	18.1	(56	/3,090,478)	24.7	(75	/3,031,223)	31.0	(99	/3,190,617)	36.8	(118	/3,204,967)	40.3	(102	/2,529,219)	42.4	(99	/2,336,993)
	55–64	52.8	(124	/2,349,482)	59.7	(144	/2,411,232)	75.1	(197	/2,624,303)	85.9	(231	/2,688,474)	95.2	(209	/2,194,982)	102.3	(210	/2,053,379)
	All Female	18.8	(212	/11,289,685)	23.6	(262	/11,117,647)	28.5	(343	/12,046,731)	33.7	(415	/12,311,420)	37.6	(372	/9,892,233)	39.3	(365	/9,292,258)
Male	18–24	5.2	(6	/1,147,214)	3.5	(4	/1,129,804)	2.6	(4	/1,549,206)	2.3	(4	/1,705,487)	1.4	(2	/1,431,673)	0.0	(0	/1,365,613)
	25–34	2.3	(4	/1,760,823)	4.8	(8	/1,669,422)	3.9	(7	/1,788,710)	4.9	(9	/1,850,139)	4.2	(6	/1,436,317)	5.8	(8	/1,388,742)
	35–44	7.2	(17	/2,359,613)	7.1	(16	/2,250,466)	11.3	(27	/2,381,647)	9.2	(22	/2,403,534)	8.9	(17	/1,900,182)	12.3	(22	/1,791,028)
	45–54	10.3	(28	/2,731,422)	15.9	(42	/2,636,290)	16.7	(47	/2,817,734)	21.1	(60	/2,841,640)	18.4	(41	/2,223,287)	24.2	(50	/2,066,977)
	55–64	33.7	(71	/2,104,573)	30.8	(65	/2,107,551)	38.3	(88	/2,296,348)	45.7	(107	/2,342,101)	42.7	(81	/1,897,684)	52.1	(93	/1,783,325)
	All Male	12.5	(126	/10,103,645)	13.8	(135	/9,793,533)	16.0	(173	/10,833,645)	18.1	(202	/11,142,901)	16.5	(147	/8,889,143)	20.6	(173	/8,395,685)
All Gender	18–24	3.4	(8	/2,347,428)	2.6	(6	/2,309,605)	1.6	(5	/3,084,889)	2.7	(9	/3,373,896)	2.5	(7	/2,835,707)	0.4	(1	/2,708,458)
	25–34	3.7	(14	/3,793,358)	6.6	(24	/3,631,530)	4.9	(19	/3,841,599)	7.9	(31	/3,939,235)	7.2	(22	/3,076,859)	7.1	(21	/2,951,040)
	35–44	7.4	(37	/4,976,589)	8.6	(41	/4,783,749)	12.1	(61	/5,024,886)	12.0	(61	/5,064,008)	14.2	(57	/4,023,638)	16.9	(64	/3,787,771)
	45–54	14.4	(84	/5,821,900)	20.6	(117	/5,667,513)	24.3	(146	/6,008,351)	29.4	(178	/6,046,607)	30.1	(143	/4,752,506)	33.8	(149	/4,403,970)
	55–64	43.8	(195	/4,454,055)	46.3	(209	/4,518,783)	57.9	(285	/4,920,651)	67.2	(338	/5,030,575)	70.9	(290	/4,092,666)	79.0	(303	/3,836,704)
	All Patients	15.8	(338	/21,393,330)	19.0	(397	/20,911,180)	22.6	(516	/22,880,376)	26.3	(617	/23,454,321)	27.6	(519	/18,781,376)	30.4	(538	/17,687,943)
		Adjusted Rate (No. Of Cases Per Million Per Year)[b]																	
All Female[c]		19.2			23.5			28.6			34.0			37.9			39.8		
All Male[d]		12.6			13.5			15.9			18.3			16.7			20.9		
All Patients[e]		16.0			18.7			22.5			26.4			27.6			30.7		

[a] Cases of adults with ≥1 inpatient or ≥ 2 outpatient claims for Lung NET in listed year and continuous enrollment in year listed ÷ number of members with continuous enrollment in same period
[b]APC (95% CI; P value): female 16.2% (11.4–21.1; <.001); male 9.9% (4.7–15.3; 0.006); all patients: 14.0% (10.2–17.9; <.001)
[c]Adjusted based on distribution of age among males from both databases in 2014
[d]Adjusted based on distribution of age among females from both databases in 2014
[e]Adjusted based on combined distribution of age among males from both databases in 2014

Table 5 PharMetrics Database: Lung NET Prevalence, Cases per Million per Year[a]

