A Population-Based Study of Incidence and Survival of 1588 Thymic Malignancies: Results From the California Cancer Registry

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Abstract

Because of limited population-based epidemiological studies on thymic malignancies in the current literature, we sought to evaluate incidence and survival trends in thymic malignancies in the California Cancer Registry. Among 1588 adult cases of thymic malignancy diagnosed between 1988 and 2015, we found that thymic malignancy incidence is rising and there is a variation in incidence according to race/ethnicity. As in previous studies, advanced stage and thymic carcinoma were found to be associated with worsened survival. There also appears to be a trend toward detecting more localized stage disease over time, possibly because of the increased use of thoracic imaging studies. Treatment with surgery was associated with improved overall survival in all stages of disease and improved cause-specific survival in local and regional disease. Further research is required to evaluate and better understand contemporary incidence and prognostic factors in thymic malignancies.

Background: Thymic malignancies are rare and there are limited contemporary population-based epidemiological studies for this uncommon cancer. **Patients and Methods:** Adults aged 20 years and older diagnosed with thymic malignancies between 1988 and 2015 were identified from the California Cancer Registry (n = 1588). Trends in age-adjusted incidence rates were examined overall and according to race/ethnicity, and the proportion diagnosed according to stage was evaluated over time. Cox proportional hazards regression was used to estimate hazard ratios (HRs) for overall survival (OS), and Fine and Gray competing risks regression for cause-specific survival (CSS). **Results:** Age-adjusted incidence increased on average 2.08% per year over the study period (95% confidence interval [CI], 1.30%-2.86%; $P < .0001$), with an incidence of 0.277 cases per 100,000 in 2015. Incidence was highest among Asian/Pacific Islander and non-Hispanic black individuals. The proportion of unknown stage at diagnosis declined as localized diagnoses increased over time. Compared with patients with thymoma, those with thymic carcinoma had significantly worse OS (HR, 1.63; 95% CI, 1.33-2.01; $P < .0001$) and CSS (subdistribution HR, 2.99; 95% CI, 2.29-3.91; $P < .0001$). Advanced stage at diagnosis was also associated with worse survival. Surgical intervention was associated with better prognosis for patients with localized (HR, 0.08; 95% CI, 0.02-0.30; $P = .0002$) or regional disease (HR, 0.14; 95% CI, 0.06-0.34; $P < .0001$). **Conclusion:** Thymic malignancy incidence is increasing in California. There was incidence variation across race/ethnicity, which warrants future study. These findings provide contemporary insight into the incidence and prognostic factors of thymic malignancies.

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Introduction

The thymus is a primary lymphoid organ located in the superior anterior mediastinum within which T cells mature.[1] Tumors of the thymus are rare, and only represent 0.2% to 1.5% of all malignancies.[2] Nonetheless, thymic malignancies are the most common primary anterior mediastinal tumor because they account for up to

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Table 1 Characteristics of Adults Aged 20 and Older Diagnosed With Thymus Cancer in California, 1988 to 2015

	n	%
Total	1588	100.0
Sex		
Male	918	57.8
Female	670	42.2
Age at Diagnosis		
20-49 Y	516	32.5
50-64 Y	539	33.9
≥65 Y	533	33.6
Race/Ethnicity		
Non-Hispanic white	823	51.8
Non-Hispanic black	146	9.2
Hispanic	229	14.4
Asian/Pacific Islander	379	23.9
Other/unknown	11	0.7
Neighborhood Socioeconomic Status		
Lowest	192	12.1
Lower-Middle	254	16.0
Middle	350	22.0
Upper-Middle	350	22.0
Highest	413	26.0
Unknown	29	1.8
Year of Diagnosis		
1988-1991	123	7.7
1992-1995	180	11.3
1996-1999	157	9.9
2000-2003	232	14.6
2004-2007	266	16.8
2008-2011	308	19.4
2012-2015	322	20.3
Stage at Diagnosis		
Localized	367	23.1
Regional	705	44.4
Remote	394	24.8
Unknown	122	7.7
Histology		
Thymoma	1383	87.1
Thymic carcinoma	205	12.9
Treatment		
No treatment	109	6.9
Chemotherapy and/or radiation	300	18.9
Surgery only	434	27.3
Surgery and single modality	508	32.0
Surgery, chemotherapy, and radiation	209	13.2
Unknown	28	1.8

