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RESEARCH ARTICLE

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Malignant pleural mesothelioma characteristics and outcomes: A SEER-Medicare analysis

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Abstract

Background: Pleural mesothelioma is rare cancer linked to asbestos exposure. Previous research has indicated that female individuals have better survival than male individuals, but this has never been examined in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database.

Materials and Methods: Malignant pleural mesothelioma cases diagnosed from 1992 to 2015 were queried from the linked SEER-Medicare database. Multivariable logistic regression was used to assess the clinical and demographic factors associated with sex. A multivariable Cox proportional hazards model and propensity matching methods were used to assess sex differences in overall survival (OS) while accounting for potential confounders.

Results: Among 4201 patients included in the analysis, 3340 (79.5%) were males and 861 (20.5%) females. Females were significantly older, with more epithelial histology than males were, and had significantly better OS, adjusted for confounders (adjusted hazard ratio, 0.83, 95% confidence interval: 0.76–0.90). Other variables independently associated with improved survival included younger age at diagnosis, having a spouse/domestic partner, epithelial histology, lower comorbidity score, and receipt of surgery or chemotherapy.

Conclusions: The study describes sex differences in mesothelioma occurrence, treatment, and survival and is the first to examine SEER-Medicare. It provides directions for future research into potential therapeutic targets.

KEYWORDS

rare cancers, sex differences, survival

1 | INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare and aggressive form of thoracic cancer,[1,2] which has been widely linked to asbestos exposure.[2–4] Surveillance, Epidemiology, and End Results (SEER) data through 2002 has estimated the incidence of MPM in the United States to be 1.2 and 0.3 per 100 000 people[5] for males and females, respectively, although this has decreased over time.[6] MPM is characterized by a long latency period, often of many decades,[1,2,7] and poor prognosis,[1,8] with little improvement over time, despite the introduction of new therapeutic interventions.[1] Although asbestos is heavily regulated in the United States at the state and local level, there currently is no nationwide ban on its use in the United States.[6]

Previous research in international and US-based registry datasets[9–13] including SEER and the National Cancer Data Base (NCDB), and single-center studies[14–16] have found that females have significantly better overall survival (OS) compared to males. It has been hypothesized that females may be younger and healthier[10] or

may present with more favorable tumor characteristics,[17] including earlier stage and/or less aggressive histology.[9,15,18] Females may also differ in the type, duration, and amount of asbestos exposure,[19] as they may be less likely to have direct occupational exposure and more likely to be exposed environmentally.[20,21] Other evidence suggests that circulating estrogen may bind estrogen receptors and impart tumor suppression imparting survival benefit.[22,23] Given the aggressiveness of MPM, the identification of prognostic factors for improved survival can help guide the treatment approach and may identify therapeutic targets.

Registries provide an invaluable analytic resource because single-center studies have too few cases to have enough power to draw significant conclusions, and often lack generalizability. Although the association between sex and survival has been explored in SEER and other databases, prior work has lacked detail with regard to treatment, such as specific surgery type, chemotherapy, and secondary treatments. The linked SEER-Medicare database offers unique and more granular information that can be used to understand better the specific impact of sex on survival. Our goal with this study was to draw on the size strength of the SEER registry, combined with the treatment specificity of Medicare claims, to examine survival patterns for MPM patients by sex.

2 | METHODS

2.1 | Data source and selection criteria

All MPM cases diagnosed from 1992 to 2015 were queried from the linked SEER-Medicare database. SEER publishes data on incidence and survival information, compiled from population-based cancer registries across the United States. Registries currently included in SEER cover approximately 35% of the US population.[24] Eligibility for Medicare coverage begins at age 65 years. Demographics and tumor characteristics at the time of diagnosis were extracted from SEER, while comorbidities and receipt of treatment were defined using Medicare claims.

There were 13 054 patients who were diagnosed with mesothelioma between 1992 and 2015. Only those with the date of birth and date of death agreement between the two data sources, microscopically confirmed first or only primary cancer diagnosis of pleural mesothelioma, and a reporting source other than autopsy or death certificate were considered for analysis (n = 7865). To allow sufficient claims information to assess comorbidities and treatment, participants were excluded if they were <66 years old at diagnosis or had incomplete fee-for-service Medicare coverage for 1 year before diagnosis and 6 months after, or until death ($n_{excluded}$: 3505). As codes were updated from the International Classification of Diseases, Ninth Revision (ICD-9) to ICD-10 as of October 1, 2015, analysis was limited to patients diagnosed through March 2015, to allow at least 6 months after diagnosis with consistent coding, for a final sample of 4201 patients (Figure 1). This research was approved by the Mount Sinai Program for the Protection of Human Subjects (FWA# 00005656, IRB#19-00500).