		No. Of Cases Per Million Per Year (Numerator/Denominator)																	
		2009			2010			2011			2012			2013			2014		
Gender	Age																		
Female	18–24	2.9	(4	/1,388,059)	2.3	(3	/1,318,141)	3.5	(5	/1,431,236)	4.4	(6	/1,360,555)	2.2	(3	/1,335,252)	1.9	(2	/1,048,351)
	25–34	6.6	(13	/1,960,213)	3.8	(7	/1,849,997)	8.1	(15	/1,851,913)	4.7	(8	/1,708,390)	7.1	(12	/1,684,490)	3.7	(5	/1,341,604)
	35–44	6.0	(15	/2,508,808)	10.7	(25	/2,335,199)	6.6	(15	/2,269,096)	12.2	(25	/2,055,088)	20.3	(40	/1,969,715)	16.1	(25	/1,553,850)
	45–54	18.7	(59	/3,149,529)	24.0	(71	/2,959,455)	26.5	(76	/2,867,408)	31.9	(82	/2,574,529)	32.8	(80	/2,436,504)	35.2	(66	/1,875,797)
	55–64	38.2	(101	/2,643,692)	55.5	(143	/2,576,843)	65.6	(169	/2,575,456)	77.4	(184	/2,377,377)	92.0	(212	/2,305,347)	91.9	(165	/1,796,085)
	All Female[b]	16.5	(192	/11,650,301)	22.6	(249	/11,039,635)	25.5	(280	/10,995,109)	30.3	(305	/10,075,939)	35.7	(347	/9,731,308)	34.5	(263	/7,615,687)
Male	18–24	1.4	(2	/1,387,054)	1.5	(2	/1,322,440)	1.4	(2	/1,462,310)	2.8	(4	/1,406,293)	2.9	(4	/1,386,541)	3.6	(4	/1,097,662)
	25–34	4.5	(8	/1,759,919)	3.0	(5	/1,671,459)	3.0	(5	/1,687,428)	1.9	(3	/1,609,181)	6.2	(10	/1,604,977)	2.3	(3	/1,323,432)
	35–44	4.3	(10	/2,300,612)	12.6	(27	/2,147,076)	10.5	(22	/2,093,812)	9.3	(18	/1,928,820)	10.2	(19	/1,864,293)	10.6	(16	/1,505,314)
	45–54	11.2	(32	/2,850,321)	14.9	(40	/2,681,967)	16.1	(42	/2,602,786)	20.2	(48	/2,375,529)	19.4	(44	/2,267,225)	17.9	(32	/1,786,707)
	55–64	25.1	(60	/2,392,616)	33.5	(78	/2,331,410)	37.4	(87	/2,325,581)	33.8	(73	/2,158,306)	39.3	(83	/2,110,883)	44.5	(75	/1,684,375)
	All Male[c]	10.5	(112	/10,690,522)	15.0	(152	/10,154,352)	15.5	(158	/10,171,917)	15.4	(146	/9,478,129)	17.3	(160	/9,233,919)	17.6	(130	/7,397,490)
All Gender	18–24	2.2	(6	/2,775,113)	1.9	(5	/2,640,581)	2.4	(7	/2,893,546)	3.6	(10	/2,766,848)	2.6	(7	/2,721,793)	2.8	(6	/2,146,013)
	25–34	5.6	(21	/3,720,132)	3.4	(12	/3,521,456)	5.7	(20	/3,539,341)	3.3	(11	/3,317,571)	6.7	(22	/3,289,467)	3.0	(8	/2,665,036)
	35–44	5.2	(25	/4,809,420)	11.6	(52	/4,482,275)	8.5	(37	/4,362,908)	10.8	(43	/3,983,908)	15.4	(59	/3,834,008)	13.4	(41	/3,059,164)
	45–54	15.2	(91	/5,999,850)	19.7	(111	/5,641,422)	21.6	(118	/5,470,194)	26.3	(130	/4,950,058)	26.4	(124	/4,703,729)	26.8	(98	/3,662,504)
	55–64	32.0	(161	/5,036,308)	45.0	(221	/4,908,253)	52.2	(256	/4,901,037)	56.7	(257	/4,535,683)	66.8	(295	/4,416,230)	69.0	(240	/3,480,460)
	All Patients[d]	13.6	(304	/22,340,823)	18.9	(401	/21,193,987)	20.7	(438	/21,167,026)	23.1	(451	/19,554,068)	26.7	(507	/18,965,227)	26.2	(393	/15,013,177)
		Adjusted Rate (No. Of Cases Per Million Per Year)[b]																	
All Female[c]		16.2			21.8			24.8			29.5			34.9			34.0		
All Male[d]		10.2			14.4			15.1			15.1			17.0			17.3		
All Patients[e]		13.3			18.2			20.1			22.6			26.3			25.9		

[a] Cases of adults with ≥1 inpatient or ≥ 2 outpatient claims for Lung NET in listed year and continuous enrollment in year listed ÷ number of members with continuous enrollment in same period
[b]APC (95% CI; P value): female 16.3% (9.6–23.5; 0.002); male 9.5% (2.3–17.2; 0.021); all patients: 13.9% (7.4–20.9; 0.004)
[c]Adjusted based on distribution of age among males from both databases in 2014
[d]Adjusted based on distribution of age among females from both databases in 2014
[e]Adjusted based on combined distribution of age among males from both databases in 2014

