Original Study

Effects of Sex on Mortality in Patients With Lung Cancer: A Multiple Mediation Analysis of The Boston Lung Cancer Study

Adriana Araceli Rodriguez Alvarez,[1,#] Yuming Sun,[2,#] Yi Li,[3] David C. Christiani[1,4]

Abstract

In a cohort of 5129 patients with non–small cell lung cancer from the Boston Lung Cancer Study, women demonstrated significantly longer survival than men (median 4.5 vs. 2.6 years; HR 0.73, 95% CI, 0.68-0.78). Multiple mediation analysis showed that surgery and stage at diagnosis explained the largest proportion of the survival advantage, while smoking burden, comorbidities, and EGFR mutations contributed more modestly. Two-thirds of the sex difference in mortality remained unexplained, underscoring the need for further investigation into biological and systemic drivers of disparity.

Objective: Identify the specific variables that can explain the sex difference in lung cancer mortality. **Material and Methods:** This retrospective cohort study analyzed data from the Boston Lung Cancer Study (1992-2022). We employed descriptive statistics, Wilcoxon rank-sum test, and Pearson's Chi-square test to compare demographic and clinical variables by sex. Kaplan–Meier survival curves and Cox proportional hazards models were used to evaluate survival differences. Mediation analysis was conducted to investigate causal pathways through which sex influences mortality, incorporating cancer stage, smoking status, and treatment modalities. **Results:** Among 7642 patients, 53.7% were women. Men were older, had heavier smoking histories, and more frequently received chemotherapy and radiotherapy, whereas women underwent more surgeries. Median survival was significantly longer for women (4.54 vs. 2.59 years), with a 29% reduced hazard of lung cancer–related death (HR: 0.71; 95% CI, 0.66-0.75; $P < .0001$). Approximately 32% of this survival difference was mediated by early-stage diagnosis, surgical intervention, and smoking history. **Conclusion:** Women exhibited a survival advantage, of which only about one-third was explained by earlier diagnosis and higher surgical intervention rates. The remaining two-thirds of the mortality difference remains unexplained. Addressing these modifiable factors may reduce sex inequalities in lung cancer outcomes.

Clinical Lung Cancer, Vol. 000, No.xxx, 1–9 Published by Elsevier Inc.
Keywords: Sex differences, Survival, Modifiable factors, Surgery, Smoking history

Introduction

Over the last 4 decades, the incidence of lung cancer decreased by 35% in men but increased by 87% in women[1,2] likely driven by the increasing rate of smoking among women.[3] While women were previously less likely to smoke than men, smoking rates have recently become more comparable.[4] Lung cancer mortality in women has also risen by more than 600% since 1950, and it is still the leading cause of cancer death in women.[1] Despite this, women often have better lung cancer survival rates than men, with 63.5 deaths per 100,000 men and 39.2 per 100,000 women, according to the NCI-SEER data.[5,6] This survival advantage may be partly attributed to women being diagnosed at younger ages and at earlier stages of the disease compared to men.[5,6]

A range of factors, including biological characteristics, socioeconomic status, and treatment[5,7,8] influence other sex-based differences in lung cancer survival. Hormonal factors, particularly estrogen, play a significant role in lung cancer development, especially in adenocarcinomas, which are more common in premenopausal women. Estrogen's role in modulating immune function may contribute to improved survival outcomes in women.[9] Genetic factors, such as polymorphisms in genes like CYP1A1, also increase women's susceptibility to lung cancer by influencing the metabolism of carcinogens from tobacco smoke, even at lower exposure levels.[10,11] Higher socioeconomic status has been associated with

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Submitted: Apr 24, 2025; Revised: Sep 14, 2025; Accepted: Sep 20, 2025; Epub: xxx

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1525-7304/$ - see front matter Published by Elsevier Inc.
https://doi.org/10.1016/j.cllc.2025.09.007

Please cite this article as: Adriana Araceli Rodriguez Alvarez et al, Effects of Sex on Mortality in Patients With Lung Cancer: A Multiple Mediation Analysis of The Boston Lung Cancer Study, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2025.09.007

longer lung cancer survival than those in lower socioeconomic status.[8] These sex-based differences in metabolism and genetic factors may explain the heightened vulnerability of women to lung cancer.

Given the observed survival advantage in women, particularly those with adenocarcinoma, and the earlier age at diagnosis, it is essential to evaluate the impact of treatment modalities such as surgery, chemotherapy, and radiotherapy on lung cancer survival.

Sex differences in lung cancer incidence and outcomes are well established. However, the specific variables contributing to lung cancer mortality in each sex remain unexplored. Thus, the aim of our study was to identify the specific covariates that could either amplify or mitigate the influence of sex on lung cancer mortality.

Methods

Boston Lung Cancer Study (BLCS)

The BLCS is a cancer epidemiology database of 12,000 lung cancer cases from Dana-Farber Cancer Institute (DFCI) and Massachusetts General Hospital (MGH) gathered since 1992 under the support of the National Cancer Institute (NCI). The BLCS collected data regarding demographics, smoking, occupation, diet, pathology, imaging, treatments, oncogenic mutation status, and biosamples data.[12]

Study Design and Subject Population

This retrospective cohort analysis included lung cancer patients enrolled in the BLCS from 1992 to 2022. This study was conducted per the ethical principles outlined in the Declaration of Helsinki and approved by the Mass General Brigham Institutional Review Board.