2.2 | Outcomes and covariates

The primary outcome of interest was OS and the primary predictor of interest was sex. Additional covariates included: age at diagnosis, race, marital status, histology, stage, comorbidity score, and receipt of surgery, radiotherapy, and chemotherapy. Race was categorized as

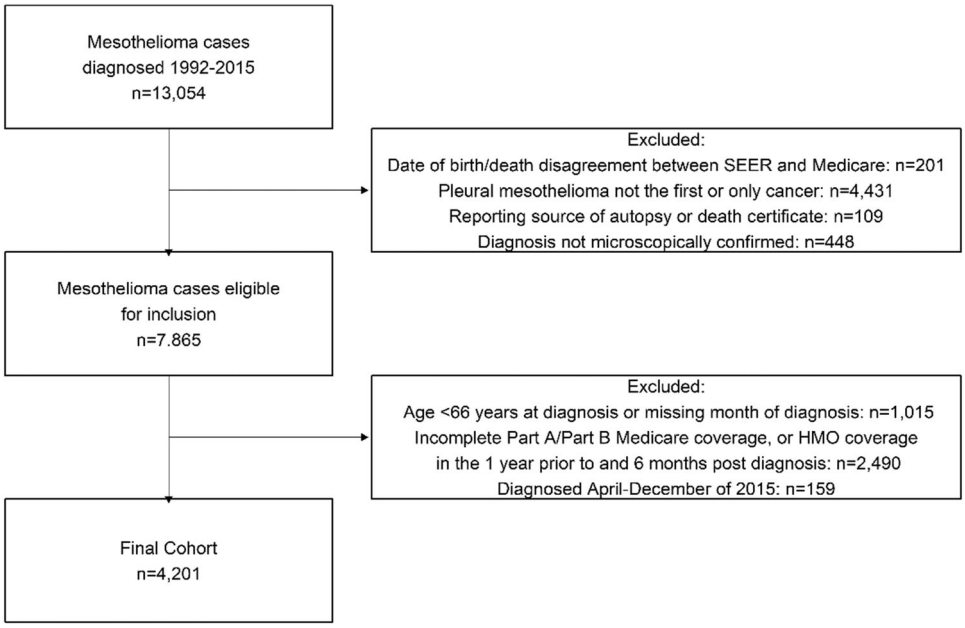

FIGURE 1 Selection criteria. HMO, Health Maintenance Organization; SEER, Surveillance, Epidemiology, and End Results.

White, Black, or other. Marital status was defined as either currently married/living with a domestic partner, or unmarried (including single, divorced, and widowed). Comorbidities were defined using the NCI Charlson comorbidity index,[25] based on the claims from the 12 months before the month of diagnosis. Receipt of treatments, including radiotherapy, chemotherapy, and surgery, was defined based on Medicare claims in the 6 months after diagnosis. Radiotherapy and chemotherapy were defined using ICD-9, Healthcare Common Procedure Coding System, and revenue center codes, based on published algorithms,[26,27] and surgery was defined using ICD-9 procedure codes for extrapleural pneumonectomy or pleurectomy/decortication (Supporting Information: Table 1).

2.3 | Statistical analysis

Males and females were compared on all covariates using χ^2 tests and *t* tests for categorical and continuous variables, respectively. Multivariable logistic regression was conducted to assess the factors independently associated with sex. Kaplan–Meier curves, with a log-rank test, were used to assess the unadjusted association between sex and OS. A multivariable Cox proportional hazards model was used to assess the association of sex with OS, adjusting for possible confounders. Sex differences in OS were also assessed using a 1:1 propensity-matched analysis, matching on all covariates, using an optimal matching (max difference = 0.0001) algorithm[28] and Cox-proportional hazards models, accounting for matched pairs. Differential responses to therapy in the overall cohort were assessed by including an interaction term between sex and receipt of each treatment. Subanalyses were conducted on patients with epithelial histology and those missing detailed histology information. All analyses were conducted using SAS software, v 9.4 (SAS Institute).