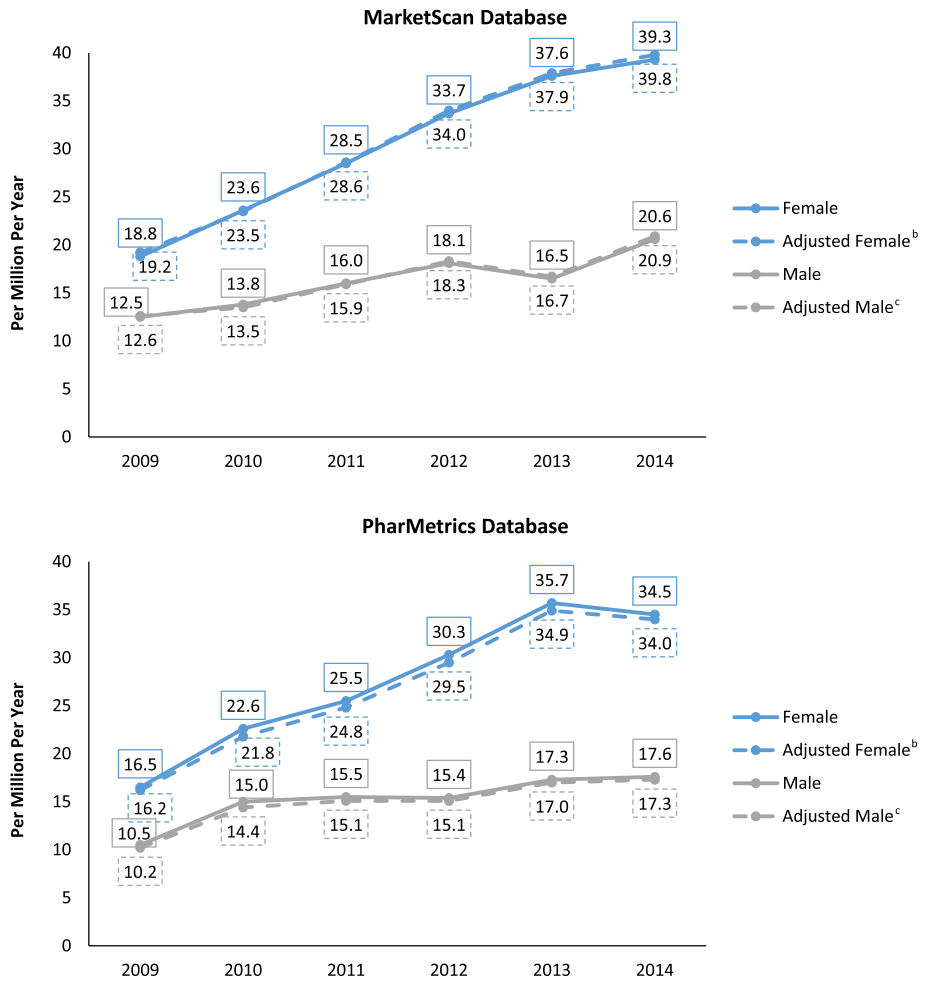

Fig. 2 Lung NET Prevalence, Cases per Million/Year[a]. [a] In the combined database (adjusted for age and gender) the no. of cases per million per year was 14.6 (2009), 18.4 (2010), 21.3 (2011), 24.6 (2012), 26.9 (2013), and 28.5 (2014) for all patients. [b] Adjusted based on distribution of age among males from both databases in 2014. [c] Adjusted based on distribution of age among females from both databases in 2014

Estimates from the current study are consistent with that reported from SEER for 2012 [10]. The incidence of all NET was reported as 69.8 PMPY for 2012 and lung NET as 16.3, and our combined, adjusted estimate was 16.2 PMPY in 2014 (although this rate from the combined databases should be interpreted with caution since it obscures differences between different sources). Although these numbers are quite similar, comparing our results directly to prior estimates presents several challenges. First, we were able to use data through 2014, 2 years more recent than SEER. Second, SEER, the source of data for the 2008 and 2017 studies, is a coordinated system of population-based cancer registries located across the US. The SEER Program collects cancer incidence and survival data from 18 geographic areas, together representing about 1/4 of the US population [22]. The insurance claims used in the present study, in contrast, are a convenience sample, albeit an extremely large one. Based on information provided by MarketScan and PharMetrics, the combined databases have claims for a geographically dispersed sample representing about 1/3 of the US population. Third, SEER includes patients of all ages; the current study only included individuals 18–64 years of age. About 95% of individuals ≥65 are covered by Medicare [12]. A small number of individuals in this age group would have been available for inclusion in our study (e.g. they had commercial insurance as the primary payer, and therefore, their data were included in our databases), but they do not represent typical Medicare-age individuals, and thus were excluded from analysis. The incidence of NET is twice as high in individuals ≥65 compared to those 50–64 [10]. Our estimates are thus likely to understate the actual incidence and prevalence. Fourth, SEER registrars are trained and provided with software to improve their ability to accurately code reportable cancers. Claims coding is performed by a mix of care providers and professional coders. Fourth, the coding systems differ between SEER and insurance claims. SEER currently uses the

International Classification of Diseases for Oncology system (ICD-O-3), whereas claims use ICD-9-CM (since 2015, ICD-10). While the systems can be mapped to each other, the mapping is not one-to-one. NET represent an unusual tumor type for which the traditional labels of benign and malignant are a poor fit. While classification has evolved considerably in the last several decades, NET are now generally described by their anatomic location (e.g., GI or lung), degree of differentiation (either "well" or "poorly"), and proliferative index (mitotic activity). Small, well differentiated NET may thus have been overlooked for inclusion into SEER [4]. Insurance claims, relying as they do on ICD-9-CM codes, cannot be used to identify stage or tumor size. Claims data cannot be used to identify with certainty whether a case is truly incident or represents a patient who simply did not present for care for a prolonged period. We required continuous enrollment for 2 years before the first NET claim to reduce this source of uncertainty. Prevalent patients would have to have had no care for their condition for more than 2 years to have been incorrectly counted as incident cases. Other limitations of insurance claims include the lack of information on race/ethnicity or health behaviors that might explain the observed rise in lung NET. Finally, we had no information on occurrence of, timing, or cause of death, making it impossible to comment on survival.

Despite these differences and data limitations, both the prior SEER study and the current study have identified some, although not entirely consistent, evidence of increasing incidence and prevalence of lung NET. The consistent pattern in 3 databases over more than 4 decades strongly suggests the increase in lung NET cases is not an artifact of the database chosen, the method used, or changes in patient enrollment over time. Recent increases in other cancer types have a variety of explanations. At least some portion of the recent increases in thyroid cancer appears to result from improved screening [23], but there also appears to be an underlying increase in disease incidence as well [24]. In NET, multiple mechanisms may be operating, and studies using other sources of data will be required to determine the extent to which each contributes to the observed rise.

Conclusions

The incidence and prevalence of lung NET appears to be increasing over time, although in the current study the gender- and database-specific findings are inconsistent. Although lung cancer overall appears to be on the decline in the US [25], an increase in NET in multiple anatomic locations, including lung NET, has been observed [10]. Pulmonologists, gastroenterologists, oncologists, and other physicians may see patients with these tumors with increasing frequency in years to come and may thus need to become more familiar with its presentation and treatment. Health plans will also see an increase in this previously rare disease and should consider ways to effectively manage this population. Finally, because higher incidence brings higher costs, studies assessing the increasing economic burden of this disease are warranted.

Abbreviations

5-HIAA: 5-hydroxyindoleacetic acid; APC: annual percent change; CPT-4: Current Procedural Terminology 4; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; ICD-O-3: International Classification of Diseases for Oncology system; NET: Neuroendocrine tumors; PMPY: Per million person-years; SEER: Surveillance Epidemiology, and End Results

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Availability of data and materials

The data that support the findings of this study are available from Truven Health and IMS Health but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Truven and IMS.

