World J Surg (2019) 43:3239–3247
https://doi.org/10.1007/s00268-019-05132-6

ORIGINAL SCIENTIFIC REPORT

Largely Unchanged Annual Incidence and Overall Survival of Pleural Mesothelioma in the USA

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Published online: 19 August 2019

Abstract

Background Projections based on regulations curtailing asbestos use in the USA suggest that peak incidence of pleural mesothelioma would occur between 2000 and 2005 and then decline. We analyzed the National Cancer Database (NCDB) to assess current trends in disease incidence, patient demographics, cancer treatment, and survival.

Methods The NCDB was queried to identify patients diagnosed with pleural mesothelioma from 2004 through 2014. Clinical and pathologic characteristics, treatments, and survival were analyzed. Risk factors for death were identified by multivariable Cox regression.

Results A total of 20,988 patients with pleural mesothelioma were reported to the NCDB. The number of cases per year increased from 1783 to 1961, accounting for roughly 0.3% of all reported cancers each year. The proportion of elderly patients increased from 75 to 80%, but distribution by sex remained constant (20% female). The proportion of patients undergoing treatment increased from 34 to 54%. One-year survival increased from 37 to 47% and 3-year survival from 9 to 15% ($p < 0.001$). Factors associated with improved survival included younger age, female sex, epithelioid histology, treatment in an academic center, health insurance, higher income, and multimodality therapy.

Conclusions The annual incidence of mesothelioma has not declined this century and remains stable. Reporting of histologic and clinical staging has improved. National trends suggest that survival is slowly increasing despite an aging cohort. Multimodal therapy and treatment at academic centers are modifiable risk factors associated with improved survival.

Hari B. Keshava and Andrew Tang have contributed equally to the study.

Disclosures Dr. Raja is a consultant for Smiths Medical, which does not pertain to this manuscript.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00268-019-05132-6) contains supplementary material, which is available to authorized users.

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Abbreviations

CD	Charlson–Deyo
NCDB	National Cancer Database
NOS	Not otherwise specified

Introduction

Asbestos was once considered an ideal building material because of its high tensile strength, flexibility, resistance to chemical and thermal degradation, and high electrical resistance. Mining and processing of asbestos began in the 1800s, with industries from shipping to automotive and

residential insulation accounting for much of its widespread use. In the 1920s, a relationship was noted between exposure to asbestos and development of mesothelioma [1–3]. Regulation of use and production began in 1963 with the Clean Air Act, which cited asbestos as a controlled air pollutant. In 1989, the Environmental Protection Agency banned the mining, importing, and processing of asbestos in US products. This led to a dramatic decrease in the use and production of asbestos, with the last domestic asbestos mine closing in 2002. Nonetheless, the height of asbestos use and production in the USA occurred in the 1970s.

While it is not the only risk factor, mesothelioma has been estimated to develop over several decades after exposure to asbestos. Peak incidence of the disease in the USA was projected to occur in the early 2000s [4–6]. However, there is little to suggest that the decrease in industrial use over the past several decades has translated into a decreased incidence of pleural mesothelioma.

The aim of this study was to use the National Cancer Database (NCDB) to evaluate trends in the incidence, demographics, histology, treatment, and survival of malignant pleural mesothelioma in the modern era.

Methods

Data source

The NCDB is a database capturing about 70% of all new cancers occurring in the USA. This is a joint effort of the American College of Surgeons and the Commission on Cancer to capture and maintain demographic, facility, survival, and cancer-related variables [7–10]. Only deidentified data from accredited hospitals are collected [7]. Because the NCDB contains data from different centers, it is ideal for studying rare cancers like pleural mesothelioma at a national level [11].

Patient selection

The NCDB was queried for patients diagnosed with pleural mesothelioma from 2004 through 2014. All patients were older than 18 years of age, treated in the USA, and had known survival and treatment information. This project was approved by the institutional review board, with patient consent waived.