3 | RESULTS

Among 4201 patients included in the analysis, 3340 (79.5%) were males and 861 (20.5%) females. Female patients were statistically significantly older at diagnosis than male patients (mean age: 78.2 vs. 76.8 years; $p < 0.0001$), less likely to be currently married (35.3% vs. 71.5%; $p < 0.0001$), and more likely to have epithelial histology (32.4% vs. 29.1%; $p = 0.0001$). Females were significantly less likely to receive chemotherapy compared to males (33.6% vs. 38.9%; $p = 0.0043$). There was no statistically significant difference in race, comorbidity score, receipt of surgery, or receipt of radiotherapy (Table 1). The stage was reported in 1973/4063 cases; 459 were stage I, 318 were stage II, 405 were stage III, and 791 were stage IV.

After adjusting for all covariates, females remained significantly more likely to be unmarried (adjusted odds ratio [OR_{adj}]: 4.76, 95% confidence interval [CI]: 4.03–5.62), less likely to have nonepithelial histology (OR_{adj}: 0.63, 95% CI: 0.48–0.82) and to have a comorbidity score ≥3, compared to 0 (OR_{adj}: 0.71, 95% CI: 0.54–0.94), than males. There was no statistically significant difference in age, race, or receipt of treatments (Table 1).

OS was significantly better for females than males on univariate analysis (Figure 2A) and after adjusting for potential confounders, with an adjusted hazard ratio (HR_{adj}) (female): 0.83, 95% CI: 0.76–0.90. Other variables independently associated with improved survival included younger age at diagnosis, having a spouse/domestic partner, epithelial histology, lower comorbidity score, and receipt of surgery or chemotherapy. Receipt of radiotherapy was significantly associated with worse survival (Table 2). After propensity matching, there were 637 balanced pairs (range of standardized difference: 0.00–0.10). On propensity-matched analysis, women maintained a significant survival benefit (HR: 0.83, 95% CI: 0.74–0.93) (Figure 2B).

To assess for potential differential effects of treatment by sex, the interaction between receipt of treatment and sex was included in the multivariable logistic regression model. Results for all other covariates remained consistent with the original analysis (data not shown). Both males and females derived a significant survival benefit from surgery (HR_{adj} [male]: 0.78, 95% CI: 0.70–0.86; HR_{adj} [female]: 0.68, 95% CI: 0.55–0.85) and chemotherapy (HR_{adj} [male]: 0.76, 95% CI: 0.71–0.82; HR_{adj} [female]: 0.74, 95% CI: 0.64–0.86). Although the interaction term was not statistically significant ($p = 0.3277$), males had significantly worse survival when they received radiotherapy (HR_{adj}: 1.21, 95% CI: 1.08–1.35), while females had no statistically significant difference in survival when receiving radiotherapy (HR_{adj}: 1.07, 95% CI: 0.86–1.33). We also compared sex outcomes between patients who received surgery and those who did not and observed that females had better survival than males in both groups, those who received and those who did not receive surgery (data not shown).

To account for significantly different distributions in histology between male and female patients, a sensitivity analysis was conducted on the subset of patients with epithelial histology (n = 1251; 972 (77.7%) males and 279 (22.3%) females). Similar to the overall cohort, females were significantly older at diagnosis, and less likely to be married. They were also significantly less likely to receive surgery (Supporting Information: Table 2). At the multivariable level, only marital status remained significantly associated with sex (OR_{adj} [unmarried]: 4.52, 95% CI: 3.37–6.07 for females, compared to males) (Supporting Information: Table 2). Like the overall cohort, the female sex was independently associated with lower mortality (HR_{adj}: 0.82, 95% CI: 0.71–0.94) (Supporting Information: Figure 1). A secondary sensitivity analysis was conducted among those without detailed histology information (n = 2232; 1756 [78.7%] males and 476 [21.3%] females). Results were similar, with females having significantly better OS than males (HR_{adj}: 0.84, 95% CI: 0.75–0.94).

4 | DISCUSSION

This analysis of the SEER-Medicare database including a large sample of 4201 patients (age 66+ years) diagnosed with MPM from 1992 to 2015 shows important differences in disease profile and outcome with sex. The first observation is the overwhelming number of male

TABLE 1 Univariate and multivariable associations of demographic and clinical characteristics with sex among patients with malignant pleural mesothelioma.