Authors' contributions

All authors meet the ICMJE criteria for authorship. MSB was involved in the conception, design, interpretation and writing of the manuscript. EC was involved in the conception, design, interpretation and statistical analyses and had final approval of the manuscript. BC was involved in the design, interpretation and had final approval of the manuscript. MN was involved in the conception, design, interpretation and had final approval of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

BC and MPN are employees of Novartis. MB and EC are employees of Partnership for Health Analytic Research, a health services research firm paid by Novartis to conduct this research.

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ORIGINAL REPORT

Changing Epidemiology of Small-Cell Lung Cancer in the United States Over the Last 30 Years: Analysis of the Surveillance, Epidemiologic, and End Results Database

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ABSTRACT

Purpose
Small-cell lung cancer (SCLC) is a histologic subtype of lung cancer with a distinct biology and clinical course. It has been observed that the incidence of SCLC has been decreasing over the last several years.

Methods
We used the Surveillance, Epidemiologic, and End Results (SEER) database to determine the incidence of SCLC over the last 30 years. In addition, we sought to determine sex- and stage-based differences in the incidence and survival of SCLC among a proportion of reported cases of lung cancer over the last 30 years (1973 to 2002). Joinpoint analyses were applied to test the trends in annual percentage change for statistical significance.

Results
The proportion of SCLC (among all lung cancer histologic types) decreased from 17.26% in 1986 to 12.95% in 2002. Of all patients with SCLC, the proportion of women with SCLC increased from 28% in 1973% to 50% in 2002. A modest but statistically significant improvement in 2- and 5-year survival was noted among both limited-stage SCLC and extensive-stage SCLC cohorts during the study period.

Conclusion
Our analysis indicates that the incidence of SCLC is decreasing in the United States, and only modest improvements have been seen in survival over the last 30 years. Possible explanations for the decreasing incidence include the decrease in the percentage of smokers and the change to low-tar filter cigarettes. Despite trends toward modest improvement in survival, the outcome remains very poor.

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INTRODUCTION

Small-cell lung cancer (SCLC) is distinct from the more common non–small-cell lung cancer by its rapid doubling time, high growth fraction, early development of widespread metastases, and dramatic initial response to chemotherapy and radiation.[1] However, despite high initial responses to therapy, most patients die from recurrent disease.[2]

The distribution of histologic lung cancer subtypes has been changing over the last few decades. Although squamous cell carcinoma (SCC) and SCLC were the most frequent histologic subtypes of lung cancer in the initial period of the smoking-related cancer epidemic, more recent studies have consistently reported the predominance of adenocarcinoma, which is now recognized as the most common histologic type of lung cancer.[3-7]

The American Cancer Society estimated that SCLC represented 25% of the 170,000 new cases of lung cancer in the United States in 1993.[8] Recent studies however have shown a decrease in the total number of lung cancer cases, particularly in men with SCLC and SCC.[9,10] We analyzed the Surveillance, Epidemiologic, and End Results (SEER) program of the National Cancer Institute (Bethesda, MD) to determine the changes in incidence, proportion of SCLC among new cases of lung cancer, and survival rates for patients with SCLC during the period from 1973 to 2002.

METHODS

Database

We used the SEER Cancer Incidence Public Use Database 1973 to 2002 that was submitted in November 2004 and issued in April 2005 (http://seer.cancer.gov). SEER cancer registries collect data from 13 geographic samples: the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii, and the metropolitan areas of Detroit, MI;

Atlanta, GA; San Francisco, CA; Seattle, WA; San Jose, CA; and Los Angeles, CA; plus 10 counties in rural Georgia and a sample of Alaskan natives. Together these 13 groups represent approximately 14% of the total US population. Data from nine of these registries were used. Lung tumors (site codes, C34.0-C34.9) were extracted from the SEER database for the years 1973 through 2002. Histologic codes 8041 to 8045 were designated as SCLC. The ICD-*O*-3 histology code for non–small-cell carcinoma (8046) is distinct. The SEER database uses its own staging system, local, regional, and distant, to describe the extent of tumor. In the SEER database system, local and regional disease describes limited-stage SCLC and distant disease indicates extensive-stage SCLC. Approximately 10% of SCLC patients each year are not staged.

Data Analysis

We used the SAS system for Windows version 8.02 (SAS Institute, Cary, NC) to analyze the data for the following: (1) incidence of SCLC each year as a percentage of all reported lung cancer; (2) incidence of SCLC as a percentage of all reported lung cancers for each sex; (3) incidence of limited-stage and extensive-stage SCLC each year as a percentage of all reported lung cancers; and (4) all-cause survival rates over time for limited- and extensive-stage SCLC. Joinpoint regression analyses were used to identify significant changes and trends in the data. This method uses a statistical algorithm to define a best-fitting regression line through incidence data across time, determining how many, if any, joinpoints should be used to determine where significant changes take place. In the final models, the most significant numbers of joinpoints are used, and an annual percentage change is calculated for each slope. Joinpoint trends were calculated using age-adjusted rates weighted by the proportion of persons in corresponding age groups of a standard million population (2000 US standard population). We used Joinpoint Software version 3.0 (distributed by the Statistical Applications and Research Branch of the National Cancer Institute, Bethesda, MD; http://srab/cancer.giv/joinpoint/) to calculate annual percentage change and to analyze these trends for statistical significance.

RESULTS

Incidence

Table 1 outlines the characteristics of patients with small-cell lung cancer as identified in the SEER data set from 1973-2002. The percentage of SCLC among all cases of lung cancer rose to a peak of 17.26% in 1986 in our analysis (Fig 1). As of 2002, SCLC comprised only 12.95% of all lung cancers. Joinpoint regression analyses confirm these changes. Figure 2 reveals that the absolute incidence of SCLC increased at an annual rate of 6.5% until 1982 ($P < .0001$). It increased modestly between 1982 and 1989 at an annual percentage change rate of 1.2% that was not statistically significant. Since then, the incidence of SCLC has decreased at a statistically significant annual rate of 2.4%. This downward trend is statistically significant ($P < .0001$), suggesting that this decrease is a real trend rather than random fluctuation.