Variables collected

Clinical and pathologic data obtained from the NCDB included age, sex, race (white, black, other), modified Charlson–Deyo (CD) score, insurance status, education level, income, facility type, facility location, histology, laterality, and clinical stage [12]. These variables are further described in the NCDB Participant User File data dictionary (for details, see https://ncdbpufbeta.facs.org/?q=node/259) [13]. Clinical staging was defined according to the 6th (n = 9971) and 7th (n = 9947) AJCC TNM staging criteria for the majority of the patients [14, 15].

Treatment variables

Patients with the surgical treatment codes "Simple/Partial Surgical Removal of Primary Site," "Total Surgical Removal of Primary Site, Enucleation," "Surgery Stated to be Debulking," and "Radical Surgery—en bloc" were deemed to have had surgery for mesothelioma.

Before 2006, timing of chemotherapy was determined by comparing the start date of chemotherapy to the date of surgery. After 2006, the NCDB defined the order of treatment relative to surgery. Timing of radiation was determined using the specific sequence code for radiation that defined the order of treatment relative to surgery for all years. Only patients who received "beam radiation" or "radiation therapy, NOS" to the chest, lung, chest wall, or ribs were coded to radiation. Whether chemotherapy and radiation are given concurrently or sequentially is not captured by the NCDB. For patients who did not undergo surgery, timing of chemotherapy and radiation was determined from the sequence code.

Patients were categorized as having received no treatment, chemotherapy only, surgery only, bimodality treatment (chemotherapy and surgery), or trimodality treatment (chemotherapy, radiation, and surgery).

Analysis of trends

Variables were stratified according to the year of diagnosis. Categorical variables were compared using the Chi-squared test and continuous variables using analysis of variance with Student's t test. Continuous variables are presented as means and ranges and categorical variables as number and percentage. Because the NCDB captures 70% of all new cancers occurring in the USA each year, the absolute number of patients for a given region in that year was compared with 70% of a region's total population as reported in the 2010 US Census. This was used to estimate the true annual incidence of mesothelioma in the region.

Survival analysis

Survival was assessed nonparametrically by the Kaplan–Meier method and stratified by sex, histology, and treatment. The log-rank test was used for comparisons between groups. Survival was assessed parametrically using a multivariable Cox proportional hazards model to

characterize predictors of survival. Clinically relevant variables or variables with a p value < 0.2 on bivariate analysis were chosen. Backward elimination was used to retain variables with a $p < 0.05$ significance value in the final parsimonious model. The primary endpoint was last-known survival (in months) from the date of diagnosis. Missing data were reclassified as "unknown" or "other" to allow associations between missing information and survival. The final model is reported as hazards ratio (HR), 95% confidence interval, and p value. Model discrimination was assessed using C-statistics, which were greater than 0.7 for all models. The final variables included year of diagnosis, age, race, CD score, insurance type, income, population, facility location, facility type, clinical stage, histology, and treatment type.

Results

Mesothelioma incidence

Over the 11-year study period, 20,998 patients were diagnosed with pleural mesothelioma (Table 1). The absolute number of new cases per year over the study period remained fairly constant (Supplemental Table 1). Pleural mesothelioma comprised 0.23% of all cancers reported in the NCDB and was constant over time (Table 2).

Demographic trends

In 2004, 75% of patients were older than 65 years at diagnosis, compared with 80% in 2014; mean age at diagnosis was 71.9 years in 2004 versus 73.3 years in 2014. Nearly 80% of the mesothelioma cohort were men, with an increasing proportion of women diagnosed over the study period (Supplemental Table 1). Most patients had no associated comorbidities; 70% had a CD score of 0, 23% a score of 1, and 7% a score of 2. Although the majority of patients were treated at non-academic facilities, the annual incidence of those treated at academic facilities rose from 35% in 2004 to 39% in 2014 ($p < 0.0001$; Supplemental Table 1). The greatest proportion of cases by geographic region were in the South (31%), Midwest (26%), and Northeast (25%), followed by the Pacific (13%) and Mountain (5%) regions. Regional cases of mesothelioma per capita were highest in the Northeast, with 13 cases/1 million, and lowest in the Mountain region, with 6 cases/1 million (Fig. 1).