Key demographic and clinical variables, such as age, sex, race, smoking status, cancer stage, histology, treatment type, and survival data were extracted for analysis. Smoking status was classified as either smoker or non-smoker, while pack-years were treated as a continuous mediating variable.

Staging was based on the TNM classification system, and for the purpose of this study, we focused on patients with non–small cell lung cancer (NSCLC). Disease stage was categorized as early stage (TNM stages I-II), locally advanced stage (TNM stage III), or metastatic stage (TNM stage IV).

Time to death was defined from the date of diagnosis to the date of death from lung cancer or censored at the date of last follow-up or last known alive. All deaths were considered events, while patients alive at the last follow-up or last known alive were censored at that date. Tumor genetic data were also incorporated, including EGFR exon 19 and exon 20 somatic mutations, KRAS G12C (c.34G > T) mutations, ALK rearrangements, and other relevant alterations.

The study focused on comparing clinical characteristics and survival patterns between sexes and identifying mediators of sex-based mortality disparities.

Treatment Era

We have conducted a stratified analysis based on diagnosis date, dividing the dataset into 3 treatment eras that reflect major advances in lung cancer therapy. The first era (1992-2004) preceded the introduction of new targeted or immunotherapy agents. The second era (2005-2015) followed the introduction of tyrosine kinase inhibitors (TKIs) for patients with adenocarcinoma and EGFR mutations. The third era (2015-2022) coincided with the introduction of immune checkpoint inhibitors, including PD-L1 inhibitors.

Statistical Analysis

We reported the mean and standard deviation for the continuous variables (age, BMI, and pack-years), as well as the frequency and percentage for the categorical variables (race, smoking status, cancer stage, surgery, chemotherapy, and radiotherapy) in the descriptive analysis. We used the Wilcoxon rank sum test and Pearson's Chi-squared test to compare the distribution of continuous and categorical characteristics between men and women patients.

We used the Kaplan–Meier method to estimate the survival probability of patients and plotted the survival curves to visualize the differences in survival probability between men and women patients with lung cancer. We also performed the Log-rank test to assess the statistical significance of this unadjusted difference between women and men patients in survival. Cox proportional hazards model was used to estimate adjusted hazard ratios (HRs).

We applied causal mediation analysis to study whether the effects of sex on lung cancer patients' survival rates were mediated by changes in demographics, cancer stage, smoking status, and treatments patients received, as well as the extent of the effects mediated by these variables. Mediation analysis based on the Cox hazard model and generalized linear models with bootstrap methods was performed using the R package of Multiple Mediation Analysis.[13] We assessed the indirect effect of sex on lung cancer mortality through potential mediators and quantified the relative mediation effects using 95% confidence intervals (CIs).

In the primary analysis using the entire cohort, we adjusted for diagnosis age, number of comorbidities, pack-years, surgery, radiotherapy, smoking status, cancer stage, education, and histology. In the subgroup analysis of genetic mediators, the Cox model was additionally adjusted for EGFR exon 19 and exon 20 somatic mutations, ALK rearrangements, KRAS G12 variants, as well as diagnosis age, pack-years, chemotherapy, cancer stage, and histology.

We identified mediators using a 2-step procedure. First, we assessed each candidate variable for its association with survival. Specifically, we fit a Cox proportional hazards model including sex and all potential mediators (surgery, chemotherapy, radiotherapy, smoking status, pack-years, age, body mass index (BMI), race, comorbidities, education, cancer stage). Wald tests were conducted for each candidate, and variables with a significance level below 0.40 were retained. Second, we evaluated whether each retained variable was also significantly associated with sex. Depending on variable type, we applied chi-squared tests or ANOVA. Variables meeting both conditions were included as mediators; those associated with survival but not with sex were included as covariates.

Missing values for BMI, pack-year and age were imputed using the population mean, while patients with missing data on surgery, smoking status, race, education, or sex were excluded from the analysis.

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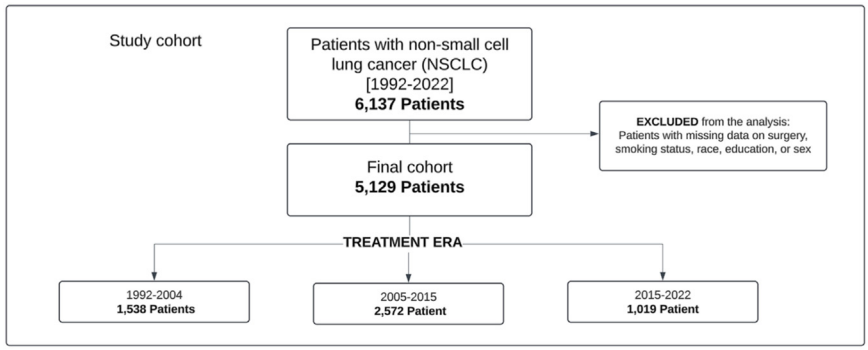
Figure 1 Study cohort. A total of 6137 patients diagnosed with non-small cell lung cancer (NSCLC) between 1992 and 2022 were identified. After excluding patients with missing data on surgery, smoking status, race, education, or sex, the final analytic cohort included 5129 patients. Patients were further stratified by treatment era: 1992-2004 (n = 1538), 2005-2015 (n = 2572), and 2015-2022 (n = 1019).