Table 1. Characteristics of Patients With Small-Cell Lung Cancer (N = 60,045)

Characteristic	No. of Patients	%
Men	35,048	58
Women	24,997	42
Limited-stage disease	23,418	39
Men	13,026	22
Women	10,392	17
Extensive-stage disease	31,971	53
Men	19,292	32
Women	12,679	21

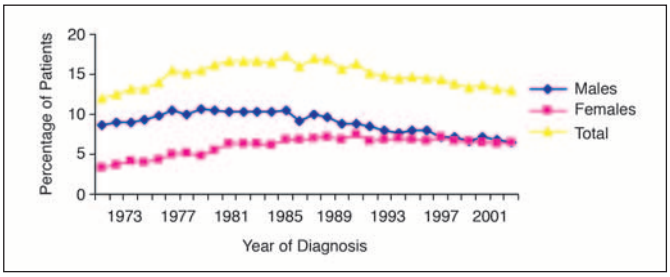

Fig 1. The diagnosis of small-cell lung cancer, as a percent of all lung cancers, over 30 years.

Sex and Stage

Figure 3 shows that the initial strong male predominance among SCLC patients in 1973 (72.37% of all patients with SCLC) has steadily decreased over the subsequent 20 years. In 2002, the male-to-female ratio of patients with SCLC was 1 to 1. In addition, we analyzed the incidence of all lung cancers represented by SCLC, stratified by sex. The average annual age-adjusted incidence rate of SCLC during the early decades of the monitoring period was higher among men, compared with women. Figures 1 and 3 illustrate the changes in the proportion of women with SCLC from 1973 to 2002. Joinpoint analyses confirm that these changes are statistically significant (Fig 4).

The percentages of SCLC represented by limited- and extensive-stage subtypes in relation to each other have not changed significantly during the last 30 years, although the absolute numbers do appear to increase (Fig 5). The increase in overall percentages is a reflection of the increased number of patients who were staged in 2002 compared with in 1973. In 1973, 32.5% of SCLC patients had limited-stage disease, 49.5% of patients had extensive-stage disease, and 17.9% of patients were unstaged. In 2002, a similar pattern emerged: 39.6% of patients were staged with limited-stage disease and 56.6% of patients were staged with extensive-stage disease, and only 3.8% of patients

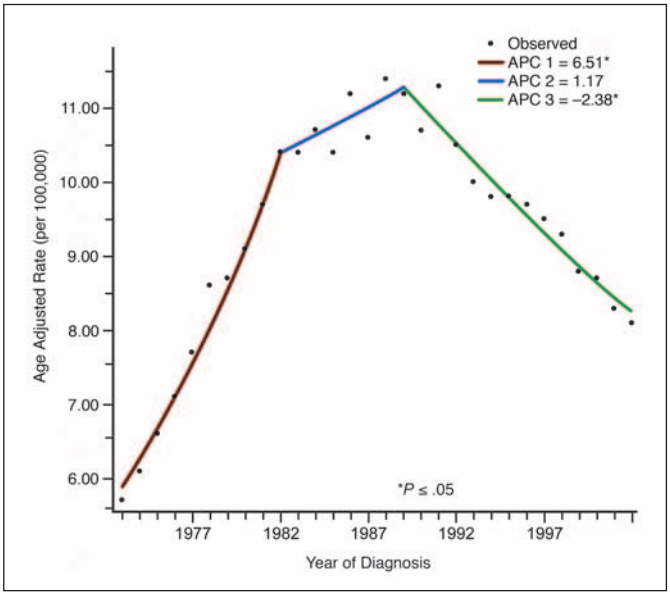

Fig 2. Joinpoint regression of diagnosis of small-cell lung cancer, by year. (*) $P \leq .05$. APC, annual percentage change.

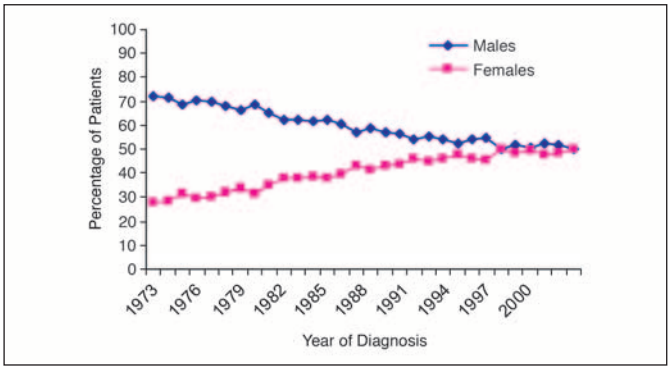

Fig 3. The diagnosis of small-cell lung cancer by sex.

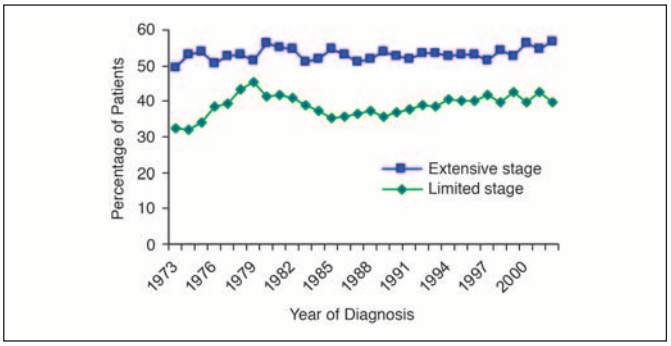

Fig 5. The diagnosis of small-cell lung cancer by stage.

were left unstaged. Joinpoint analyses of the changes in distribution of stages over time are illustrated in Figure 6.

