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Article

Smoking status and the association between patient-level factors and survival among lung cancer patients

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Abstract

Background: Declines in the prevalence of cigarette smoking, advances in targeted therapies, and implementation of lung cancer screening have changed the clinical landscape for lung cancer. The proportion of lung cancer deaths is increasing in those who have never smoked cigarettes. To better understand contemporary patterns in survival among patients with lung cancer, a comprehensive evaluation of factors associated with survival, including differential associations by smoking status, is needed.

Methods: Patients diagnosed with lung cancer between January 1, 2010, and September 30, 2019, were identified. We estimated all-cause and lung cancer-specific median, 5-year, and multivariable restricted mean survival time (RMST) to identify demographic, socioeconomic, and clinical factors associated with survival, overall and stratified by smoking status (never, former, and current).

Results: Analyses included 6813 patients with lung cancer: 13.9% never smoked, 54.2% formerly smoked, and 31.9% currently smoked. All-cause RMST through 5 years for those who never, formerly, and currently smoked was 32.1, 25.9, and 23.3 months, respectively. Lung cancer–specific RMST was 36.3 months, 30.3 months, and 26.0 months, respectively. Across most models, female sex, younger age, higher socioeconomic measures, first-course surgery, histology, and body mass index were positively associated, and higher stage was inversely associated with survival. Relative to White patients, Black patients had increased survival among those who formerly smoked.

Conclusions: We identify actionable factors associated with survival between those who never, formerly, and currently smoked cigarettes. These findings illuminate opportunities to address underlying mechanisms driving lung cancer progression, including use of first-course treatment, and enhanced implementation of tailored smoking cessation interventions for individuals diagnosed with cancer.

Lung cancer is the leading cause of cancer-related deaths in the United States, with an estimated 131 811 deaths expected in 2021 (1). Cigarette smoking is the primary cause of lung cancer in the United States (1-3). As cigarette smoking prevalence declines in the United States, the proportion of lung cancer patients who have never smoked cigarettes has been increasing (1,4-8). Approximately 15% of all lung cancer deaths occur in people who have never smoked. Thus, the burden of nonsmoking-related lung cancer is an important health issue (1).

Several studies describe clinical and demographic characteristics associated with lung cancers diagnosed in patients who never smoked (4-24). Compared with adults with a history of smoking, patients who never smoked and develop lung cancer are more likely to be female, identify as Asian, have a lower comorbidity burden, and have lung cancers with adenocarcinoma histology (5-7,9,11,13,15,24-26). Most of these studies did not describe differences in socioeconomic measures (SES), such as rurality, poverty levels, or education, between lung cancer patients who never smoked and those who ever smoked (4-6,9,11-13,16-22,24,25). Some studies that did report SES did not report survival (19), and other studies did not include tumor specific factors (5,11,16,21). All studies that did report SES and survival are from data collection ending prior to 2017 (9,10,12,16-18,20-22).

Given the high burden of lung cancer on the United States and that the lung cancer landscape is rapidly changing (27-30), it is important to describe contemporary, comprehensive characteristics and patterns among lung cancer patients by smoking status

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who receive health-care services in diverse community settings. Our objective was to fill this gap by describing and quantifying survival differences between lung cancer patients by smoking status in a contemporary sample.

Methods

Study setting and data sources

This retrospective analysis was completed within the Population-based Research to Optimize the Screening Process (PROSPR) Lung consortium (31). As described in detail elsewhere, the PROSPR-Lung Common Data Model is a standardized resource containing data on individuals from 5 diverse health-care systems: Henry Ford Health, Kaiser Permanente Colorado, Kaiser Permanente Hawaii, Marshfield Clinic Health System, and the University of Pennsylvania Health System (31,32). The PROSPR-Lung Common Data Model includes data on patient demographics, census-based measures of SES, procedures, diagnoses, vital status, and tumor data (collected from each site's tumor registry).

Study population

The study population included patients aged 35-89 years diagnosed with lung cancer between January 1, 2010, and September 30, 2019. We calculated the Yost Index, an area-level composite measure of SES, and rural-urban commuting area (RUCA) codes, a census-based characterization of rural and urban and journey-to-work commuting status, for the census tract of residence for each individual (33-35).The Yost Index was chosen to characterize overall SES because it is a robustly validated metric to measure SES that is comprised of household income, poverty, rent, home value, employment, education, and working class, and RUCA was added to control for variation in rurality (36,37). We collected information on sex, self-reported race and ethnicity, tumor characteristics, and first-course treatment. Those identifying in a racial or ethnic group that comprised less than 1% of the study population and those with unknown race were categorized as "Unknown/another race." A modified Charlson Comorbidity Index was calculated for each person in the year prior to lung cancer diagnosis (38,39). We identified the closest recorded smoking status and body mass index (BMI) (kg/m^2) before lung cancer diagnosis. Smoking status was categorized as never, current, and former.