Variable	Male (n = 3340) n (%)	Female (n = 861) n (%)	p value*	Female vs. male (n = 4063) OR_{adj} (95% CI)
Mean age, years (SE)	76.8 (0.1)	78.2 (0.2)	<0.0001	1.01 (1.00–1.02)
Race			0.1319	
White	3158 (94.6)	804 (93.4)		1.0 (Ref.)
Black	95 (2.8)	36 (4.2)		1.22 (0.80–1.87)
Other	≥11[a]	21 (2.4)		0.92 (0.54–1.56)
Missing/unknown	<11[a]	0 (0.0)		
Marital status			<0.0001	
Married/domestic partner	2387 (71.5)	304 (35.3)		1.0 (Ref.)
Unmarried	850 (25.4)	524 (60.9)		4.76 (4.03–5.62)
Missing/unknown	103 (3.1)	33 (3.8)		
Histology			0.0001	
Epithelial	972 (29.1)	279 (32.4)		1.0 (Ref.)
Nonepithelial	612 (18.3)	106 (12.3)		0.63 (0.48–0.82)
Missing/unknown	1756 (52.6)	476 (55.3)		0.90 (0.75–1.08)
NCI comorbidity score			0.0877	
0	1682 (50.4)	443 (51.5)		1.0 (Ref.)
1	903 (27.0)	211 (24.5)		0.81 (0.67–0.99)
2	375 (11.2)	119 (13.8)		1.01 (0.79–1.31)
≥3	380 (11.4)	88 (10.2)		0.71 (0.54–0.94)
Surgery			0.0848	
No	2848 (85.3)	754 (87.6)		1.0 (Ref.)
Yes	492 (14.7)	107 (12.4)		1.01 (0.79–1.29)
Radiotherapy			0.5492	
No	2939 (88.0)	764 (88.7)		1.0 (Ref.)
Yes	401 (12.0)	97 (11.3)		1.13 (0.88–1.46)
Chemotherapy			0.0043	
No	2042 (61.1)	572 (66.4)		1.0 (Ref.)
Yes	1298 (38.9)	289 (33.6)		0.96 (0.80–1.15)

Abbreviation: NCI, National Cancer Institute.

[a]Exact cell sizes masked to prevent accidental identification of patients.

*The p value for χ^2 or t test for categorical and continuous variables, respectively.

cases (70% of the sample). This disproportionate number of males mesothelioma is related to the main risk factor, asbestos exposure, accounting for 70% of cases.[29] Although we do not have occupational exposure information, therefore we are not able to assess the specific association between occupational exposure and the mesothelioma patients' sex in this data set, we know that mesothelioma is common in shipbuilders and construction workers, occupational categories historically composed of males, while the main source of occupational asbestos exposure in females is textile work. Secondary risk factors for mesothelioma include radiation,[30] carbon nanotubes,[31] Simian virus,[32] and *BAP1* gene variants,[33] which are equally distributed between sexes.

We found that females were diagnosed on average at a later age than males. This parallels a study from the United Kingdom. Senek et al. attribute this age difference to males knowing to be at risk for the disease and having more screenings for mesothelioma because of their more frequent past occupational exposure.[34] Yet, some literature indicates that females are diagnosed at an earlier age than