Survival

Figure 7 depicts the 2-year all-cause survival of patients with extensive-stage (ES) SCLC. Although there are fluctuations from year to year, there is an overall trend toward increased survival. In 1973, 1.5% of all patients with ES-SCLC survived 2 years. This number increased to 4.6% by 2000. Joinpoint analyses confirm this trend of a subtle but steady increase in the 2-year survival rate for these patients; the 2-year survival rate for all patients with ES-SCLC increased at an annual percentage change of 2.96% ($P < .0001$) throughout the monitoring period (Fig 8). Stratification by sex revealed that 2-year survival among men with ES-SCLC increased at an annual rate of 3.45% ($P < .0001$) and 2-year survival rates among similar women increased by 1.74% annually ($P = .015$; Fig 9). In each year represented, the 2-year survival rate among women with ES-SCLC is greater than that of men. Survival rates among women in this cohort increased from 1.96% in 1973 to 5.94% in 2000. The 2-year survival rate among men with ES-SCLC increased from 1.32% in 1973 to 3.57% in 2000.

Figure 10 illustrates the 5-year all-cause survival data of patients with limited stage (LS) SCLC. The 5-year survival rate for patients with limited-stage disease increased from 4.9% in 1973 to 10% in 1998. The survival rates for men in this cohort increased from 3.95% in 1973 to 7.51% in 1997 (the last year for which 5-year survival data was available). The survival rate for women with LS-SCLC increased from 6.74% in 1973 to 12.25% in 1997. Joinpoint analyses support this trend, and suggest that the relative survival for patients with LS-SCLC increased moderately throughout the study period (annual percentage change, 2.62%; $P < .0001$; Fig 11). For men, an initial decline in survival (19.31%; $P = .57$) was followed by a statistically significant increase in survival with an annual percent change of 3.34% ($P < .0001$). The female patient model was not fit with any joinpoints, and the annual percentage change across the range of study was not statistically significant (0.3%; $P = .225$; Fig 12).

DISCUSSION

Our analysis of the SEER database indicates that the incidence of SCLC has been steadily decreasing in the United States over the last

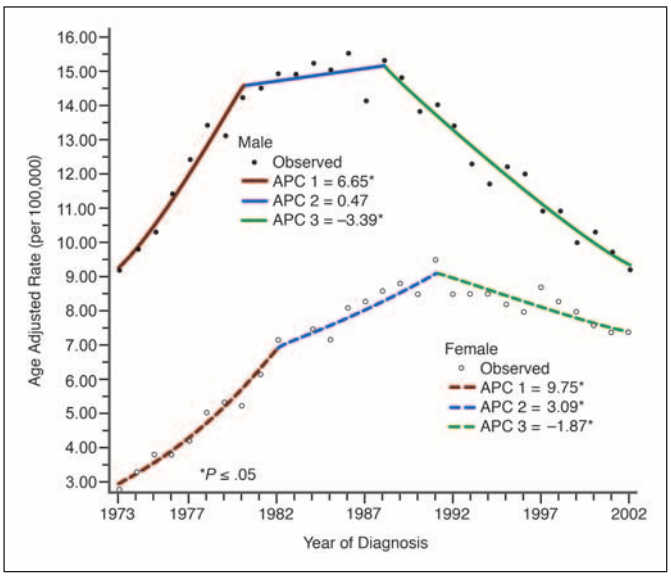

Fig 4. Joinpoint analyses of the distribution of sex in the diagnosis of small-cell lung cancer over 30 years. (*) $P \leq .05$. APC, annual percentage change.

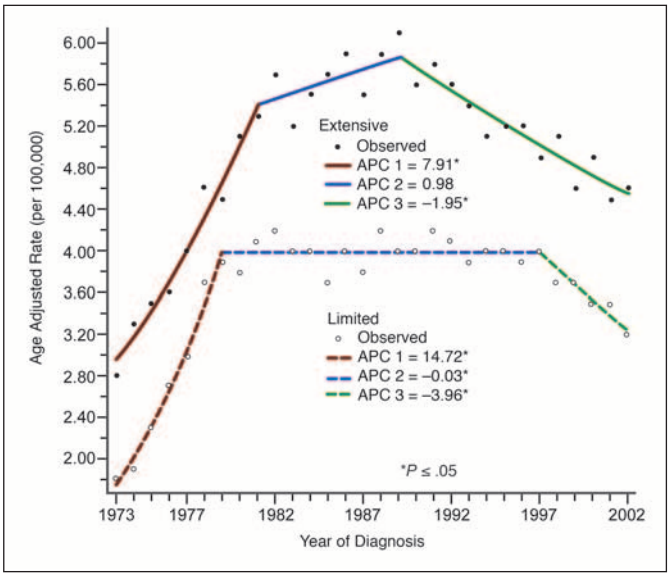

Fig 6. Joinpoint analyses of the distribution of stage in the diagnosis of small-cell lung cancer over 30 years. (*) $P \leq .05$. APC, annual percentage change.

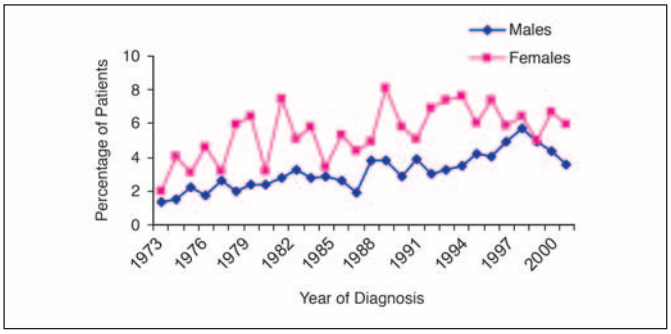

Fig 7. The all-cause survival trends in extensive-stage small-cell lung cancer.

several years. The use of joinpoint regression analyses support that this decrease is a real trend, as opposed to fluctuations within a normal distribution.