Table 2 Age-Adjusted Incidence Rates[a] of Thymus Cancer Among Adults Aged 20 Years and Older in California, 1988 to 2015 (n = 1588)

Year of Diagnosis	Age-Adjusted Rate (95% CI)	Number of Cases
1988	0.191 (0.131-0.268)	34
1989	0.160 (0.106-0.231)	29
1990	0.157 (0.104-0.225)	29
1991	0.157 (0.106-0.224)	31
1992	0.233 (0.168-0.314)	44
1993	0.179 (0.124-0.250)	35
1994	0.217 (0.158-0.292)	45
1995	0.280 (0.212-0.365)	56
1996	0.184 (0.130-0.254)	38
1997	0.203 (0.146-0.275)	42
1998	0.211 (0.154-0.283)	45
1999	0.147 (0.100-0.208)	32
2000	0.279 (0.214-0.358)	62
2001	0.289 (0.224-0.368)	66
2002	0.214 (0.158-0.283)	49
2003	0.234 (0.176-0.305)	55
2004	0.245 (0.186-0.317)	58
2005	0.265 (0.204-0.338)	65
2006	0.311 (0.244-0.389)	76
2007	0.264 (0.204-0.336)	67
2008	0.312 (0.247-0.389)	81
2009	0.304 (0.240-0.380)	79
2010	0.285 (0.224-0.357)	77
2011	0.255 (0.198-0.323)	71
2012	0.238 (0.184-0.304)	67
2013	0.281 (0.222-0.351)	80
2014	0.301 (0.240-0.372)	88
2015	0.277 (0.221-0.343)	87

[a]Rates are per 100,000 and age-adjusted to the 2000 US standard population (19 age groups; Census P25-1130) standard.

50% of all such tumors.[3] Up to 50% of patients with thymoma might present with a paraneoplastic syndrome such as myasthenia gravis.[4] Thymic carcinoma is a more aggressive thymic epithelial tumor with higher potential for local and distant spread, often presenting with metastatic (bone, lungs, pleura, or liver) or lymphatic disease.[5]

Previous published population-based epidemiological studies in the United States on thymic malignancies are limited. In 2003, Engels and Pfeiffer described demographic patterns of thymic malignancy incidence in the United States and studied 9 states and metropolitan regions: Connecticut, Hawaii, Iowa, New Mexico, Utah, as well as metropolitan Atlanta, Detroit, Seattle, and San Francisco/Oakland.[6] Their study of 849 cases diagnosed between 1973 and 1998 showed that the incidence of thymomas is 0.15 per 100,000 person-years in the United States on the basis of data collected by the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. In addition, the study also showed that thymoma incidence is higher in black and Asian/Pacific Islander (API) than in white or Hispanic individuals. A follow-up study in 2010 by Engels suggested a decrease in the incidence of thymoma, particularly from 1998 to 2006.[7] Using data from the California Cancer Registry (CCR) between 1988 and 2015, we sought to provide a contemporary update on incidence and trends in thymic malignancies in the state of California, the

largest state according to population in the United States. In addition, we aimed to evaluate prognostic factors for thymic malignancies and assess how treatment affects survival across stages at diagnosis.

Patients and Methods

Data in this study were obtained from the CCR, the largest population-based state cancer registry in the United States. The CCR contains demographic, diagnostic, initial treatment, and outcome information on all reportable cancers diagnosed in California residents since January 1988. The registry was queried to identify patients who were at least 20 years old when diagnosed with a first primary invasive tumor of the thymus (International Classification of Diseases for Oncology, third edition [ICD-O-3] site codes C37.9 and histology codes 8580-8586) in California between 1988 and 2015. Autopsy- and death certificate-only diagnoses were excluded.