All statistical analyses were conducted using R version 4.4.2, with a 2-tailed *P*-value < .05 considered statistically significant.

Results

Study Population

A total of 6137 patients diagnosed with non–small cell lung cancer (NSCLC) between 1992 and 2022 were identified. We conducted analyses restricted to this NSCLC cohort. After excluding 1008 patients (16%) due to missing data on surgery, smoking status, race, education, or sex, the final analytic sample comprised 5129 patients (Figure 1). The median age at diagnosis was 66 years, with females presenting at a slightly younger age than males (65 vs. 66 years, $P < .001$). The mean BMI was 32.5, which was significantly higher in females compared with males (32.9 vs. 32.0, $P < .001$). Smoking was highly prevalent in the cohort, with 86% identified as smokers, and males were more likely to smoke compared with females (89% vs. 83%, $P < .001$). Adenocarcinoma was the predominant histologic subtype, accounting for 61% of cases overall, and was more frequent among females than males (66% vs. 55%, $P < .001$). Genetic alterations showed sex-specific distributions, with EGFR exon 19 somatic mutations more common in females than in males (11% vs. 5.0%, $P < .001$), while ALK rearrangements were more frequent in males (6.6% vs. 4.0%, $P = 0.036$). KRAS mutations were also observed, although without a significant sex difference (Table 1).

Kaplan–Meier Analysis

Figure 2 illustrates the Kaplan–Meier survival curves for male and female patients, revealing a statistically significant difference in survival probabilities ($P < .001$). The median overall survival time was 4.54 years (95% confidence interval (CI), 4.27-4.89) for females and 2.59 years (95% CI, 2.41-2.78) for males. The crude hazard ratio (HR) comparing females to males was 0.71 (95% CI, 0.67-0.75; $P < .001$), indicating a 29% reduction in the risk of lung cancer-related mortality for women.

Mediation Analysis

In multivariable survival analysis, female sex was associated with a significantly lower risk of mortality compared with male sex (HR 0.73, 95% CI, 0.68-0.78; $P < .001$) (Table 2). Among potential mediators, younger age at diagnosis, lower comorbidity burden, fewer pack-years, and early-stage disease were each associated with improved survival. Surgical intervention emerged as the strongest protective factor (HR 0.53, 95% CI, 0.45-0.62; $P < .001$) and accounted for the largest proportion of the observed survival difference (14.58%; 95% CI, 10.58%-18.58%), followed by cancer stage (8.57%; 95% CI, 0.03%-17.11%). In contrast, radiotherapy and chemotherapy demonstrated no significant protective effects, while education, histology, and race contributed only modestly. In addition, the number of comorbidities, pack-years, surgery, and cancer stage remained significant mediators of the sex difference in survival among patients with non–small cell lung cancer (Table 2). Mediation analysis further demonstrated that surgery and cancer stage explained the largest proportion of the survival advantage observed in women, followed by smoking burden, comorbidities, and age (Figure 2). Other variables, including radiotherapy, education, and histology, showed minimal relative effects with wide confidence intervals overlapping the null (Figure 3).

In addition to these clinical mediators, genetic factors also contributed to the observed sex difference in survival. In this subgroup, EGFR Exon 19 mutations emerged as significant mediators, accounting for 5.99% (95% CI, 0.38%-11.61%) of the sex difference in survival (Table 3). The absence of complete genetic data for the entire cohort may have led to an underestimation of the contribution of biological mediators in the primary analysis.

When stratified by histology (Table A1), distinct patterns were observed. In adenocarcinoma, comorbidities, pack-years, surgery, and cancer stage were significant mediators, with cancer stage (19.39%; 95% CI, 11.26%-27.51%) and surgery (18.77%; 95% CI, 14.05%-23.49%) accounting for the largest mediated effects. In contrast, among other NSCLC histologies, pack-years was the only significant mediator (17.30%; 95% CI, 5.37%-29.22%).

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Table 1 Descriptive Analysis of The Study Population[1,2]