Histology and staging trends

Histologic assessment improved over time. In 2004, 53% of cases were not otherwise specified (NOS) histology,

Table 1 Demographics, facility characteristics, and treatment

Variable	Total
Age (Mean range)	72.7 (18–90)
Gender	
Male	16,483
Female	4505
Race	
White	19,475
Black	931
Asian/other	582
CD Score[a]	
CD 0	14,404
CD 1	4748
CD 2+	1836
Insurance	
Medicare	14,423
Medicaid	470
Private	5004
Other	737
Not insured	354
Income	
$63,000+	7150
$48,000–$62,999	5850
$38,000–$47,999	4692
<$38,000	2762
Unknown	534
Population	
Metro	16,623
Urban	3005
Rural	406
Unknown	954
Facility location	
Northeast	5317
Midwest	5459
Mountain	962
Pacific	2650
South	6474
Unknown	126
Facility type	
Other	13,658
Academic/research	7330
Laterality	
Right	11,606
Left	7605
Bilateral	519
Unknown	1258
Histology	
Mesothelioma, NOS[a]	9103
Epithelioid	7741
Sarcomatoid	2594

Table 1 continued

Variable	Total
Biphasic	1550
Clinical stage	
I	3452
II	2165
III	3178
IV	6618
Unknown	5575
Treatment	
None	10,765
Chemotherapy only	7551
Surgery only	1041
Bimodality	1297
Trimodality	334

[a]*CD Score* Charlson–Deyo score, *NOS* not otherwise specified

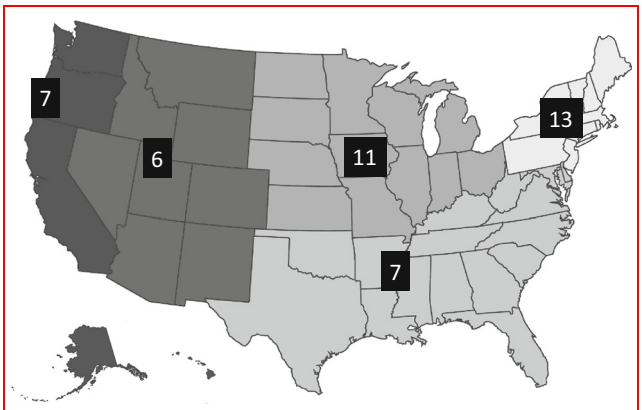


Fig. 1 Incidence of pleural mesothelioma in areas of the USA per 1,000,000 people from 2004 to 2014

which decreased to 35% by 2014 ($p < 0.001$). With the decline in NOS diagnoses, there was a corresponding increase in the proportion of epithelioid mesothelioma diagnosed, from 30% in 2004 to 45% in 2014 ($p < 0.001$). Sarcomatoid and biphasic histology remained constant over time, with each making up less than 15% of all mesotheliomas. Concurrently with reduction in NOS diagnoses, a dramatic reduction occurred in the percentage of "unknown" clinically staged cases, from close to 40% in 2004 to less than 20% in 2014 ($p < 0.001$; Supplemental Table 1).

Treatment trends

Annually, more than 50% did not receive any form of treatment, until 2014. Use of chemotherapy increased from only 30% in 2004 to 40% in 2014 ($p < 0.001$). Surgery and multimodality therapy remained constant, with each comprising less than 10% of treated cases (Supplemental Table 1).