Age at diagnosis was categorized into 20 to 49 years, 50 to 64 years, and 65 years or older. Race/ethnicity was categorized as non-Hispanic white (NHW), non-Hispanic black (NHB), Hispanic, or API. Neighborhood socioeconomic status (nSES) was on the basis of US Census data on neighborhood characteristics of the patient address at the time of diagnosis, including educational attainment, occupation type, employment rate, median household income, poverty level, median rent, and house values. For patients diagnosed from 1988 to 2005, nSES was estimated using census-block group data from the Census 2000 Summary File. For cases diagnosed from 2006 to 2015, the American Community Survey was used to compute nSES. These 2 sources were combined to form quintiles at the block group level across the state. To ensure stable estimates for stratified analysis, the 28 years in the study period were collapsed into 7 four-year periods.

Stage at diagnosis was on the basis of SEER summary staging and was categorized as localized (noninvasive or invasive disease confined to the thymus), regional (extension to adjacent tissues or the organs/structures in mediastinum), and remote (involvement of distant lymph nodes or metastasis). Thymoma (ICD-O-3 codes 8580-8585) and thymic carcinoma (code 8586) were included. First course of treatment was defined as cancer-directed therapy documented in a patient's medical record and given before disease progression, recurrence, or treatment failure. Treatment was categorized as receipt of: (1) chemotherapy and/or radiation (no surgery); (2) surgery only; (3) surgery with single-modality treatment (chemotherapy or radiation); (4) surgery, chemotherapy, and radiation; and (5) no treatment.

Age-adjusted incidence rates were calculated overall and according to race/ethnicity in SEER*Stat version 8.3.5, and trends were analyzed with Joinpoint Regression Program 4.6.0 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). The proportion of cases diagnosed according to stage at diagnosis was assessed over time. Cox proportional hazards regression was used to estimate hazard ratios (HRs) for overall survival (OS), and Fine and Gray competing risks regression was used to calculate subdistribution HRs (SHRs) for thymic malignancy cause-specific survival (CSS). Models were adjusted for sex, age at diagnosis, nSES, stage at diagnosis, histology, and first course of treatment. To better account for treatment differences according to stage, an additional analysis was conducted stratified according to stage at diagnosis. Survival analysis was conducted using SAS version 9.4 (SAS Institute Inc).

The CCR database is linked annually to the National Death Index, hospital discharge data, Medicare files, the Department of Motor Vehicles, and other administrative databases to ensure accurate vital status and cause of death information. SEER's cause-specific death classification was used to determine if the patient died of their cancer or another cause.

Results

Between 1988 and 2015, a total of 1588 adult cases of thymic malignancy were identified in California (Table 1). Men represented 57.8% of these cases, whereas women represented 42.2%. Just over half (51.8%) of patients were NHW, whereas 23.9% were API. As

Figure 1 Age-Adjusted Incidence Rates of Thymus Cancer Among Adults Aged 20 Years and Older in California, 1988 to 2015 (n = 1588)