Statistical analysis

Differences in patient characteristics stratified by smoking status were evaluated using χ^2 tests. Overall survival was assessed by restricted mean survival time (RMST) through 5 years (40-44). Overall survival was defined as the time from lung cancer diagnosis to death from any cause. Patients who were alive on the date of their last documented encounter within the health system were censored on that date (45). A multivariable adjusted model was estimated to quantify the effect of the following covariates on survival: Yost Index, RUCA, smoking status, sex, race and ethnicity, age, American Joint Committee on Cancer (AJCC) stage, histology, previously diagnosed nonlung cancer, Charlson Comorbidity Index, BMI, first-course radiation, surgery, and systemic therapy indicators from each site's tumor registry, year of diagnosis, and health system. All variables were selected a priori based on clinician confirmation of variables that have shown an association in the prior literature (4,7,9,10,12,23,25) and were included regardless of statistical significance. We also estimated models stratified by smoking status and calculated interaction P values to determine if the effect of each of these covariates varied by smoking status. Median survival and 5-year survival probabilities were estimated to facilitate comparability with other published literature. Kaplan-Meier curves were created to graphically depict unadjusted survival and compared with a log-rank test. Additional multivariable RMST models were estimated: 1) a model excluding stage to address the prognostic value of histology alone (46); and 2) a model based on the subset of patients with adenocarcinoma histology to address variation by smoking status.

Lung cancer–specific RMST was estimated on patients from 4 of the 5 health systems where the ascertainment of cause of death was available through linkages to state death registries. Lung cancer–specific survival was defined as the time from lung cancer diagnosis to death from lung cancer (International Classification of Diseases, Tenth Revision [ICD-10] code: C34*). Patients who were alive on the date of their last documented encounter within the health system were censored on that date. The competing event of death from nonlung cancer causes was treated as a censored observation at the date of death (47). All covariates used in the all-cause multivariable–adjusted model were also used in this model.

Analyses were performed using SAS Software version 9.4M6 (SAS Institute Inc, Cary, NC, USA). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria were followed (48). P values were 2-sided, and P less than .05 was considered statistically significant. Study protocols and human participant protection considerations were reviewed and approved by the institutional review board at Kaiser Permanente Colorado (KPCO), which is the institutional review board of record for PROSPR-Lung.

Results

Patient characteristics

A total of 6813 patients with lung cancer were identified: 946 (13.9%) patients who never smoked, 3695 formerly smoked (54.2%), and 2172 (31.9%) currently smoked (Table 1; Figure 1). Compared with patients who formerly or currently smoked, patients who never smoked were more likely to be female than male (68.1% vs 51.0% vs 52.9%) and more likely to identify as Asian than White (14.9% vs 6.3% vs 3.5%), have adenocarcinomas than other histologies (64.0% vs 47.5% vs 40.3%), and have the highest Yost index (ie, most affluent; 27.1% vs 20.9% vs 14.1%). The largest proportion of those who never and formerly smoked was 75-89 years (39.0% and 43.4%, respectively), whereas the largest proportion of those who currently smoked was 65-74 years (37.2%). Compared with patients who never smoked, those who formerly or currently smoked were more likely to have 2 or more comorbid conditions (63.7% vs 76.6% vs 69.8%). Patients who currently smoked were more likely to have a BMI less than 25 kg/m^2 compared with patients who never and formerly smoked (51.7% vs 37.9% vs 36.8%, respectively).

All cause survival

Median follow-up time was 36.2 months (95% confidence interval [CI] = 34.2 to 40.0 months), 40.2 months (95% CI = 38.4 to 42.3 months), and 39.7 months (95% CI = 36.6 to 43.6 months) for patients who never, formerly, and currently smoked, respectively. Patients who never smoked had the longest median time from diagnosis to death (29.0 months, 95% CI = 24.2 to 33.2 months), followed by those who formerly smoked (16.1 months, 95% CI = 15.3 to 17.4 months) and those who currently smoked (13.0 months, 95% CI = 11.9 to 14.6 months) (Figure 2, A;

Table 1. Demographic and clinical characteristics of patients diagnosed with lung cancer