Survival

One-year overall survival improved from 37% in 2004 to 47% in 2013, and 3-year survival, from 9% in 2004 to 15% in 2013 (Fig. 2). Kaplan–Meier survival for women was significantly greater than for men at 1 year (46.7% vs. 40%), 3 years (17.7% vs. 9.8%), and 5 years (10.0% vs. 4.5%) (log rank $p < 0.001$; Fig. 3). Histologic subtypes were also associated with survival differences. Those with epithelioid tumors had the best survival relative to biphasic and sarcomatoid tumors at 1 year (54.5% vs. 38.2% and 17.7%), 3 years (16.3% vs. 9.4% and 4.0%), and 5 years (7.8% vs. 2.0% and 2.5%) (log rank $p < 0.001$; Fig. 4).

Later year of diagnosis, female sex, treatment at an academic facility, and epithelioid histology were associated with improved survival. Older age, higher CD score, Medicaid and lack of insurance, lower income, urban area, higher clinical stage, sarcomatoid, biphasic, and NOS histology were associated with worse survival (Table 3).

Table 2 Number cases of pleural mesothelioma compared to the total number of cancer cases in the National Cancer Database

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Pleural mesothelioma cases	1783	1829	1817	1818	1869	1894	2031	2000	1961	2025	1961
Total cancer cases	711,376	736,230	768,240	805,385	825,206	840,725	836,348	863,283	864,081	887,838	884,768
Percentage of pleural mesothelioma cases	0.25%	0.25%	0.24%	0.23%	0.23%	0.23%	0.24%	0.23%	0.23%	0.23%	0.22%