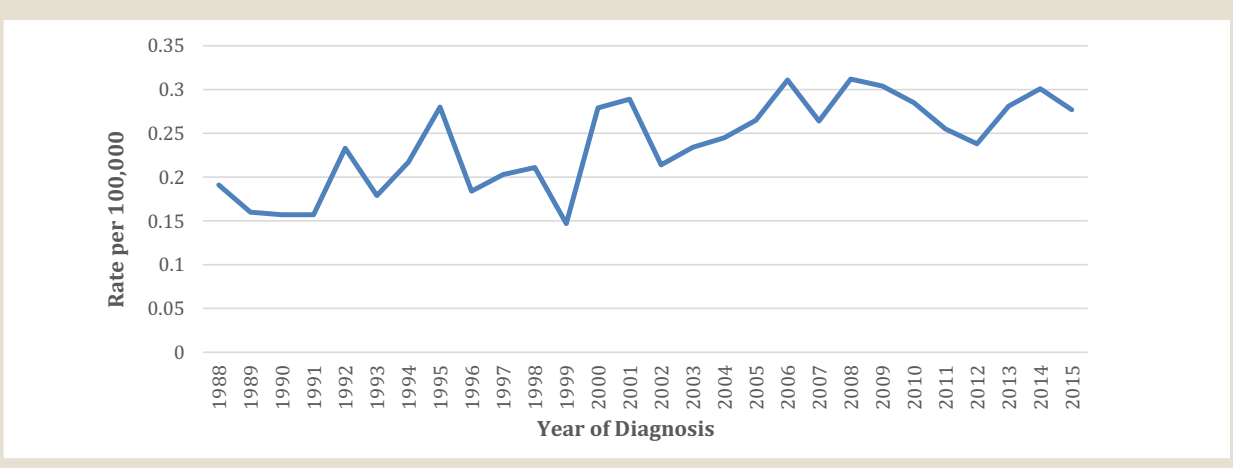

Table 3 Age-Adjusted Incidence Rates[a] of Thymus Cancer Among Adults Aged 20 Years and Older in California According to Race/Ethnicity, 1988 to 2015

Year of Diagnosis	Rate			
	NHW	NHB	Hispanic	API
1988-1991	0.176 (0.141-0.217)	[b]	[b]	0.286 (0.16-0.474)
1992-1995	0.191 (0.155-0.233)	0.351 (0.202-0.568)	0.17 (0.105-0.263)	0.537 (0.386-0.731)
1996-1999	0.159 (95% 0.127-0.197)	0.302 (0.175-0.49)	0.138 (0.036-0.077)	0.368 (0.253-0.517)
2000-2003	0.243 (0.203-0.289)	0.419 (0.262-0.634)	0.116 (0.07-0.182)	0.499 (0.373-0.653)
2004-2007	0.250 (0.209-0.297)	0.44 (0.286-0.648)	0.204 (0.144-0.28)	0.453 (0.343-0.586)
2008-2011	0.251 (0.21-0.298)	0.452 (0.301-0.654)	0.244 (0.14-0.248)	0.491 (0.387-0.615)
2012-2015	0.241 (0.201-0.286)	0.381 (0.251-0.556)	0.188 (CI 0.14-0.248)	0.514 (0.414-0.632)

Abbreviations: API = Asian/Pacific Islander; NHB = non-Hispanic black; NHW = non-Hispanic white.
[a]Rates are per 100,000 and age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130) standard.
[b]Statistic not displayed because there were fewer than 15 cases.

nSES quintile increased, so did the number of patients—individuals from the highest nSES quintile constituted the largest proportion of cases (26.0%) whereas the lowest nSES constituted the smallest proportion (12.1%). Most patients were diagnosed with thymoma (87.1%) and nearly three-quarters (72.5%) of patients received surgery as part of the first course of treatment.

The age-adjusted incidence rate of thymus malignancies significantly increased from 0.191 cases per 100,000 in 1988 to 0.277 cases per 100,000 in 2015 (Table 2), with an estimated annual percent change (APC) of 2.08% per year over the study period (95% confidence interval [CI], 1.30-2.87; $P < .0001$) (Figure 1). As shown in Table 3, incidence varied according to race/ethnicity, with rates highest among API individuals. Between 2012 and 2015, the incidence rate among API individuals was 0.514 per 100,000 (95% CI, 0.414-0.632), compared with 0.381 per 100,000 in NHB individuals (95% CI, 0.251-0.556), 0.241 per 100,000 in NHW individuals (95% CI, 0.201-0.286), and 0.188 per 100,000 in Hispanic individuals (95% CI, 0.14-0.248). Although incidence appeared to increase for each race/ethnicity group over the study period, the yearly increase only reached statistical significance for NHW individuals (APC = 1.65%; 95% CI, 0.23-3.10; $P = .0306$).