Characteristic	Never	Former	Current	Total	P[a]
Total, no. (%)	946 (13.9)	3695 (54.2)	2172 (31.9)	6813	
Sex, no. (%)					<.001
Female	644 (68.1)	1883 (51.0)	1148 (52.9)	3675 (53.9)	
Male	302 (31.9)	1812 (49.0)	1024 (47.1)	3138 (46.1)	
Race and ethnicity, no. (%)					<.001
Asian	141 (14.9)	231 (6.3)	75 (3.5)	447 (6.6)	
Black	90 (9.5)	485 (13.1)	386 (17.8)	961 (14.1)	
Hispanic	40 (4.2)	122 (3.3)	89 (4.1)	251 (3.7)	
Native Hawaiian/Pacific Islander	31 (3.3)	129 (3.5)	85 (3.9)	245 (3.6)	
White	604 (63.8)	2578 (69.8)	1443 (66.4)	4625 (67.9)	
Another race/unknown race	40 (4.2)	150 (4.1)	94 (4.3)	284 (4.2)	
Age at diagnosis, no. (%), y					<.001
35-54	107 (11.3)	124 (3.4)	214 (9.9)	445 (6.5)	
55-64	186 (19.7)	611 (16.5)	695 (32.0)	1492 (21.9)	
65-74	284 (30.0)	1358 (36.8)	807 (37.2)	2449 (35.9)	
75-89	369 (39.0)	1602 (43.4)	456 (21.0)	2427 (35.6)	
Yost State quintile (census based), no. (%)					<.001
Quintile 1 (lowest)	166 (17.5)	808 (21.9)	640 (29.5)	1614 (23.7)	
Quintile 2	177 (18.7)	737 (19.9)	445 (20.5)	1359 (19.9)	
Quintile 3	164 (17.3)	733 (19.8)	454 (20.9)	1351 (19.8)	
Quintile 4	183 (19.3)	643 (17.4)	326 (15.0)	1152 (16.9)	
Quintile 5 (highest)	256 (27.1)	774 (20.9)	307 (14.1)	1337 (19.6)	
RUCA (census based), no. (%)					<.001
Urban focused	798 (84.4)	3244 (87.8)	1836 (84.5)	5878 (86.3)	
Large rural city/town	77 (8.1)	226 (6.1)	167 (7.7)	470 (6.9)	
Small rural town/isolated small rural town	71 (7.5)	225 (6.1)	169 (7.8)	465 (6.8)	
AJCC stage, no. (%)					<.001
I	294 (31.1)	1121 (30.3)	442 (20.3)	1857 (27.3)	
II	72 (7.6)	290 (7.8)	179 (8.2)	541 (7.9)	
III	107 (11.3)	633 (17.1)	433 (19.9)	1173 (17.2)	
IV	426 (45.0)	150 (4.1)	999 (46.0)	1575 (23.1)	
Other/unknown	47 (5.0)	151 (4.1)	119 (5.5)	317 (4.7)	
Histology, no. (%)					<.001
Adenocarcinoma	605 (64.0)	1756 (47.5)	875 (40.3)	3236 (47.5)	
Large cell	11 (1.2)	27 (0.7)	28 (1.3)	66 (1.0)	
Non-small cell/other	130 (13.7)	640 (17.3)	337 (15.5)	1107 (16.2)	
Squamous	74 (7.8)	775 (21.0)	487 (22.4)	1336 (19.6)	
Small cell	35 (3.7)	412 (11.2)	419 (19.3)	866 (12.7)	
Carcinoids	91 (9.6)	85 (2.3)	26 (1.2)	202 (3.0)	
Year of diagnosis, no. (%)					.10
2010-2012	169 (17.9)	662 (17.9)	440 (20.3)	1271 (18.7)	
2013-2015	329 (34.8)	1256 (34.0)	758 (34.9)	2343 (34.4)	
2016-2019	448 (47.4)	1777 (48.1)	974 (44.8)	3199 (47.0)	
Previously diagnosed non-lung cancer, no. (%)	118 (12.5)	510 (13.8)	238 (11.0)	866 (12.7)	.007
Modified Charlson Co-morbidity Index[b], no. (%)					<.0001
0-1 condition	343 (36.3)	866 (23.4)	657 (30.2)	1866 (27.4)	
2 or more conditions	603 (63.7)	2829 (76.6)	1515 (69.8)	4947 (72.6)	
First course therapy (tumor registry based), no. (%)					
Radiation	255 (27.0)	1356 (36.7)	893 (41.1)	2504 (36.8)	<.001
Surgery	331 (35.0)	928 (25.1)	446 (20.5)	1705 (25.0)	<.001
Systemic therapy	413 (43.7)	1638 (44.3)	1148 (52.9)	3199 (47.0)	<.001
BMI status at time of diagnosis, no. (%)					<.001
<25 (underweight/normal)	359 (37.9)	1359 (36.8)	1122 (51.7)	2840 (41.7)	
25-29 (overweight)	289 (30.5)	1274 (34.5)	612 (28.2)	2175 (31.9)	
30+ (obese)	290 (30.7)	1045 (28.3)	411 (18.9)	1746 (25.6)	
Unknown	8 (0.8)	17 (0.5)	27 (1.2)	52 (0.8)	

[a] Differences in patient characteristics between smoking status categories were evaluated using χ^2 tests. AJCC = American Joint Committee on Cancer; BMI = body mass index; NSCLC = non–small-cell lung cancer; RUCA = rural-urban commuting area.
[b] Modified Charlson Comorbidity Index excludes HIV/AIDS diagnoses.