The decrease in the incidence of SCLC may be explained by the decreased percentage of smokers and by the change in cigarette composition. It is estimated that there were 55 million smokers (36%) in a US total population of 151.3 million in 1950 and 50.1 million cigarette smokers (20%) among 248.8 million US residents in 1990.[11] Although the annual consumption of cigarettes increased from 248.8 billion in 1964 to 511.2 billion in 1981, it declined to 465 billion in 1998.[11] In addition, the yearly consumption of cigarettes per adults older than 18 years decreased from 3,800 in 1965 to 2,800 in 1993.[12] Cigarette smoking is a very strong risk factor for the development of SCLC. More than 90% of patients with SCLC are current or past smokers and the risk is related to the duration and intensity of the smoking.[13] Barbone et al[14] reported an increased odds ratio (OR) for the development of SCLC based on the number of cigarettes consumed daily and the age of starting smoking. Furthermore, the OR decreased from 14.5 in current smokers to 10.9 in patients who had quit smoking for fewer than 4 years to 2.2 in patients with more than 25 years of abstinence.[14] A case-control series evaluating the characteristics of

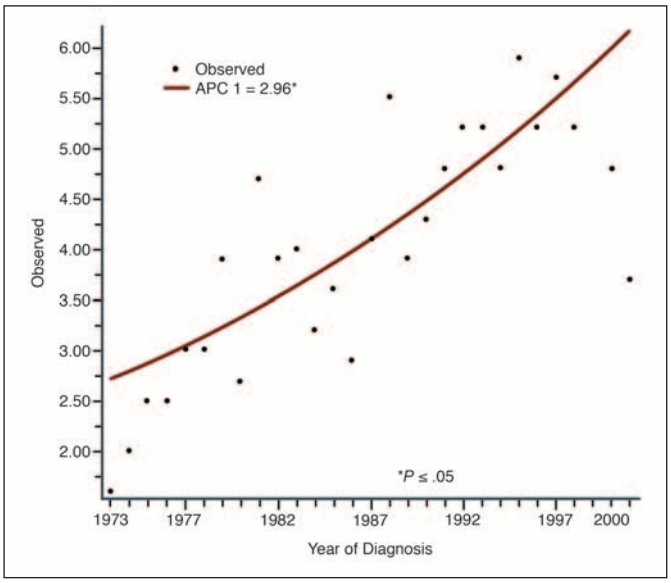

Fig 8. Joinpoint regression of all-cause 2-year survival trends in extensive-stage small-cell lung cancer. (*) $P \leq .05$. APC, annual percentage change.

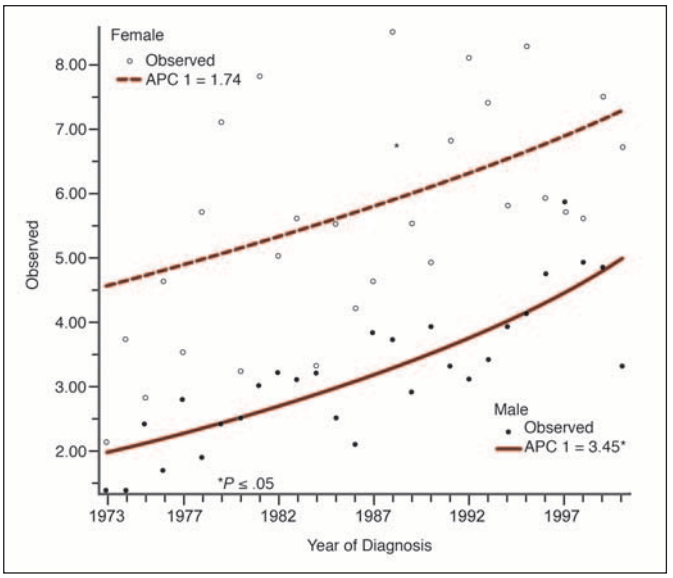

Fig 9. Joinpoint regression of the distribution of sex in all-cause 2-year survival trends in extensive-stage small-cell lung cancer. (*) $P \leq .05$. APC, annual percentage change.

patients with lung cancer showed that none of the 117 men and only six (2.9%) of the 207 women who never smoked had SCLC.[15] A recent meta-analysis evaluating the effects of cigarette smoking on the histologic subtypes of lung cancer showed a stronger association with SCLC and SCC than large cell lung cancer and adenocarcinoma, for both current and former smokers.[16] The highest OR, 72.5, was seen in current smokers with SCLC. The OR was higher for current female smokers than for men (79.9 *v* 20.3).[16] Therefore, the decrease in the percentage of smokers may account for the proportionally higher decrease in the incidence of SCLC and SCC, the histologic subtypes more strongly associated with cigarette smoking, and the increase in the proportion of adenocarcinoma, the most common subtype in nonsmokers.

Most of the carcinogens in the tobacco smoke are present in the tar, a complex mixture including several chemicals capable of cancer initiation or promotion. Since 1954, the sales-weighted average tar and nicotine yields of American cigarettes, defined as the yield of tar and nicotine in each cigarette available in the United States weighted by the number of packages of each brand sold annually in the United States, decreased from about 38 mg and 2.7 mg to 12 mg and 0.95 mg, respectively.[12] The lower tar emissions have been achieved with the use of efficient filter tips, highly porous cigarette paper, and changes in the

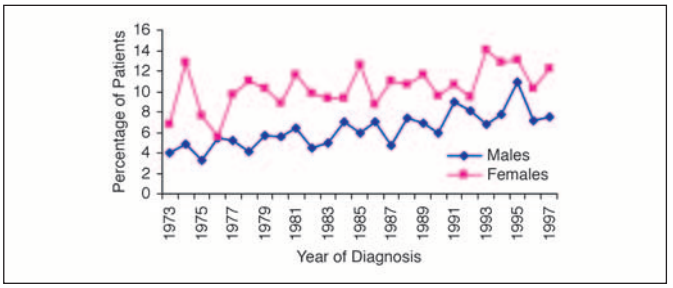

Fig 10. The all-cause survival trends in limited-stage small-cell lung cancer.