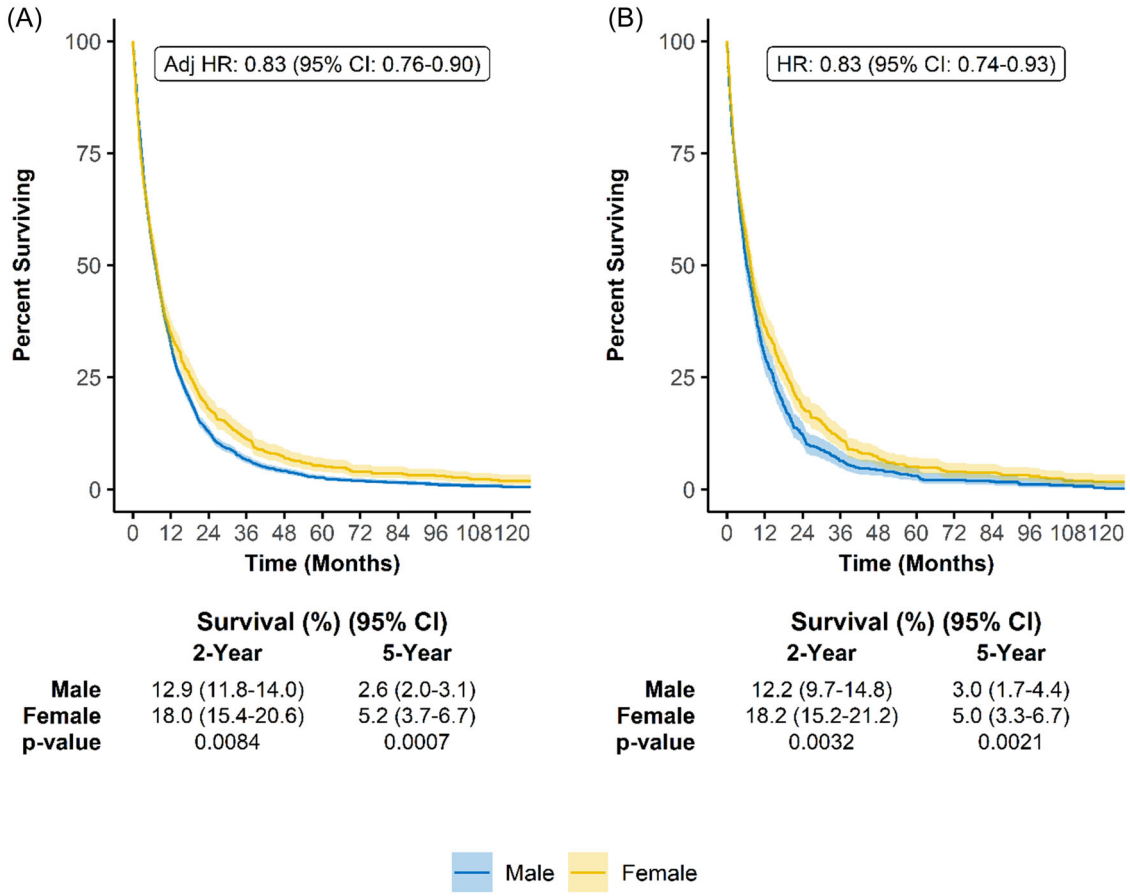

FIGURE 2 Overall survival according to sex in (A) the overall cohort ($n = 4201$); (B) the propensity-matched cohort ($n = 1274$).

males.[10,21] The reason for this discrepancy across the literature is unknown.

Younger age at diagnosis has been associated with longer survival[35]; however,[36] this observation is confounded by the fact that the biological profile of mesothelioma differs with age at diagnosis. Younger mesothelioma patients are less likely to have had the long-term asbestos exposure often observed in older patients, instead, they may present a history of exposure to other risk factors, for example, radiation. Such exposures generate distinct genetic mutations that may contribute to divergent prognoses.[37,38] In support of this hypothesis, it has been reported that young patients have fewer CDKN2A and BAP1 mutations[36] than older mesothelioma patients.

We also observe in the SEER-Medicare database that females are over four times more likely than males to be unmarried, a category which includes single, widowed, or divorced. This result is unexpected since it does not reflect the composition of the general US population, where the ratio of unmarried females to males is about 1.11.[39] Since our finding is almost all driven by widowers, it may indicate past exposure to a spouse who worked in an occupational setting where asbestos was present.[21] Another possible explanation for the fact that females are less likely than males to be married in this cohort is that they are older at diagnosis and that males have a shorter life expectancy than females. Females in their late 70s are less likely to be married than a male of similar age given the shorter life expectancy of males.

Our study confirms that having a spouse is associated with better survival in both sexes. This is a known phenomenon[40] in cancer patients and may be due to the better support systems associated with having a spouse, including being more often encouraged to seek medical attention for symptoms and having more support in better adhering to prescribed medications.

Our study also indicates histological differences with sex, with the epithelial type, which is also associated with better prognosis, more common in females (32.4%) than males (29.1%).[41-43] Prior data[16,17] shows that the effect of sex on survival is only present among those with epithelial histology. However, it is important to acknowledge that there is debate on the reliability of a pathology diagnosis of epithelial-type tumor, and there are reports that mesothelioma is more likely to be classified as biphasic when using a larger biopsy.[44] There are also limitations in the SEER-Medicare database for what relates to histology since for 50% of the patients the record is missing. That said, our analysis still includes a large number of patients with information on histology. To address if the

TABLE 2 Factors independently associated with survival ($n = 4063$).