The proportion of patients diagnosed with localized disease increased, from 10.6% between 1988 and 1991 to 32.6% between 2012 and 2015 (Table 4). This increase in early-stage diagnoses appeared to coincide with a notable decline in diagnoses of unknown stage, from 19.5% between 1988 and 1991 to 3.4% between 2012 and 2015. The proportion of regional diagnoses also decreased, although these still constituted the highest percentage of diagnoses in the population. There was no clear pattern in the proportion of remote diagnoses over time; approximately one-fifth to one-quarter of patients were diagnosed with advanced disease throughout the study period. Of note, the proportion of disease staging at the time of diagnosis was not different according to nSES.

The predictors of OS and CSS are shown in Table 5. Women had significantly better survival than men with respect to OS, but this effect became insignificant for CSS. Similarly, older age at diagnosis was associated with worse OS, but age was not associated with CSS. There did not appear to be any significant differences in OS according to race/ethnicity, but Hispanic patients had significantly worse CSS than NHW patients (SHR, 1.70; 95% CI, 1.24-2.32; $P = .0009$). Lower nSES appears to be associated with worse OS compared with the highest nSES group, but nSES was not significantly associated with death due to thymic malignancies. For OS and CSS, prognosis was worse with later stage at diagnosis, with patients diagnosed at the remote stage having nearly 3 times worse survival from any cause (HR, 2.83; 95% CI, 2.18-3.66; $P < .0001$) and over 5 times the hazard of death from thymic malignancies (SHR, 5.44; 95% CI, 3.24-9.15) compared with patients with localized disease. Thymic carcinoma patients had significantly

Table 4 Proportion of Adults Aged 20 Years and Older Diagnosed With Thymic Malignancies in California According to Stage at Diagnosis, 1988 to 2015

Year of Diagnosis	Localized (n = 367)		Regional (n = 705)		Remote (n = 394)		Unknown (n = 122)	
	n	Row %	n	Row %	n	Row %	n	Row %
1988-1991	13	10.6	60	48.8	26	21.1	24	19.5
1992-1995	34	18.9	84	46.7	29	16.1	33	18.3
1996-1999	30	19.1	83	52.9	29	18.5	15	9.6
2000-2003	35	15.1	109	47.0	68	29.3	20	8.6
2004-2007	66	24.8	124	46.6	66	24.8	10	3.8
2008-2011	84	27.3	125	40.6	90	29.2	9	2.9
2012-2015	105	32.6	120	37.3	86	26.7	11	3.4

Table 5 Overall and Cause-Specific Survival of Adults Aged 20 Years and Older Diagnosed With Thymus Cancer in California, 1988 to 2015

	Overall Survival		Cause-Specific Survival	
	HR (95% CI)	*P*	SHR (95% CI)	*P*
Sex				
Male	Reference		Reference	
Female	0.85 (0.73-0.99)	.0419[a]	0.90 (0.71-1.14)	.3825
Age at Diagnosis				
20-49 Y	Reference		Reference	
50-64 Y	1.22 (1.01-1.48)	.0448[a]	1.04 (0.79-1.36)	.7824
≥65 Y	2.13 (1.76-2.58)	<.0001[a]	1.13 (0.84-1.50)	.4232
Race/Ethnicity				
Non-Hispanic white	Reference		Reference	
Non-Hispanic black	1.08 (0.84-1.40)	.5428	1.15 (0.78-1.70)	.4740
Hispanic	1.06 (0.84-1.34)	.6224	1.70 (1.24-2.32)	.0009[a]
Asian/Pacific Islander	0.89 (0.73-1.07)	.2150	0.82 (0.60-1.12)	.2132
Neighborhood Socioeconomic Status				
Lowest	1.25 (0.95-1.63)	.1107	0.72 (0.47-1.11)	.1356
Lower-Middle	1.51 (1.19-1.91)	.0008[a]	1.41 (1.00-1.99)	.0530
Middle	1.13 (0.90-1.41)	.2844	0.98 (0.71-1.37)	.9120
Upper-Middle	1.16 (0.93-1.45)	.1786	0.96 (0.69-1.34)	.8096
Highest	Reference		Reference	
Stage at Diagnosis				
Localized	Reference		Reference	
Regional	1.70 (1.34-2.15)	<.0001[a]	2.55 (1.56-4.15)	.0002[a]
Remote	2.83 (2.18-3.66)	<.0001[a]	5.44 (3.24-9.15)	<.0001[a]
Histology				
Thymoma	Reference		Reference	
Thymic Carcinoma	1.63 (1.33-2.01)	<.0001[a]	2.99 (2.29-3.91)	<.0001[a]
First Course of Treatment				
No treatment	Reference		Reference	
Chemotherapy and/or Radiation	0.80 (0.60-1.08)	.1498	0.94 (0.59-1.51)	.8035
Surgery Only	0.37 (0.27-0.51)	<.0001[a]	0.32 (0.18-0.58)	.0001[a]
Surgery and Single Modality	0.40 (0.29-0.54)	<.0001[a]	0.45 (0.27-0.73)	.0011[a]
Surgery, Chemotherapy, and Radiation	0.45 (0.32-0.63)	<.0001[a]	0.59 (0.36-0.98)	.0401[a]