Supplementary Table 1, available online). Unadjusted RMST was 32.1, 25.9, and 23.3 months for patients who never, formerly, and currently smoked, respectively. Kaplan-Meier plots depict unadjusted survival for each smoking status stratified by Yost Index, RUCA, sex, race and ethnicity, and age (Figure 3).

After adjusting for all factors, patients who formerly and currently smoked had decreased survival compared with patients who never smoked (−3.3 and −2.6 months, respectively; both $P < .001$). Multivariable analysis identified 10 factors associated with RMST (Table 2): higher stage, male sex, small cell histology, and a higher comorbid burden were statistically significantly associated with decreased survival, whereas highest quintile Yost Index, identifying as Black, younger age, adenocarcinoma, carcinoid histologies, receipt of first-course systemic therapy, radiation and/or surgery, and higher BMI were associated with increased survival.

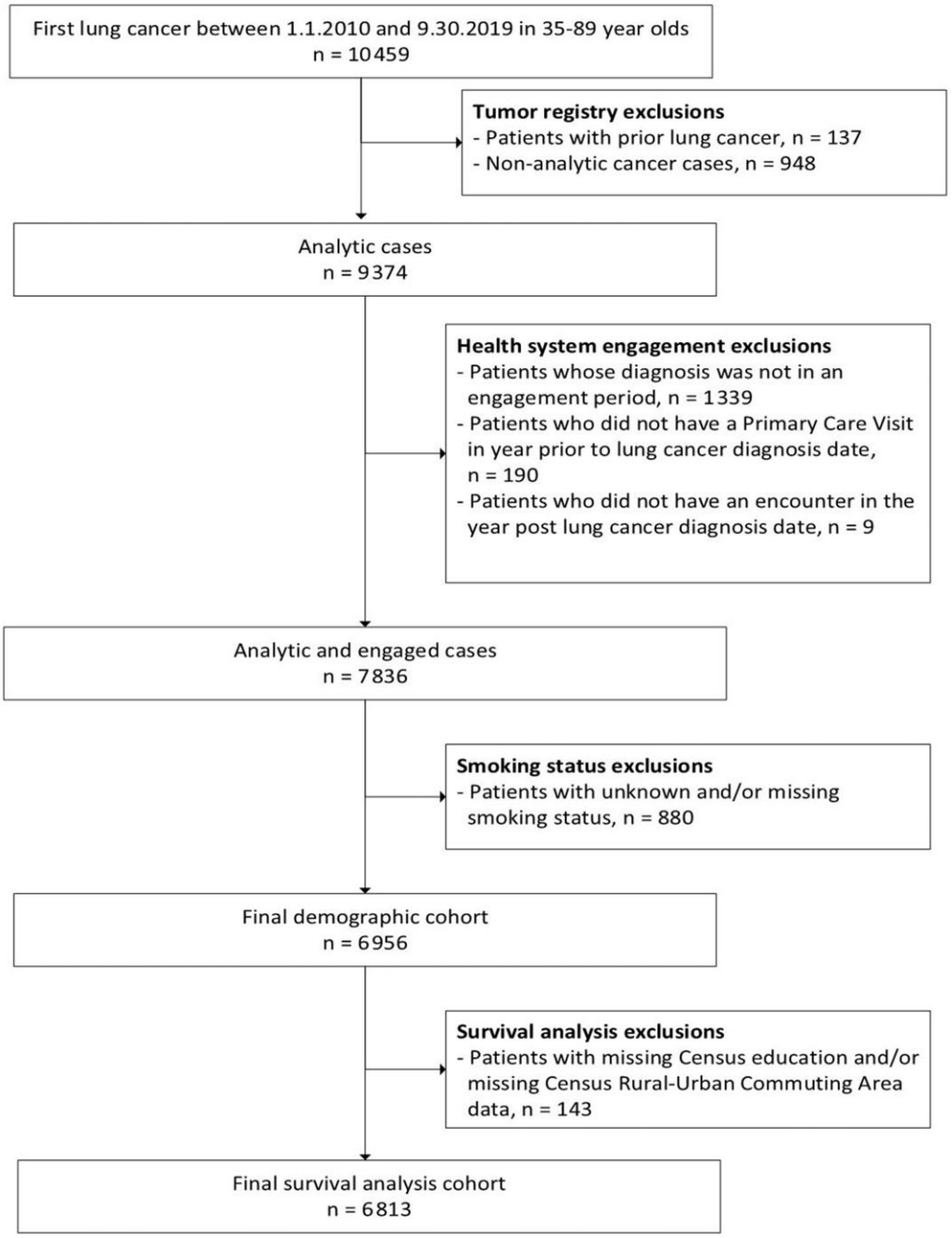
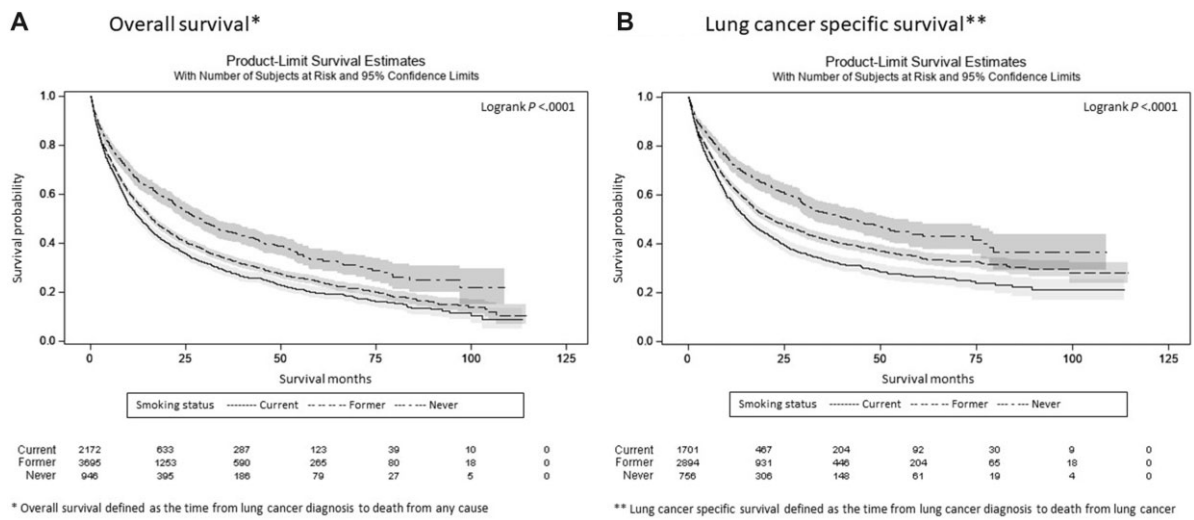