Characteristic	Overall n = 5129[a]	Female n = 2804[a]	Male n = 2325[a]	*P*-Value[b]
Age at diagnosis	66 (11)	65 (11)	66 (11)	< .001
Missing	162	98	64	
BMI	32.5 (211.0)	32.9 (226.7)	32.0 (190.4)	< .001
Missing	40	22	18	
Smoking status				< .001
Non-smoker	737 (14%)	490 (17%)	247 (11%)	
Smoker	4392 (86%)	2314 (83%)	2078 (89%)	
Race				.060
White	4859 (95%)	2668 (95%)	2191 (94%)	
Asian	109 (2.1%)	54 (1.9%)	55 (2.4%)	
Black	86 (1.7%)	51 (1.8%)	35 (1.5%)	
Other	75 (1.5%)	31 (1.1%)	44 (1.9%)	
Education				.5
Less than or equal to high school	2217 (43%)	1195 (43%)	1022 (44%)	
Postsecondary (non-degree)	1390 (27%)	762 (27%)	628 (27%)	
College or higher	1468 (29%)	813 (29%)	655 (28%)	
Other	54 (1.1%)	34 (1.2%)	20 (0.9%)	
Comorbidity counts	1.41 (1.65)	1.34 (1.65)	1.50 (1.65)	< .001
Surgery	3338 (65%)	1869 (67%)	1469 (63%)	.009
Chemotherapy	2115 (41%)	1101 (39%)	1014 (44%)	.002
Radiotherapy	1329 (26%)	673 (24%)	656 (28%)	< .001
Cancer stage				< .001
I	2283 (45%)	1319 (47%)	964 (41%)	
II	551 (11%)	276 (9.8%)	275 (12%)	
III	1035 (20%)	507 (18%)	528 (23%)	
IV	1260 (25%)	702 (25%)	558 (24%)	
Histology				< .001
Adenocarcinoma	3139 (61%)	1854 (66%)	1285 (55%)	
Other	1990 (39%)	950 (34%)	1040 (45%)	
Other Mutation/amplification	422 (32%)	239 (31%)	183 (33%)	.6
Missing	3797	2034	1763	
EGFR exon 19 somatic mutation	113 (8.5%)	85 (11%)	28 (5.0%)	< .001
Missing	3797	2034	1763	
EGFR exon 20 somatic mutation	20 (1.5%)	8 (1.0%)	12 (2.1%)	.10
Missing	3797	2034	1763	
EGFR Exon L858 Mutation	79 (5.9%)	59 (7.7%)	20 (3.6%)	.002
Missing	3797	2034	1763	
ALK rearrangement	68 (5.1%)	31 (4.0%)	37 (6.6%)	.036
Missing	3797	2034	1763	
KRAS G12C (c.34G > T)mutation	163 (12%)	101 (13%)	62 (11%)	.3
Missing	3797	2034	1763	
KRAS G12D (c.35G > A)mutation	129 (9.7%)	85 (11%)	44 (7.8%)	.050
Missing	3797	2034	1763	

[a] Mean (SD); n (%)
[b] Wilcoxon rank sum test; Pearson's Chi-squared test

To further evaluate whether the mediating effects varied by disease stage, a stage-stratified analysis was performed (Table A2). In early-stage lung cancer, age, pack-years, smoking status, radiotherapy, and histology were significant mediators, with pack-years (9.31%, 95% CI, 3.30%-15.32%) and age (8.01%, 95% CI, 1.78%-14.23%) explaining the largest proportions of the survival advantage in women. In locally advanced disease, pack-years (20.71%, 95% CI, 4.42%-37.00%) and surgery (16.64%, 95% CI, 2.38%-30.90%) were significant mediators. No statistically significant mediators were identified in the metastatic stage.

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Figure 2 Kaplan–Meier curves of overall survival for female and male patients with lung cancer. The median survival time was 4.54 years (95% CI, 4.27-4.89) for females and 2.59 years (95% CI, 2.41-2.78) for males. The shaded areas represent the 95% confidence intervals.

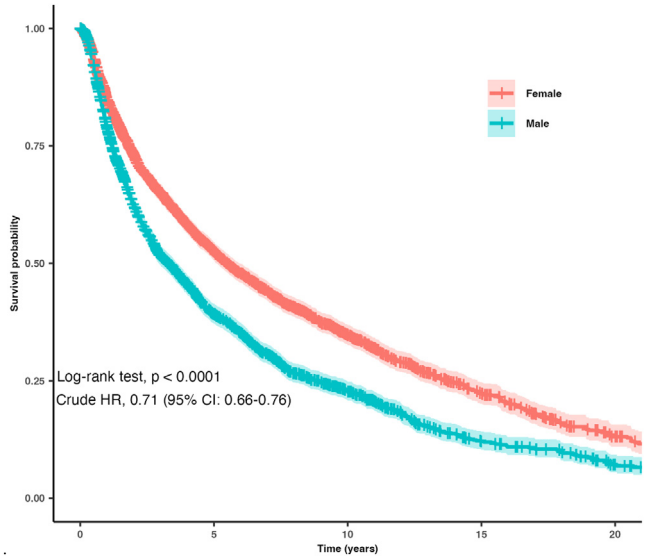

Table 2 Survival Analysis and Multiple Mediation Analysis Non-Small Cell Lung Cancer Population (n = 5129)

Characteristics	Hazard Ratio (95% CI)	*P*-Value	Relative Effect (%, 95% CI)
Sex			
Male	Ref		
Female	0.726 (0.677, 0.779)	< .001	
Age at diagnosis	1.021 (1.018, 1.025)	< .001	4.07 (−0.37, 8.50)
Education			−0.18 (−3.20, 2.84)
Less than or equal to high school	Ref		
Postsecondary (non-degree)	0.881 (0.812, 0.955)	< .01	
College or higher	0.706 (0.644, 0.774)	< .001	
Other	0.746 (0.506, 1.101)	.14	
Pack-years	1.003 (1.002, 1.004)	< .001	10.76 (5.51, 16.01)
Smoking status			1.61 (−0.43, 3.65)
Non-smoker	Ref		
Smoker	0.906 (0.805, 1.020)	.10	
No. of comorbidities	1.073 (1.052, 1.094)	< .001	4.61 (1.73, 7.49)
Surgery	0.534 (0.484, 0.589)	< .001	14.58 (10.58, 18.58)
Radiotherapy	1.080 (0.990, 1.179)	.08	1.66 (−0.77, 4.08)
Cancer stage			8.57 (0.03, 17.11)
Early stage	Ref		0.89 (−0.95, 2.73)
Locally advanced stage	2.033 (1.842, 2.244)	< .001	
Metastatic stage	3.964 (3.560, 4.413)	< .001	
Histology			0.89 (−0.95, 2.73)
Adenocarcinoma	Ref		
Other	1.038 (0.968, 1.114)	.30	

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Figure 3 Multiple mediation analysis of non-small cell lung cancer. Each bar shows the direct effect and relative effect of each potential mediator for the decreased mortality of lung cancer in women patients compared to men. The error bars show the 95% confidence interval.