Variable	HR_{adj}[a] (95% CI)
Sex	
Female vs. male	0.83 (0.76–0.90)
Age, years	1.02 (1.01–1.02)
Race	
White	1.0 (Ref.)
Black	1.20 (1.00–1.43)
Other	1.02 (0.84–1.24)
Marital status	
Unmarried vs. married/domestic partner	1.09 (1.02–1.27)
Histology	
Epithelial	1.0 (Ref.)
Nonepithelial	1.70 (1.54–1.86)
Missing/unknown	1.33 (1.23–1.42)
NCI comorbidity score	
0	1.0 (Ref.)
1	1.12 (1.04–1.21)
2	1.19 (1.07–1.32)
≥3	1.32 (1.19–1.47)
Surgery	
Yes vs. no	0.76 (0.70–0.84)
Radiotherapy	
Yes vs. no	1.18 (1.07–1.30)
Chemotherapy	
Yes vs. no	0.76 (0.71–0.81)

Abbreviations: Adj, adjusted; CI, confidence interval; HR, hazard ratio; NCI, National Cancer Institute.

[a]Adjusted for all listed variables.

missing histology was not distributed randomly across the data set, and could therefore affect the observed associations, we conducted a sensitivity analysis and looked at the association of sex with survival in those without histological classification, and still confirmed the same findings as in the overall data set.

In terms of treatment, we also observed important differences with sex. Despite the fact that chemotherapy is the standard of care, females are less likely to receive it according to SEER-Medicare data. This is a common finding in other cancer types. For example, Rose et al[45] found there also are sex disparities in the treatment of bladder cancer. Possible reasons include physician bias, disparities in access to care, differences in patients' decisions, and comorbidities. We also observed here that females not receiving chemotherapy still outlived males who received chemotherapy, and the reason for this finding is unknown.

Surgery was also less frequently used in females, although it was associated with better OS in our data set.[46] It is possible that some selection operates at the time of the choice of optimal treatment, as the surgical approach is generally decided on a case-by-case basis, and is more likely to be proposed in healthier, younger patients.[47]

Differences with sex were also observed with radiotherapy: we found males who received radiotherapy had worse survival, while females had no significant difference in survival with receipt of radiotherapy. It is possible that males have a worse pulmonary function to start with because of occupational exposure and/or smoking, but also that the biology of the tumor might be different. The reduced response to a direct agent (radiotherapy), suggests differences in local tissue inflammation patterns in males.

The main result of this analysis is that females experience overall better survival than males, after accounting for all the possible differences described above. In fact, the result holds in both the multivariate analysis and the propensity-matched analysis. Previous studies hypothesized that the better survival observed in females may be due to circulating estrogen, and estrogen-associated receptors.[22,48] Ras-like estrogen-regulated growth inhibitor (RERG) was found to be associated with epithelioid, lower-stage histology mesothelioma in females. In contrast, high RERG conferred no prognostic benefit for mesothelioma in males.[49] Our previous research shows the sex survival difference decreases in older cohorts when stratified by age, somehow supporting this hypothesis. However, in this SEER-Medicare cohort, the sex difference in survival still persists in patients who are ≥65 years, and the size of the association is relatively consistent with our previous analyses.[10,11]

This study has several strengths: it is a large, population-based sample of mesothelioma cases, and we were able to remove the confounding effect of insurance since they are all Medicare patients. Compared to other previous analyses,[10,11] this analysis is not limited to the first course of treatment, and treatment definitions are more specific. For example, NCDB/SEER use site-specific surgery codes and mesothelioma falls into an "other" category. This is not the case for the present analysis. The analyses of registry data from other countries may not follow the same surgical guidelines as the United States, for example, in our previous analysis of a UK database,[9] surgery was always considered palliative, as per UK national guidelines.

However, the results should be interpreted within the context of the limitations of the SEER-Medicare database. As mentioned, some critical variables, such as histology and staging, are missing in half the population or are incomplete. We do not have information on past occupational exposure, smoking, or the exact dates of diagnosis and treatment. Further, complications and adverse effects of therapies are not available in SEER-Medicare.

However, this is the largest population-based study on how personal and clinical characteristics and treatment contribute to the sex-survival relationship in mesothelioma. Future research should focus on the mechanisms of these associations, hopefully informing better treatments.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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