Figure 1. Flow diagram of lung cancer patients included in these analyses.

Interaction analyses revealed the effect of histology and surgery as part of first-course therapy on survival varied by smoking status (Table 3). Among patients who never smoked, those with squamous cell histology had −7.2 (95% CI = −12.9 to −1.5) months decreased survival relative to those with non–small-cell lung cancer or other, whereas this estimate was −0.9 (95% CI = −1.2 to 3.0) and −2.8 (95% CI = −5.5 to −0.2) months among those who formerly and currently smoked, respectively ($P_{interaction} = .007$). Among patients who formerly and currently smoked, those who received surgery had 16.8 (95% CI = 14.6 to 19.0) and 15.0 (95% CI = 12.0 to 18.0) months increased survival, whereas those who never smoked had 8.1 (95% CI = 3.3 to 12.8) months ($P_{interaction} = .01$). Although not statistically significant, we observed relatively large differences in the effect of age by smoking status. Relative to the oldest age, patients who never and formerly smoked had similar survival that was significant (8.7 [95% CI = 3.7 to 13.7] and 7.0 [95% CI = 3.2 to 10.8] months, respectively), whereas survival among those who currently smoked was null (2.3 [95% CI = −0.9 to 5.5] months).

Multivariable models show the factor with the largest association with increased survival for both patients who formerly and currently smoked was surgery as part of first course therapy (16.8 and 15.0 months, respectively). For patients who never smoked, the factor with the largest association with increased survival was



Figures 2. A) and **B**) Kaplan-Meier plots and 95% confidence intervals of survival following lung cancer diagnosis through 5 years of follow-up stratified by smoking status.

younger age (8.7 months for those aged 40-54 years). Across all patients, a diagnosis of stage IV disease had the largest association with decreased survival: −32.6, −27.1, and −31.0 months for patients who never, formerly, and currently smoked, respectively.

Lung cancer–specific survival

Similar survival trends were observed in those for whom we had cause of death data (N = 5351). Consistent with all-cause death results noted above, patients who never smoked had the longest median time from diagnosis to death from lung cancer compared with patients who formerly and currently smoked (43.3, 21.7, and 15.3 months, respectively) (Figure 2, A). In the multivariate-adjusted models (Supplementary Table 3, available online), relative to White patients, a statistically significant protective survival effect was found for Black patients who never smoked (RMST = 7.4 months, $P = .01$). The effect of sex varied by smoking status ($P_{interaction} = .047$). Among those who currently smoked, males had decreased survival relative to females (−4.6 [95% CI = −6.7 to −2.5]) months, whereas the effect of sex was not statistically significant among those that never and formerly smoked: −1.3 (95% CI = −4.9 to 2.2) and −1.6 (95% CI = −3.3 to 0.1) months, respectively. The effect of histology did not vary across smoking status ($P_{interaction} = .15$).