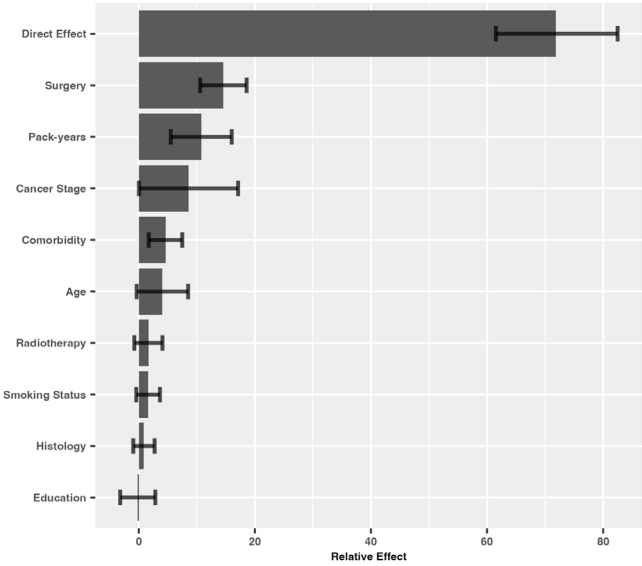

Table 3 Subgroup Analysis of Relative Effects of Genetic Mutations (n = 1332)

Mediators	Relative Effect (%, 95% Confidence Interval)
Age	2.12 (−6.06, 10.31)
Pack-years	9.17 (−2.68, 21.03)
Chemotherapy	−6.57 (−14.80, 1.66)
Cancer stage	12.85 (−2.00, 27.70)
Histology	3.93 (−2.06, 9.91)
EGFR exon 19 somatic mutation	5.99 (0.38, 11.61)
EGFR exon 20 somatic mutation	−0.04 (−1.78, 1.70)
ALK rearrangement	−2.91 (−7.79, 1.96)
KRAS G12C (c.34G > T) mutation	0.48 (−2.36, 3.31)
KRAS G12D (c.35G > A) mutation	−0.20 (−2.17, 1.77)

Treatment Era

As shown in Table 4, in the first era, surgery and pack-years were statistically significant mediators, explaining 13.38% (95% CI, 5.5%-22.16%) and 12.3% (95% CI, 5.08%-19.53%) of the survival advantage observed in women, respectively. In the second era, age, number of comorbidities, and surgery were significant mediators, with surgery (14.18%, 95% CI, 7.21%-21.16%) and age (8.85%, 95% CI, 1.82%-15.89%) showing the largest relative effects. In the third era, cancer stage and surgery emerged as the significant mediators, accounting for 24.21% (95% CI, 9.05%-39.37%) and 16.65% (95% CI, 2.14%-31.16%) of the observed sex difference in survival.

Sensitivity Analysis

In the overall cohort, the identified mediators included age, number of comorbidities, pack-years, surgery, radiotherapy, smoking status, cancer stage, education, and histology (Table A3). Among genetic alterations, EGFR exon 19 somatic mutations, EGFR exon 20 somatic mutations, ALK rearrangements, KRAS G12C (c.34G > T) mutations, and KRAS G12D (c.35G > A) mutations were also identified as mediators.

Causal mediation analysis relies on the assumption that no unmeasured confounders exist between exposure, mediator, and outcome, an assumption that cannot be empirically verified. To evaluate robustness, sensitivity analyses were conducted stratified by treatment era. The set of mediators identified in each era (Table A4) was broadly consistent with those in the overall cohort. Notable differences included the selection of chemotherapy and race as mediators in the first era (1992-2004), chemotherapy and race again in the second era (2005-2015), and the exclusion of age, comorbidities, pack-years, and smoking status in the third era (2015-2022). For genetic alterations, analyses were restricted to the second

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Table 4 Relative Effects Stratified by Treatment Era

	Relative Effect (%, 95% Confidence Interval)		
Mediators	**1992-2004 n = 1538**	**2005-2015 n = 2572**	**2015-2022 n = 1019**
Age	3.71 (−7.28, 14.70)	8.85 (1.82, 15.89)	0.75 (−4.62, 6.13)
No. of comorbidities	0.81 (−1.48, 3.10)	5.75 (0.29, 11.21)	−0.88 (−7.37, 5.61)
Pack-years	12.30 (5.08, 19.53)	7.61 (−0.25, 15.46)	2.67 (−7.07, 12.41)
Smoking status	−0.06 (−3.28, 3.16)	2.13 (−0.52, 4.78)	0.55 (−6.58, 7.69)
Education	−5.67 (−10.87, −0.48)	−1.81 (−6.00, 2.38)	1.91 (−6.22, 10.04)
Surgery	13.83 (5.50, 22.16)	14.18 (7.21, 21.16)	16.65 (2.14, 31.16)
Radiotherapy	3.22 (−1.51, 7.96)	1.33 (−1.98, 4.64)	−18.49 (−49.21, 12.22)
Cancer stage	−0.84 (−17.78, 16.09)	4.48 (−11.14, 20.11)	24.21 (9.05, 39.37)
Histology	−2.57 (−6.20, 1.06)	2.18 (−0.61, 4.98)	6.25 (−3.38, 15.87)

and third eras, since nearly all patients with molecular data were diagnosed between 2005 and 2022, with only 4 patients in the first era having such data available.