Estimates are adjusted for all variables listed in the table.
Abbreviations: HR = hazard ratio; SHR = subdistribution hazard ratio.
[a]Statistically significant.

worse OS (HR, 1.63; 95% CI, 1.33-2.01; $P < .0001$) and CSS (SHR, 2.99; 95% CI, 2.29-3.91; $P < .0001$) compared to thymoma patients, consistent with previous studies.[8,9]

Receiving surgery, chemotherapy, radiation, or a combination of these modalities was associated with significantly better prognosis for OS and CSS compared with forgoing these treatments. Table 6 indicates treatment associated with OS and CSS for each stage at diagnosis. With respect to OS, receiving surgery alone or in combination with chemotherapy and/or radiation was associated with a significantly reduced hazard of death, regardless of stage at diagnosis. For CSS, receiving surgery alone or with chemotherapy and/or radiation was associated with significantly better prognosis for patients with localized or regional disease, but not for individuals diagnosed at the remote stage.

Discussion

This study is one of the largest known epidemiological studies of thymic malignancies with 1588 total cases. In 2015, the incidence rate of thymic malignancies was 0.277 per 100,000, which is higher than the incidence rate of 0.15 per 100,000 reported by Engels and Pfeiffer in 2003 and 0.13 per 100,000 reported by Engels in 2010.[6,7] Of note, both previous studies only included cases of malignant thymomas, whereas approximately 13% of this study's population included thymic carcinoma. The inclusion of thymic carcinoma in this study might partly explain the reported increase in incidence. In addition, the Engels study population included patients of all ages, whereas this study excluded the pediatric population between ages 0 to 20 because of the rarity of thymic malignancies in children. In fact, only 13 cases from ages 0 to 20

Table 6 Overall and Cause-Specific Survival of Adults Aged 20 Years and Older Diagnosed With Thymus Cancer in California According to Stage at Diagnosis, 1988 to 2015