Additional models

The multivariable RMST model excluding stage showed an anticipated increase in the role of histology (data not shown). Specifically, survival for those with small cell histology worsened. Adjusted months lost were 10.6, 4.5, and 5.9 for patients who never, formerly, and currently smoked, respectively.

Among patients with adenocarcinoma histology, the difference in RMST persisted and increased between smoking statuses (Supplementary Table 2, available online). The effect of age on survival varied by smoking status ($P_{interaction} = .003$). Among patients who never smoked and formerly smoked, those aged 40-54 years had 7.7 (95% CI = 1.5 to 14.0) and 8.0 (95% CI = 2.6 to 13.3) months of increased survival relative to patients 75-89 years whereas those who currently smoked had 1.6 (95% CI = −3.4 to 6.6) months of increased survival. The statistically significant interacting effect of surgery as part of first-course treatment with all histologies was abated.

Discussion

In the changing landscape of lung cancer, our study uniquely provides comprehensive data documenting the association and variation of key socioeconomic, demographic, clinical, and tumor-specific factors for patients diagnosed with lung cancer between 2010 and 2019 in 5 heterogeneous community health-care settings, overall and by smoking status. This is the first study, to our knowledge, to provide comprehensively adjusted RMST estimated differentials for patients with lung cancer who currently smoked (−3.3, $P = .001$) or formerly smoked (−2.6, $P = .001$) relative to patients who never smoked. We found that even in an insured group with relatively homogenous health-care access, smoking status still predicts survival after diagnosis. After controlling for a comprehensive set of patient-level demographic and clinical characteristics, higher SES, Black race, older age at diagnosis, adenocarcinoma and carcinoid histologies, receipt of first-course therapy, and higher BMI were associated with better survival, whereas male sex, higher stage, small cell histology, and higher comorbid burden were associated with worse survival.

In contrast to literature that has examined disparities in cancer survival by race and ethnicity (49,50), in our diverse, insured cohort of patients with lung cancer, our findings were robust to model specifications and found that relative to White patients, survival was not less favorable among Asian, Native Hawaiian or Pacific Islander, Black, or Hispanic patients. Census tract measures of SES were consistently positively associated with survival and were correlated with smoking status. We found patients who never smoked were more likely to have larger proportions of patients with higher SES. Consistent with the findings of Lofling and Clement-Duchene who found patients who never smoked more likely to live in neighborhoods with higher education levels and less poverty, we found a similar result using a composite index that encompasses 7 different census variables (9,10).

Consistent with results from previous studies, we found patients who never smoked were more likely to be female (4-6,9,10,13,24), have a higher proportion of Asian patients (5,9), and have a higher proportion of patients younger than 55 years or older than 74 years at lung cancer diagnosis (10). Most patients who never smoked in our cohort had adenocarcinoma histology (64.0%), which is consistent with what is well established in the