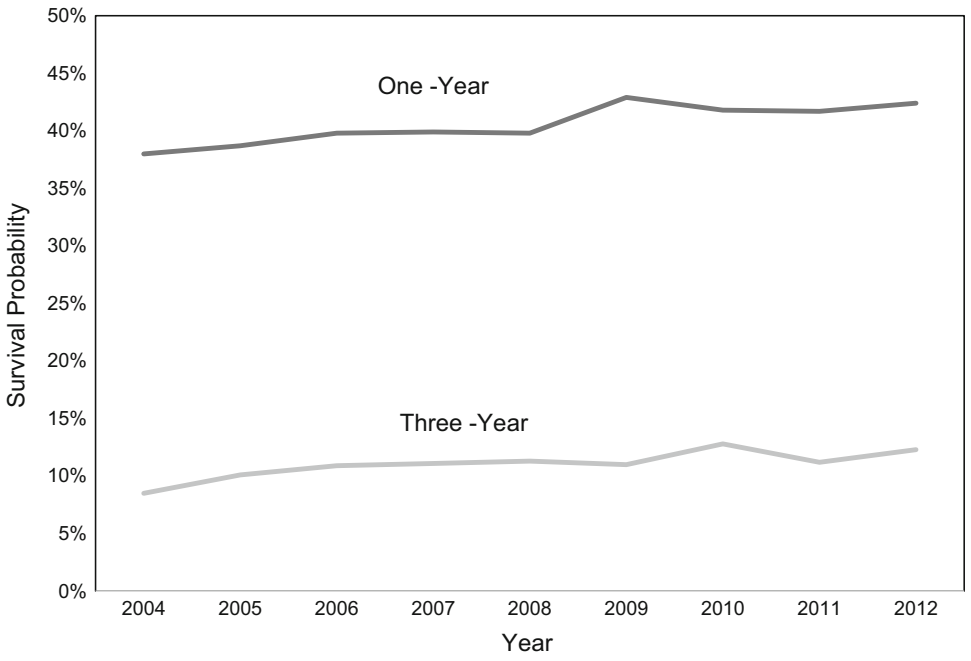


Fig. 2 One- and three-year survival of pleural mesothelioma patients over time

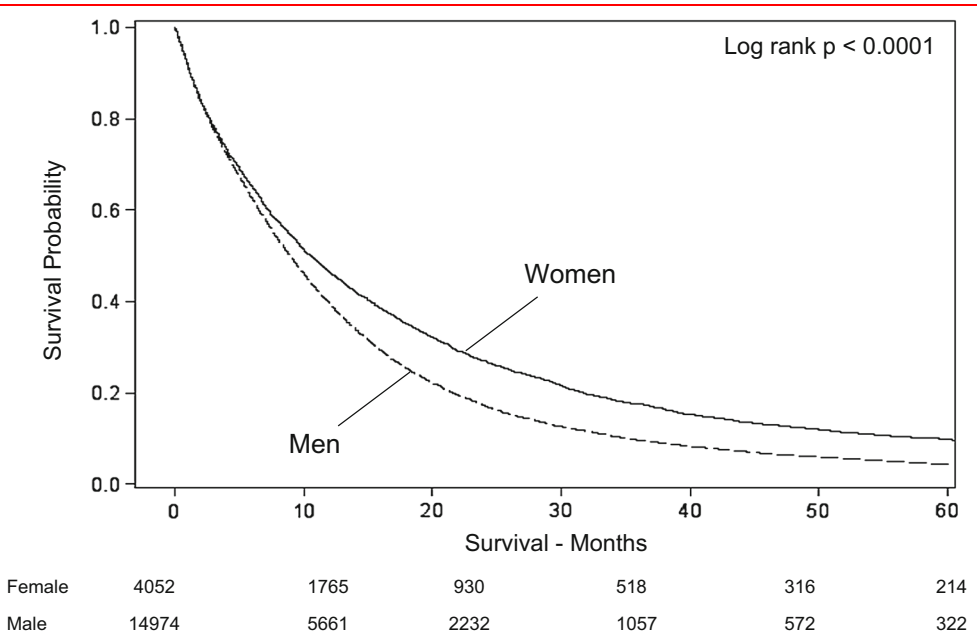


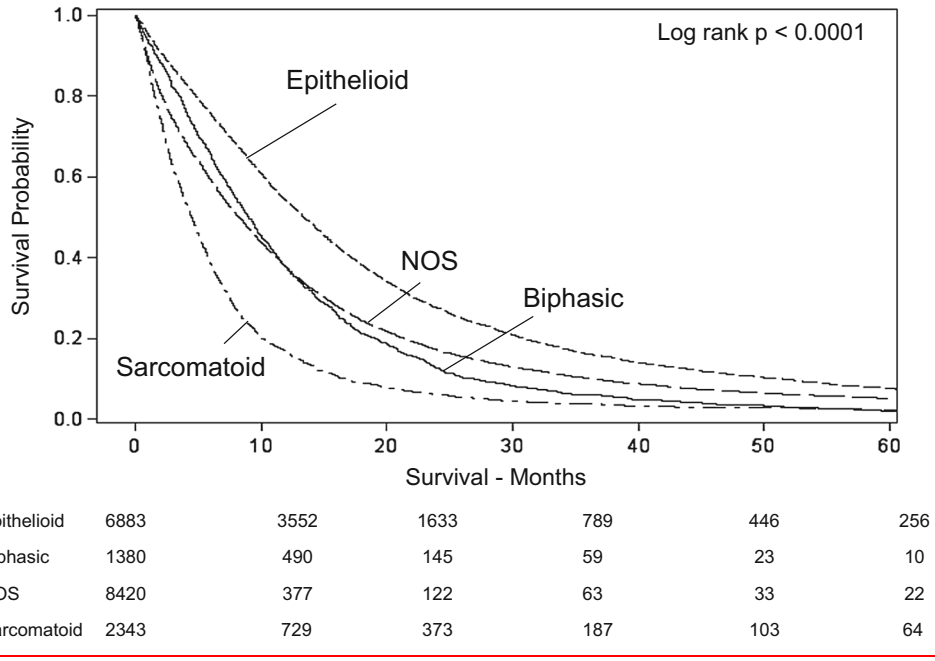
Fig. 3 Survival for men and women with pleural mesothelioma

Treatment and survival

Patients receiving trimodality therapy had the best overall survival at 1 year (79.4%), 3 years (25.2%), and 5 years (12.3%), and those receiving no treatment had the worst (32.6%, 9.1%, and 4.4%, respectively) ($p < 0.001$; Fig. 5). After adjusting for demographic, histologic, and staging variables, receiving any sort of treatment (single or multimodality) led to greater survival relative to no treatment ($p < 0.001$; Table 3).