Stage at Diagnosis	First Course of Treatment	Overall Survival		Cause-Specific Survival	
		HR (95% CI)	*P*	SHR (95% CI)	*P*
Localized	No treatment	Reference		Reference	
	Chemotherapy and/or radiation	1.62 (0.61-4.26)	.3303	0.80 (0.15-4.27)	.7903
	Surgery only	0.28 (0.15-0.53)	.0001[a]	0.08 (0.02-0.30)	.0002[a]
	Surgery and single modality	0.37 (0.19-0.72)	.0038[a]	0.08 (0.02-0.34)	.0008[a]
	Surgery, chemotherapy, and radiation	0.48 (0.18-1.32)	.1559	0.97 (0.23-4.12)	.9713
Regional	No treatment	Reference		Reference	
	Chemotherapy and/or radiation	0.58 (0.33-1.03)	.0613	0.38 (0.17-0.89)	.0260[a]
	Surgery only	0.34 (0.19-0.58)	<.0001[a]	0.14 (0.06-0.34)	<.0001[a]
	Surgery and single modality	0.34 (0.20-0.58)	<.0001[a]	0.24 (0.11-0.53)	.0004[a]
	Surgery, chemotherapy, and radiation	0.42 (0.24-0.74)	.0027[a]	0.30 (0.13-0.68)	.0041[a]
Remote	No treatment	Reference		Reference	
	Chemotherapy and/or radiation	0.94 (0.62-1.42)	.7666	1.40 (0.74-2.67)	.2994
	Surgery only	0.50 (0.27-0.93)	.0278[a]	1.01 (0.41-2.48)	.9917
	Surgery and single modality	0.43 (0.26-0.69)	.0006[a]	0.65 (0.32-1.31)	.2243
	Surgery, chemotherapy, and radiation	0.40 (0.24-0.67)	.0004[a]	0.75 (0.37-1.52)	.4256

Estimates are adjusted for sex, age at diagnosis, race/ethnicity, neighborhood socioeconomic status, and histology type.
Abbreviations: HR = hazard ratio; SHR = subdistribution hazard ratio.
[a]Statistically significant.

were identified in the study population between 1988 and 2015. Nevertheless, these findings indicate higher incidence rates of thymic malignancies than previously reported.[6,7] Incidence appears to be increasing, which differs from some earlier published studies that suggested a decline in incidence.[7]

Similar to previous studies, we found that rates of thymic malignancies were higher among API individuals than in individuals of other races/ethnicities.[6,7] Engels and Pfeiffer reported that incidence rates were highest in Hawaii and San Francisco, reflecting the high incidence among API individuals.[6] Less racially/ethnically diverse states, namely Iowa and Utah, had the lowest incidence rates of thymic malignancies in their study. California, a racially/ethnically diverse state, has a large and growing API population. According to census studies, the proportion of API individuals in the state increased from 8% in 1988 to 12% in 2015.[10] The racial/ethnic distribution of California might explain in part why incidence appears to be higher in this state than national estimates reported previously. It is unclear why API individuals have higher incidence rates of thymic malignancies than other race/ethnic groups. Further studies are needed to understand this disparity in incidence rates.

The rising incidence of thymic malignancies in California might also be partly attributable to the increased use of imaging studies in the United States over the study period. In a 2009 study, Smith-Bindman et al[11] examined the use of imaging studies in a large health plan group in Washington state between 1997 and 2006. During this time, computed tomography (CT) imaging studies increased by 14% per year, and over the 10-year study period, doubled overall. More specifically, the number of CT chest imaging studies nearly tripled from approximately 30 per 1000 enrollees in 1997 to approximately 90 per 1000 enrollees in 2006. As shown in our study, there appears to be a trend toward early stage disease at the time of diagnosis. The increasing use of diagnostic imaging studies might have led to an increased number of incidental findings of thymic malignancies at early stage disease. Another possibility is classification bias with improved pathologic diagnosis of thymoma and thymic carcinoma over time. These associations are speculative but deserve to be examined further.

In our study, sex, age, and nSES were associated with OS; however, our findings suggest these are not significant prognostic factors for survival of thymic malignancies. Rather, cancer-specific variables already known to predict survival in thymic malignancy patients were confirmed, including histology and stage at diagnosis.[11-13]

Because thymomas and thymic carcinomas are rare malignancies, there have been no randomized studies that have compared treatment regimens. Nonetheless, surgical resection is considered the gold standard treatment for resectable disease.[14,15] We observed that surgery (alone or in combination with other therapies) was associated with improved OS regardless of stage and with improved CSS for localized and regional disease. The findings in this retrospective study likely reflect substantial patient selection bias, although these outcomes according to treatment modality are congruent with the current standard of care for earlier stage resectable disease.