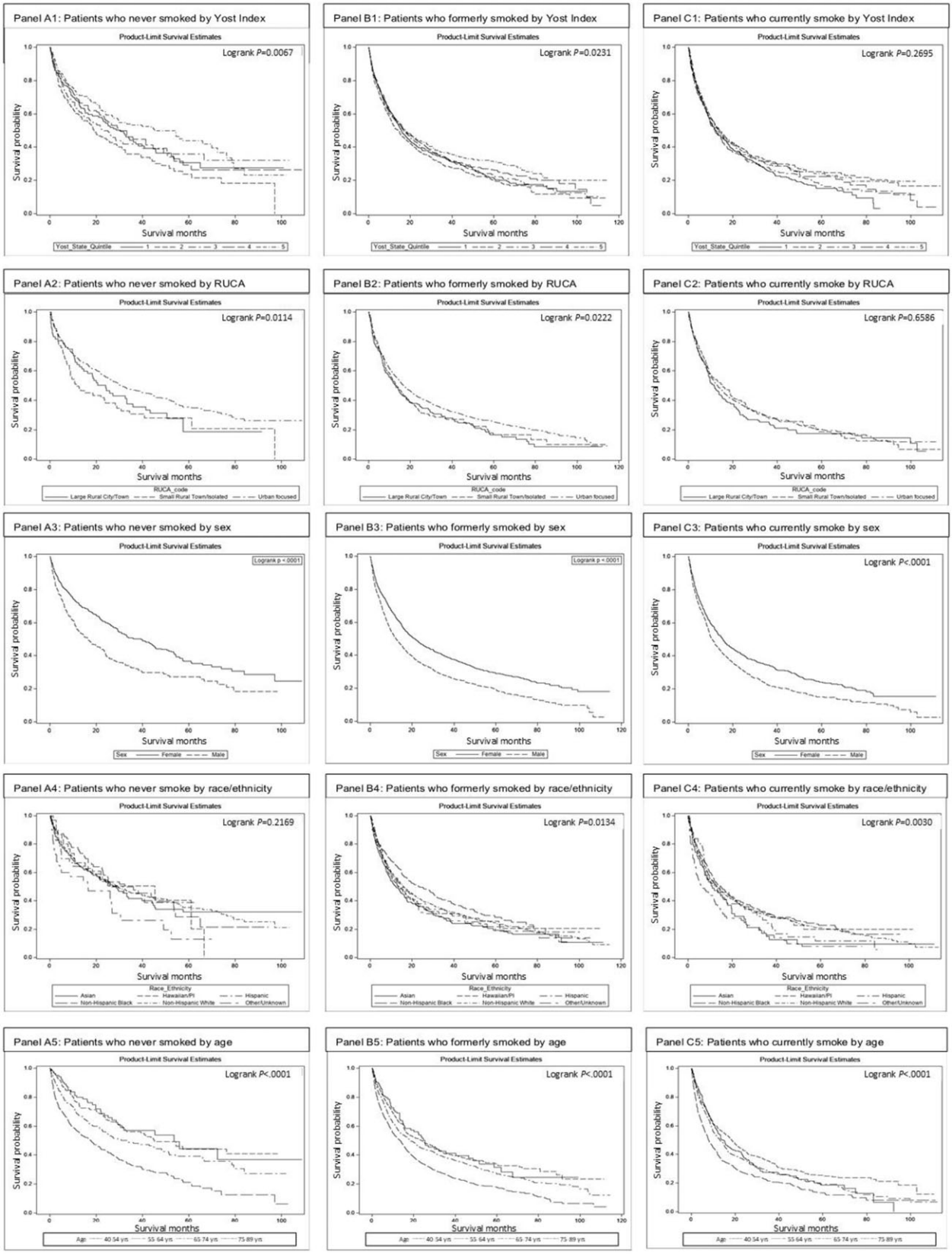


Figure 3. Kaplan-Meier plots of overall survival from diagnosis through 5 years of follow-up for patients diagnosed with lung cancer stratified by patients who never smoked (**A**) to patients who formerly smoked (**B**) to patients who currently smoked (**C**).

Table 2. Multivariable model of restricted mean survival time (RMST) through 5 years from time of diagnosis for all patients with lung cancer[a]

Characteristic	Coefficient (95% CI)[b]	*P*
Intercept	35.7 (32.4 to 38.9)	<.001
Smoking status		
Patients who never smoked	Ref	
Patients who currently smoked	−3.3 (−4.9 to −1.7)	<.001
Patients who formerly smoked	−2.6 (−4.1 to −1.2)	<.001
Sex		
Female	Ref	
Male	−3.4 (−4.4 to −2.4)	<.001
Race and ethnicity		
Non-Hispanic White	Ref	
Asian	−1.3 (−3.7 to 1.1)	.28
Black	1.7 (0.01 to 3.3)	.048
Hispanic	−0.1 (−2.7 to 2.4)	.91
Native Hawaiian/Pacific Islander	1.3 (−3.7 to 1.1)	.28
Another race/unknown race	−2.1 (−4.2 to 0.1)	.06
Age at lung cancer diagnosis (years)		
75-89	Ref	
40-54	5.1 (2.9 to 7.2)	<.001
55-64	4.6 (3.2 to 5.9)	<.001
65-74	2.1 (1.0 to 3.2)	<.001
Yost State Quintile (census based)		
Yost 1 (lowest)	Ref	
Yost 2	0.3 (−1.2 to 1.7)	.72
Yost 3	0.4 (−1.1 to 1.8)	.61
Yost 4	1.4 (−0.1 to 2.9)	.08
Yost 5 (highest)	2.3 (0.7 to 3.8)	.004
RUCA (census based)		
Urban focused	Ref	
Large rural city/town	−0.6 (−3.1 to 1.9)	.63
Small rural town focused/isolated small rural	1.2 (−1.7 to 4.0)	.42
AJCC stage at diagnosis		
I	Ref	
II	−11.4 (−13.6 to −9.2)	<.0001
III	−18.4 (−20.3 to −16.5)	<.0001
IV	−28.9 (−30.5 to −27.3)	<.0001
Other/unknown	−15.7 (−18.4 to −13.0)	<.0001
Histology		
NSCLC/other	Ref	
Adenocarcinoma	3.2 (1.8 to 4.5)	<.001
Carcinoids	4.2 (1.4 to 7.1)	.004
Large cell	−3.0 (−7.3 to 1.3)	.17
Small cell	−2.7 (−4.4 to −1.1)	.001
Squamous	−0.7 (−2.3 to 0.8)	.36
Clinical conditions		
Previous non-lung cancer	−1.4 (−2.8 to 0.05)	.06
Modified Charlson Comorbidity Index[c]		
0-1 condition	Ref	
2 or more conditions	−2.0 (−3.1 to −0.8)	<.001
Receipt of other first-course therapy[d]		
No radiation	Ref	
Radiation	2.1 (0.9 to 3.2)	<.001
No surgery	Ref	
Surgery	15.1 (13.5 to 16.8)	<.001
No systemic therapy	Ref	
Systemic therapy	8.5 (7.4 to 9.6)	<.001
BMI status at diagnosis		
<25 (underweight/normal)	Ref	
25-29 (overweight)	1.3 (0.2 to 2.4)	.03
30 + (obese)	2.1 (0.9 to 3.4)	<.001
Unknown	−5.2 (−9.4 to −0.9)	.02