Discussion

Analysis of NCDB pleural mesothelioma cases from 2004 through 2014 suggests that the incidence of pleural mesothelioma has not decreased as might have been



Epithelioid	6883	3552	1633	789	446	256
Biphasic	1380	490	145	59	23	10
NOS	8420	377	122	63	33	22
Sarcomatoid	2343	729	373	187	103	64

Fig. 4 Survival for pleural mesothelioma by histology (NOS—not otherwise specified)

anticipated. There is also a male predominance with a slowly increasing female predilection, fewer unspecified histologic and clinical staging, and increased chemotherapy use. Additionally, survival was superior in women, patients with epithelioid tumors, trimodality treatment, and treatment at an academic facility.

In the mid-1960s and 1970s a definitive causal relationship was demonstrated between asbestos exposure and mesothelioma [1, 2]. Legislation in the USA eventually led to a dramatic decrease in the production and use of asbestos, with the last US asbestos mines closing in 2002 [16–18]. It has long been postulated that a decrease in peak asbestos exposure after the 1970s would translate into a peak incidence of mesothelioma in the early 2000s followed by a subsequent decline. However, despite the decreased asbestos production, this does not appear to be the case.

Is it possible that exposure to asbestos has continued despite the legislation? There is still continued exposure to asbestos in high-risk occupations such as automotive, construction, and shipyard workers [19, 20]. Sources include products that to this day still contain asbestos (e.g., brake pads and floor tiles), products manufactured in countries that continue to mine asbestos at high levels (Russia, India, and Canada), and removal of asbestos from older homes and buildings [21–23]. Additionally, monumental events in recent history, including the collapse of the Twin Towers on September 11, 2001, have released asbestos into the atmosphere, providing inadvertent exposure to first responders and the general public [24–26]. Based on our findings, practitioners must keep mesothelioma in their differential diagnosis, especially for people who may have continued exposure to asbestos.

Although the vast majority of cases of pleural mesothelioma occur in men, an increasing proportion of women are being diagnosed. Male predominance is likely due to occupational hazards, as factory work and mining are historically male dominant. However, increases in the female workforce from the 1960s to 1980s may account for the slight increase in females diagnosed with pleural mesothelioma. Although more women are being diagnosed, they appear to have better survival than men, as has been suggested elsewhere [27]. This has not been completely explained, but speculation exists [28, 29]. Estrogen has been shown to decrease progression of mesothelioma, although a true biologic mechanism has not been identified [30].

Importantly, we found that reporting of histologic diagnoses and clinical stage has improved. Whether this represents improved recognition of histologic subtypes due to involvement of specialist pathologists or just improved capture in the database is unclear. Histologic identification remains an important prognostic indicator; our study confirms that epithelioid mesothelioma is associated with the best overall survival relative to other histologic subtypes [31–33]. Similarly, while staging modalities, especially radiographic staging techniques, have improved, it is difficult to determine whether we are seeing improved staging or improved reporting in the database [34–36].