Sensitivity analyses of the estimated mediation effects (Table A5) produced results consistent with those from the overall cohort. Surgery remained a statistically significant mediator across all 3 eras. In the first era, pack-years explained 12.53% (95% CI, 2.76%-22.30%) of the survival difference. In the second era, pack-years explained 5.99% (95% CI, 0.64%-11.35%), while in the third era, cancer stage emerged as a significant mediator, consistent with the findings in the overall cohort. With respect to genetic mutations, EGFR exon 19 somatic mutations accounted for 5.32% (95% CI, 0.32%-10.32%) of the survival difference in the second era.

Confidence intervals for all mediation proportions were estimated using bootstrap resampling, in accordance with recommended practice for causal mediation analysis.

Discussion

This study reaffirms the presence of sex differences in lung cancer survival. In this large cohort of more than 5000 patients with NSCLC, women demonstrated a clear survival advantage compared with men (HR 0.71, 95% CI, 0.67-0.75). Even after multivariable adjustment, female sex remained independently protective (HR 0.73, 95% CI, 0.68-0.78), highlighting the strength and consistency of this association.

Mediation analyses demonstrated that stage at diagnosis and surgery accounted for the largest proportion of this difference. Surgical resection reduced mortality risk by nearly half (HR 0.53, 95% CI, 0.45-0.62) and mediated 13.24% of the sex effect (95% CI, 10.20%-17.00%). Similarly, stage at diagnosis mediated 14.78% of the survival difference (95% CI, 7.19%-20.85%). Together, these findings emphasize the importance of early detection and curative treatment as central drivers of sex-based disparities. Comparable results have been reported by Stabellini et al., who found that women were more likely to undergo surgery and that this difference contributed to improved outcomes.[5]

Beyond clinical presentation, genetic alterations also influenced sex-based survival differences. In this cohort, EGFR exon 19 somatic mutations explained 5.99% (95% CI, 0.38%-11.61%) of the survival advantage observed in women. Prior studies have shown that EGFR mutations are more common in women, never-smokers, and patients with adenocarcinoma, and are associated with better prognosis and improved response to tyrosine kinase inhibitors.[14] Outcomes, however, vary depending on additional mutations. Patients with single EGFR mutations demonstrate longer progression-free survival compared with those harboring concurrent alterations, while co-mutations in KRAS, MET, and BRAF predict worse outcomes. By contrast, alterations in ALK or PIK3CA may confer more favorable prognosis.[15] These findings suggest that the mutational profile, rather than EGFR status alone, contributes to sex-specific survival differences and underscores the need for comprehensive molecular characterization in NSCLC.

In addition to genetic and clinical mediators, hormonal and immunologic factors may further explain sex-based differences in survival. Estrogen signaling has been shown to modulate the tumor immune microenvironment, influencing T-cell infiltration, cytokine production, and checkpoint receptor activity. These interactions may partly underlie observed differences in PD-L1 expression between women and men with NSCLC. Recent studies suggest that female patients may exhibit distinct responses to immune checkpoint inhibitors, potentially mediated by estrogen's effects on immune surveillance and tumor immune evasion.[16,17] These findings underscore the need for future research integrating hormonal pathways, immune modulation, and immunotherapy outcomes to better understand and address sex-specific disparities in lung cancer prognosis.

Other mediators contributed more modestly. Smoking burden and comorbidity count were associated with improved outcomes, though their mediation effects were smaller than those of surgery and stage. Chemotherapy showed only a borderline protective effect (HR 0.92, 95% CI, 0.85-1.00, $P = .05$) and mediated −2.36% (95% CI, −4.90 to 0.45) of the sex-based survival difference. Radiotherapy was associated with increased mortality risk (HR 1.11, 95% CI, 1.03-1.19) and mediated 1.34% (95% CI, −0.02 to 2.92). These findings correspond with prior controlled trials in advanced NSCLC, such as ECOG 1594, which demonstrated similar response rates between women and men treated with platinum-based chemotherapy, although women had slightly higher toxicity and longer survival (median survival: 9.2 vs. 7.3 months).[18] Moreover, broader reviews of lung cancer epidemiology and molecular distinctions underscore emerging sex differences in therapeutic susceptibility and outcomes, including differences in tolerability and effectiveness of systemic treatments.[19,20]

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Era-stratified analyses revealed shifts in mediating effects over time. In the earliest era (1992-2004), surgery mediated 13.38% (95% CI, 5.50%-22.16%) and pack-years mediated 12.30% (95% CI, 5.08%-19.53%) of the survival difference. In the second era (2005-2015), surgery mediated 14.18% (95% CI, 7.21%-21.16%) and age mediated 8.85% (95% CI, 1.82%-15.89%). In the most recent era (2015-2022), stage mediated 24.21% (95% CI, 9.05%-39.37%) and surgery mediated 16.65% (95% CI, 2.14%-31.16%). These findings reflect advances in diagnostic imaging, staging precision, and surgical care. In metastatic disease, no clinical mediators significantly explained the sex difference, suggesting that unmeasured biological or immunologic mechanisms may be more relevant in advanced-stage NSCLC.