There are several additional limitations of this study including the lack of more detailed information regarding staging and treatment. Because of availability of data over the study period, SEER's summary staging was used rather than the more often clinically used Masaoka-Koga staging system.[16-18] The CCR does not

routinely collect information on cancer recurrence, the number of rounds of chemotherapy and radiation received, or subsequent treatments. In addition, the CCR does not collect data on paraneoplastic autoimmune syndromes, which is a known complication of thymoma. Despite these limitations, this study used one of the largest known data sets of thymic malignancies to date to give insight into trends in incidence and predictors of survival in a large, diverse population.

Conclusion

Thymic malignancy appears to be increasing over time in California, with higher rates observed in API and NHB individuals. There also appears to be a trend toward detecting more localized stage disease, possibly because of the increased use of thoracic imaging studies. Advanced stage and thymic carcinoma were found to be associated with worsened survival, consistent with previous studies. Treatment with surgery was associated with improved CSS in local and regional disease.

Clinical Practice Points

- Although some previous studies have suggested a decrease in incidence, our study shows that thymic malignancy incidence appears to be increasing.
- Incidence varies among race/ethnicity, with higher incidence among API and NHB individuals.
- There is a trend toward localized stage disease possibly because of the increased use of imaging studies.
- Thymic carcinoma and advanced stage were both associated with worsened survival, which is consistent with previous studies.

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Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Miller JF. The discovery of thymus function and of thymus derived lymphocytes. *Immunol Rev* 2002; 185:7-14.
2. Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy of invasive thymoma. *J Clin Oncol* 1990; 8:1419-23.
3. Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors: Part 1. Tumors of the anterior mediastinum. *Chest* 1997; 112:511-22.
4. Riedel RF, Burfeind WR. Thymoma: benign appearance, malignant potential. *Oncologist* 2006; 11:887-94.
5. Venuta F, Rendina EA, Anile M, De Giacomo T, Vitolo D, Coloni GF. Thymoma and thymic carcinoma. *Gen Thorac Cardiovasc Surg* 2012; 60:1-12.
6. Engels EA, Pfeiffer RM. Malignant thymomas in the United States: demographic patterns in incidence and associations with subsequent malignancies. *Int J Cancer* 2003; 105:546-51.
7. Engels EA. Epidemiology of thymoma and associated malignancies. *J Thorac Oncol* 2010; 5(suppl 4):S260-5.
8. Blumberg D, Burt ME, Bains MS, et al. Thymic carcinoma: current staging does not predict prognosis. *J Thorac Cardiovasc Surg* 1998; 115:303-9.
9. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1, 320 patients from Japan. *Ann Thorac Surg* 2003; 76:878-85.
10. State of California, Department of Finance. Race/Ethnic Population With Age and Sex Detail, 1970 to 2040. Sacramento, CA: State of California, Department of Finance, 1998.
11. Smith-Bindman R, Miglioretti DL, Larson EB. Rising use of diagnostic medical imaging in a large integrated health system. *Health Aff (Millwood)* 2008; 27:1491-502.
12. Ettinger DS, Akerley W, Bepler G, et al. Thymic malignancies. *J Natl Compr Canc Netw* 2010; 8:1302-15.
13. Huang J, Rizk NP, Travis WD, et al. Comparison of patterns of relapse in thymic carcinoma and thymomas. *J Thorac Cardiovasc Surg* 2009; 138:26-31.
14. Eng TY, Fuller CD, Jagirdar J, et al. Thymic carcinoma: state of the art review. *Int J Radiat Oncol Biol Phys* 2004; 59:654-64.
15. Scorsetti M, Leo F, Trama A, et al. Thymoma and thymic carcinomas. *Crit Rev Oncol Hematol* 2016; 99:332-50.
16. Gubens MA. Treatment updates in advanced thymoma and thymic carcinoma. *Curr Treat Options Oncol* 2012; 13:527-34.
17. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. *Cancer* 1981; 48:2485-92.
18. Koga K, Matsuno Y, Noguchi M, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. *Pathol Int* 1994; 44:359-67.