Although overall survival of patients with pleural mesothelioma remains poor, subtle improvements in 1- and 3-year survival were observed. This could be due to the

Table 3 Cox proportional hazards model demonstrating factors affecting mesothelioma survival

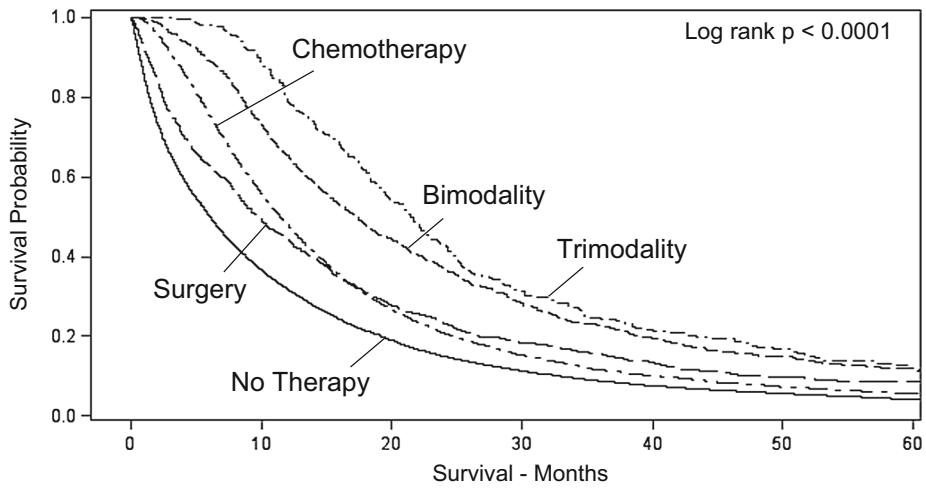
Covariate	*N*	HR [95% CI][a]	*p*
Year of diagnosis	19,026	0.99 [0.98–0.99]	<0.0001
Age	19,026	1.02 [1.02–1.02]	<0.0001
Gender			
Male	14,974	Ref	<0.0001
Female	4052	0.83 [0.80–0.86]	
Race			
White	17,654	Ref	
Black	849	1.3 [0.95–1.11]	0.4625
Asian/other/unknown	523	0.91 [0.82–1.00]	0.0438
CD score[a]			
0	13,041	Ref	
1	849	1.14 [1.10–1.18]	<0.001
2+	523	1.28 [1.21–1.35]	<0.001
Insurance			
Medicare	13,024	Ref	
Private	4584	1.03 [0.99–1.07]	0.2048
Medicaid	415	1.20 [1.07–1.34]	0.0019
Other Government	677	0.99 [0.91–1.07]	0.7421
Not insured	326	1.15 [1.01–1.31]	0.00297
Income			
$63,000+	6415	Ref	
$48,000–$62,999	5298	1.06 [1.02–1.10]	0.0073
$38,000–$47,999	4270	1.10 [1.06–1.15]	<0.0001
<$38,000	2516	1.13 [1.07–1.19]	<0.0001
Unknown	527	1.30 [1.14–1.48]	<0.0001
Facility type			
Other	12,547	Ref	
Academic/research	6569	0.89 [0.86–0.92]	<0.0001
Facility location			
Northeast	4787	Ref	
Midwest	4993	1.05 [1.01–1.10]	0.0196
Mountain	854	0.99 [0.92–1.08]	0.8740
Pacific	2395	0.95 [0.90–1.00]	0.0640
South	5884	1.02 [0.98–1.07]	0.2728
Unknown	113	1.20 [0.94–1.53]	0.1380
Population			
Metro	15,334	Ref	
Urban	2497	1.07 [1.02–1.12]	0.0098
Rural	315	0.95 [0.84–1.07]	0.4075
Unknown	880	0.99 [0.89–1.09]	0.7819
Clinical stage			
I	3084	Ref	
II	1987	1.13 [1.06–1.12]	<0.0001
III	2808	1.30 [1.23–1.37]	<0.0001
IV	5939	1.57 [1.50–1.64]	<0.0001
Unknown	5208	1.16 [1.11–1.22]	<0.0001
Histology			
Epithelioid	6883	Ref	
Sarcomatoid	2343	2.19 [2.08–2.30]	<0.0001
Biphasic	1380	1.54 [1.45–1.63]	<0.0001
NOS[a]	8420	1.25 [1.20–1.29]	<0.0001
Treatment			
None	9864	Ref	
Chemotherapy only	6760	0.71 [0.68–0.73]	<0.0001
Surgery only	965	0.81 [0.75–0.87]	<0.0001
Bimodality	1148	0.60 [0.56–0.65]	<0.0001
Trimodality	289	0.59 [0.51–0.67]	<0.0001