Overall, our findings indicate that women's survival advantage in lung cancer is primarily driven by earlier cancer stage at diagnosis and higher likelihood of undergoing surgery, with additional, though smaller, contributions from smoking status and other factors. Despite the strengths of a large cohort and comprehensive mediation analysis, several limitations are noted. As a retrospective observational study, it cannot establish causality, and unmeasured confounding remains a concern. We acknowledge that we did not collect data on patients' insurance coverage and specified immunotherapy, which may have influenced treatment decisions and clinical outcomes. Furthermore, the Boston Lung Cancer Study does not capture patients' insurance status, healthcare access, or other system-level factors that may critically influence diagnosis, treatment, and survival. These unmeasured variables could contribute to disparities in early detection, surgical access, and utilization of novel therapies. Their absence may therefore limit our ability to fully disentangle biological from structural drivers of sex-based survival differences. Additionally, the absence of complete genetic data for the entire cohort, which may have limited our ability to fully capture the contribution of biological mediators in the primary analysis. Treatment variables were classified in binary terms, without capturing intensity, dosage, or completion, particularly relevant given known sex differences in drug metabolism and side effects. Cancer stage classifications were broad and did not account for tumor biology, molecular subtypes, or genetic mutations that vary by sex and impact prognosis. The findings may not generalize to populations with different healthcare systems or demographic characteristics. Additionally, although patients missing critical data were excluded, incomplete data for other variables may introduce bias.

Future research should aim to address these gaps through prospective, longitudinal studies that allow for more robust causal inference. Studies incorporating genomic, molecular, and hormonal biomarkers would be particularly valuable in clarifying the biological mechanisms underlying sex differences in lung cancer outcomes. Evaluating the role of psychosocial factors, healthcare provider biases, and system-level barriers may also help explain disparities in surgical and treatment access between men and women patients.

Conclusion

Women have a distinct survival advantage in lung cancer, primarily due to earlier diagnosis and a greater likelihood of surgical treatment. Targeted interventions aimed at improving early detection and surgical access for men may substantially reduce the mortality gap.

Clinical Practice Points

- Sex influences lung cancer survival and should be considered in clinical risk stratification.
- Earlier diagnosis in women partly explains their survival advantage, highlighting the importance of enhanced screening efforts.
- Treatment patterns differ by sex, supporting the need for personalized therapeutic approaches.
- Smoking history remains a key modifiable factor in lung cancer outcomes.
- Addressing stage at diagnosis and treatment disparities may reduce sex-based survival differences.

Funding

NIH (NCI) grant number 5U01CA209414. W&M FRC Faculty Research Grant.

CRediT authorship contribution statement

Adriana Araceli Rodriguez Alvarez: Writing – original draft, Data curation, Conceptualization. **Yuming Sun:** Writing – original draft, Formal analysis, Conceptualization. **Yi Li:** Writing – review & editing, Conceptualization. **David C. Christiani:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Effects of Sex on Mortality in Patients With Lung Cancer

Supplementary material

Table A1 Relative Effects Stratified By Histology

	Relative Effect (%, 95% Confidence Interval)	
Mediators	**Adenocarcinoma**	**Other[a]**
n	3139	1990
Age	4.56 (−0.19, 9.32)	3.92 (−7.11, 14.96)
Comorbidity count	4.21 (1.16, 7.27)	2.93 (−1.85, 7.71)
Pack-years	7.87 (1.79, 13.96)	17.30 (5.37, 29.22)
Smoking status	1.70 (−0.50, 3.90)	0.85 (−1.78, 3.49)
Education	−0.45 (−3.87, 2.98)	−1.82 (−6.92, 3.27)
Surgery	18.77 (14.05, 23.49)	6.59 (−4.35, 17.53)
Radiotherapy	0.64 (−2.12, 3.39)	3.24 (−2.31, 8.80)
Cancer stage	19.39 (11.26, 27.51)	−11.41 (−36.77, 13.94)

[a] Other non–small cell lung cancer histologies include squamous cell carcinoma, large cell carcinoma, bronchioloalveolar carcinoma (BAC), mixed histology, and NSCLC not otherwise specified.

Table A2 Relative Effects Stratified By Cancer Stage

	Relative Effect (%, 95% Confidence Interval)		
Mediators	**Early stage[a]**	**Locally Advanced[a]**	**Metastatic stage[a]**
n	2834	1035	1260
Age	8.01 (1.78, 14.23)	3.90 (−2.05, 9.84)	3.60 (−0.40, 7.59)
No. of comorbidities	2.66 (−1.07, 6.39)	3.88 (−1.54, 9.31)	4.78 (−0.22, 9.78)
Pack-years	9.31 (3.30, 15.32)	20.71 (4.42, 37.00)	9.09 (−0.15, 18.33)
Smoking status	3.12 (0.13, 6.11)	1.11 (−3.88, 6.11)	2.83 (−0.44, 6.09)
Education	0.84 (−2.91, 4.59)	0.99 (−5.77, 7.74)	−0.77 (−5.35, 3.81)
Surgery	0.99 (−1.06, 3.05)	16.64 (2.38, 30.90)	2.18 (−3.43, 7.79)
Radiotherapy	4.14 (0.32, 7.95)	−0.19 (−3.10, 2.72)	0.16 (−1.21, 1.54)
Histology	6.01 (1.78, 10.24)	−4.30 (−10.89, 2.30)	0.12 (−2.04, 2.27)

[a] Early stage = TNM stages I-II; locally advanced stage = TNM stage III; metastatic stage = TNM stage IV.