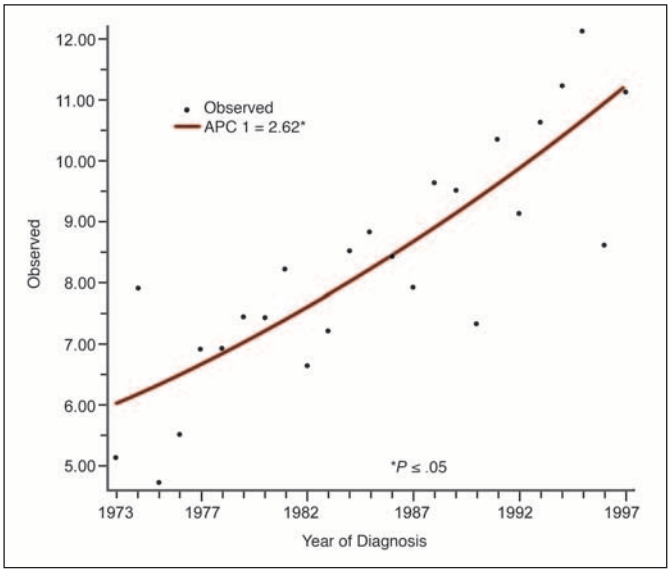

Fig 11. Joinpoint regression of all-cause 5-year survival trends in limited-stage small-cell lung cancer. (*) $P \leq .05$. APC, annual percentage change.

composition of the tobacco blend with an increased use of expanded and reconstituted tobacco. Smokers of cigarettes with low-nicotine delivery tend to smoke more intensely, with greater frequency of puff drawing, increased puff volume, and deeper inhalation, in an adaptation to achieve a desired physiologic response to nicotine.[11] Furthermore, the size use of filtered cigarettes led to the decrease in the size of aerosols, since filters appear to be less effective in the elimination of smaller particles. Whereas long-term smokers of cigarettes with high nicotine and no filter have the highest deposition of particles in the bifurcation zone of the tracheobronchial tree, the deeper inhalation of

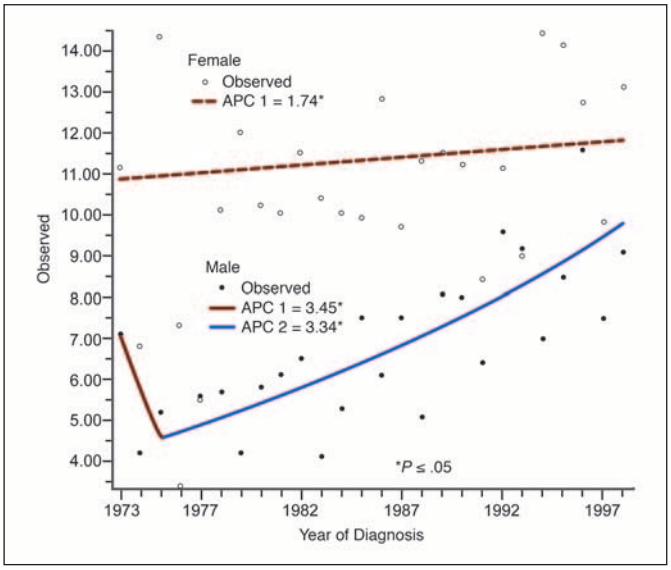

Fig 12. Joinpoint regression of the distribution of sex in all-cause 5-year survival trends in limited-stage small-cell lung cancer. (*) $P \leq .05$. APC, annual percentage change.

smaller particles leads to an increased deposition of smoke particles in the smaller airways and alveoli. This distal distribution is typical of adenocarcinomas but not of SCLC or SCC.[17,18] Recent changes in the composition of smoke may also be implicated in the increased incidence of adenocarcinoma. Over the last few decades, there has been a decrease in the amount of benzo(a)pyrene, a surrogate for the carcinogenic polynuclear aromatic hydrocarbon (PAH), and an increase in the amount of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a surrogate measure of the total tobacco specific nitrosamines (TSNAs). In several animal models, NKK has induced mainly adenoma and adenocarcinoma.[19,20]

The narrowing of the sex gap in the incidence of SCLC could be at least partially explained by the increased number of women diagnosed with lung cancer over the last 20 years. This increase in the number of women diagnosed with lung cancer is directly related with the increased prevalence of smoking in this population, which though lags behind prevalence among men, reached the peak of 55% in the cohort of women born between 1935 and 1944.[9] The estimated prevalence of smokers in the United States for the year 1997 was 25.7% among men and 20.7% among women.[9] Although there has been a significant decline in the incidence of lung cancer in men after peaking in 1984, the incidence in women has only slowed in recent years and appeared to plateau in 1994.[9,21] Although smoking has shown to increase the risk of all major histologic subtypes of lung cancer in both men and women, the OR for smokers compared with nonsmokers is highest for SCLC in women.[22] Therefore, the increased proportion of women smokers combined with the increased risk among women smokers of developing SCLC perhaps accounts for the narrowing of the sex gap in the incidence of SCLC, particularly in face of decreased smoking with consequently decreased incidence of SCLC in men.

Several studies of patients with SCLC have shown improved survival rates in women compared with men. In a study comparing the survival of women and men treated from 1973 to 1986 at the National Cancer Institute, both the rates of median survival (13 months *v* 10 months) and of survival beyond 2.5 years (15% *v* 6%) favored women.[23] Similar findings were reported in a large retrospective analysis of five studies conducted by the Cancer and Leukemia Study Group B (CALGB) between 1972 and 1986, in which women had improved response rates and long-term survival.[24] A retrospective review by the Southwest Oncology Group (SWOG) reported that the improved survival rates in women was restricted to patients with limited-stage disease.[25]

In summary, we confirmed the decreased incidence of SCLC over the last 30 years based on the analysis of the SEER database. The proportion represented by SCLC now constitutes only 12.95% of all newly diagnosed lung cancers. Such a decrease could be explained by the decrease in the prevalence of smokers, particularly among men, and by the change of cigarette composition, including decreased tar and nicotine. With the continued increase in the incidence of lung cancer in women, mostly related to cigarette smoking, the number of SCLC cases in women now equals the number seen in men. Improved outcomes for women have been previously suggested by large retrospective studies but the overall improvement in survival for both men and women over the last 30 years is very modest. SCLC is strongly associated with cigarette smoking and consequently it is a highly preventable disease.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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