[a]*CD Score* Charlson–Deyo score, *NOS* not otherwise specified, *HR* hazards ratio

increasing proportion of patients undergoing chemotherapy. We found that patients undergoing multimodality treatment involving chemotherapy, surgery, and/or radiation had the best survival; however, only 10–11% underwent such treatment. Furthermore, more than 50% of patients did not receive any form of treatment until 2014. While trimodality therapy was associated with the best overall survival, it is difficult to determine the exact chemotherapy regimen, surgical procedure, and radiation in the trimodality group. This does not definitively settle the debate of the necessity of radiation following lung-sparing treatment. Current NCCN guidelines recommend considering radiation after neoadjuvant chemotherapy and pleurectomy with decortication, but recommend adjuvant hemithorax radiation following extrapleural pneumonectomy [37]. Our findings suggest that the only modifiable risk factor for survival may be a treatment at academic institutions where multidisciplinary discussions can determine a patient's fitness for multimodal therapy.

Limitations

Although the NCDB allows for analysis of rare cancers at a national level, inherent disadvantages are evident. The database relies on hospital reporting and does not reflect true incidence in the population. In calculating the annual incidence of mesothelioma, we assumed that the reported cases represented exactly 70% of the true annual incidence. This percentage was then used to extrapolate the estimated annual incidence. Our analysis of the NCDB provides a glimpse into the realities of asbestos use in the USA and unfortunately cannot be extrapolated to describe the effectiveness of asbestos regulation in other countries. The database has broad categories in regard to treatment, but



No Therapy	9864	2970	1258	634	367	218
Chemotherapy	6351	2928	1171	559	312	184
Surgery	965	406	201	114	61	45
Bimodality	1148	729	373	187	103	64
Trimodality	289	225	111	58	33	19

Fig. 5 Survival for pleural mesothelioma treatments

lacks granular details. Surgery is captured as biopsy, partial removal, debulking resection, and en bloc resection. Specific operations commonly used to treat pleural mesothelioma, such as pleurectomy, decortication, and extrapleural pneumonectomy, are not included in the NCDB. Thus, the fine detail needed to fully assess surgical treatment of pleural mesothelioma is unavailable [38]. Chemotherapy regimens also are not captured, making it difficult to fully study the effects of various chemotherapy agents. While our study is not the only one to describe national trends of mesothelioma, we focused on the temporal trends as opposed to histologic distribution as in other studies [33]. Most importantly, the NCDB is a large retrospective database that may not fully elucidate the selection bias within various treatment groups and may produce statistically significant but clinically insignificant conclusions.

Conclusions

The assumption that decreasing asbestos production, mining and processing, and exposure would result in a declining incidence of mesothelioma is not supported. Its incidence remains largely unchanged in the modern era, several decades after government regulation was initiated. Our ability to categorize histology and clinical stage has improved with time, providing better prognostic and treatment information for patients while helping direct future research avenues. Survival, although marginally improved, remains dismal. The only modifiable risk factors to improve outcomes are treatment at academic facilities and discussion of trimodal therapy, both of which are independently associated with improved survival. There needs to be increased awareness among healthcare providers of mesothelioma, as nearly half of patients with this disease never receive any form of treatment.

Funding The Mary Elizabeth Holdsworth Fund and Cleveland Clinic Heart and Vascular Institute. Andrew Tang is a National Heart, Lung, and Blood Institute Clinical Research Scholar of the Cardiothoracic Surgical Trials Network (National Institutes of Health Grant U01 HL088955).

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