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Table A3 Mediator Identification of Non-Small Cell Lung Cancer Patients

Variables	*P*-Value[a]	
	Outcome (condition 1)[b]	Sex (condition 2)[b]
n = 5129		
Age	< .001	< .001
BMI	.646	.874
Race	.468	.021
Education	< .001	.189
Smoking status	.169	< .001
Pack-years	< .001	< .001
Comorbidity counts	< .001	< .001
Cancer stage	< .001	< .001
Histology	.313	<.001
Surgery	< .001	< .01
Chemotherapy	.887	< .01
Radiotherapy	.093	< .001
n = 1332[c]		
EGFR exon 19 somatic mutation	.026	< .001
EGFR exon 20 somatic mutation	.234	.112
EGFR exon L858 mutation	.975	< .01
ALK rearrangement	< .001	.038
KRAS G12C (c.34G > T) mutation	.18	.252
KRAS G12D (c.35G > A) mutation	.295	.051
Other mutation	.138	.555

[a] Wald tests; Chi-squared tests; ANOVA.
[b] The *P*-Value threshold for mediator identification was set at 0.40.
[c] Genetic mediators were identified in the subgroup of 1332 patients with available genetic information.

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Table A4 Sensitivity Analysis of Mediator Identification in Different Eras

Variables	*P*-Value[a,b]					
	1992-2004		2005-2015		2015-2022	
	Outcome	Sex	Outcome	Sex	Outcome	Sex
n	1538	2572	1019			
Age	< .001	.093	< .001	< .001	.461	.181
BMI	.013	.65	.583	.295	.651	.233
Race	.34	.139	.376	.073	.151	.132
Education	< .001	< .001	< .01	.052	.166	.021
Smoking status	.902	< .001	.038	< .001	.599	< .01
Pack-years	< .01	< .001	.024	< .001	.486	< .001
Comorbidity counts	.174	.243	< .001	.054	.055	.247
Cancer stage	< .001	.265	< .001	< .01	< .001	.021
Histology	< .01	< .01	.013	< .001	< .001	< .001
Surgery	< .001	.184	< .001	.072	< .001	.206
Chemotherapy	.033	.356	.063	.037	.963	.057
Radiotherapy	.174	.437	.262	< .01	.044	.161
N[c]	4	1172	156			
EGFR exon 19 mutation	–	–	.038	< .001	.187	.25
EGFR exon 20 mutation	–	–	.193	.261	.698	.995
EGFR exon L858 mutation	–	–	.932	< .01	.205	.095
ALK rearrangement	–	–	< .001	< .01	.526	.498
KRAS G12C (c.34G > T) mutation	–	–	.087	.19	.046	.83
KRAS G12D (c.35G > A) mutation	–	–	.359	.035	.823	.83
Other mutation	–	–	.121	.972	.744	.118

[a] Wald tests; Chi-squared tests; ANOVA.
[b] The *P*-value threshold for mediator identification was set at 0.40.
[c] Analyses of molecular data were limited to the second and third eras (2005-2022) due to data availability.

Table A5 Sensitivity Analysis of Relative Effects in Different Treatment Eras

	Relative Effect (%, 95 Confidence Interval)		
Mediators	1992-2004	2005-2015	2015-2022
n	1538	2572	1019
Age	4.00 (−7.29, 15.29)	8.41 (1.60, 15.22)	–
Comorbidity count	1.01 (−1.49, 3.52)	5.99 (0.64, 11.35)	−1.50 (−9.04, 6.04)
Race	1.15 (−4.46, 6.77)	−0.09 (−2.07, 1.89)	−5.26 (−14.44, 3.92)
Pack-years	12.53 (2.76, 22.30)	7.43 (−0.68, 15.54)	–
Smoking status	–	2.12 (−0.18, 4.43)	–
Education	−6.07 (−12.74, 0.60)	−1.65 (−5.60, 2.30)	2.30 (−5.53, 10.13)
Surgery	11.51 (3.76, 19.27)	15.09 (8.50, 21.68)	17.31 (0.27, 34.35)
Radiotherapy	–	1.58 (−2.12, 5.27)	−22.66 (−54.93, 9.62)
Chemotherapy	3.16 (−0.92, 7.23)	−3.34 (−8.19, 1.52)	–
Cancer stage	−1.67 (−20.82, 17.47)	2.90 (−13.20, 19.00)	25.84 (11.05, 40.64)
Histology	−2.44 (−5.64, 0.76)	2.55 (−0.40, 5.50)	6.16 (−3.53, 15.86)
n[a]	4	1172	156
EGFR exon 19 somatic mutation	–	5.32 (0.32, 10.32)	32.87 (−170.26, 236)
EGFR Exon 20 somatic mutation	–	0.02 (−1.74, 1.77)	–
ALK rearrangement	–	−3.86 (−9.08, 1.36)	–
KRAS G12C (c.34G > T) mutation	–	−0.11 (−4.13, 3.91)	–
KRAS G12D (c.35G > A) mutation	–	−0.40 (−2.38, 1.57)	–

[a] Analyses of molecular data were limited to the second and third eras (2005-2022) due to data availability.

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