[a] RUCA = Rural-Urban Commuting Area; AJCC = American Joint Committee on Cancer; BMI = body mass index; CI = confidence interval; NSCLC = non–small-cell lung cancer; Ref = reference group. Results mutually adjusted for year of diagnosis and health-care system in addition to all variables listed in table.
[b] The coefficient value represents the number of additional months of survival gained or lost if the corresponding characteristics were present relative to the reference group for that covariate.
[c] Modified Charlson Comorbidity Index excludes HIV/AIDS diagnoses.
[d] First-course therapy as documented in tumor registry data.

Table 3. Multivariable models of restricted mean all-cause survival time through 5 years from time of diagnosis stratified by smoking status[a]

Characteristic	Patients who never smoked Coefficient (95% CI)[b]	Patients who formerly smoked Coefficient (95% CI)[b]	Patients who currently smoked Coefficient (95% CI)[b]	Smoking status comparisons $P_{interaction}$
Intercept	37.0 (28.0 to 45.9)	33.8 (29.5 to 38.0)	32.0 (27.3 to 36.7)	
Sex				.24
Female	Ref	Ref	Ref	
Male	−4.6 (−7.4 to −1.7)	−2.9 (−4.2 to −1.6)	−3.8 (−5.4 to −2.2)	
Race and ethnicity				.79
White	Ref	Ref	Ref	
Asian	−6.0 (−11.0 to −1.1)	−0.9 (−4.3 to 2.4)	−1.1 (−5.9 to 3.7)	
Black	2.3 (−2.5 to 7.0)	2.5 (−2.2 to 6.5)	−0.1 (−2.7 to 2.4)	
Hispanic	−3.3 (−10.7 to 4.0)	0.7 (−2.7 to 4.2)	−0.6 (−4.4 to 3.2)	
Native Hawaiian/Pacific Islander	−6.2 (−14.6 to 2.3)	2.2 (−2.2 to 6.5)	3.5 (−1.5 to 8.5)	
Another race/Unknown race	−0.5 (−6.4 to 5.5)	−0.7 (−3.8 to 2.4)	−4.6 (−7.9 to −1.3)	
Age at lung cancer diagnosis (years)				.05
75-89	Ref	Ref	Ref	
40-54	8.7 (3.7 to 13.7)	7.0 (3.2 to 10.8)	2.3 (−0.9 to 5.5)	
55-64	7.7 (4.0 to 11.4)	3.1 (1.1 to 5.0)	4.3 (2.0 to 6.7)	
65-74	2.0 (−1.2 to 5.2)	2.4 (1.0 to 3.9)	0.8 (−1.3 to 3.0)	
Yost State Quintile (census based)				.10
Yost 1 (lowest)	Ref	Ref	Ref	
Yost 2	−1.6 (−5.6 to 2.5)	−0.9 (−2.8 to 1.0)	2.7 (0.2 to 5.1)	
Yost 3	1.0 (−3.4 to 5.5)	0.1 (−1.9 to 2.0)	0.7 (−1.7 to 3.0)	
Yost 4	1.0 (−3.1 to 5.0)	1.1 (−0.9 to 3.2)	2.1 (−0.5 to 4.7)	
Yost 5 (highest)	3.7 (−0.4 to 7.7)	2.5 (0.4 to 4.7)	0.3 (−2.4 to 3.0)	
RUCA (census based)				
Urban focused	Ref	Ref	Ref	.89
Large rural city/town	−3.4 (−9.8 to 3.0)	−1.0 (−4.5 to 2.6)	1.4 (−2.8 to 5.7)	
Small rural town focused/isolated small rural	−0.9 (−7.9 to 6.0)	0.6 (−3.4 to 4.6)	3.2 (−1.6 to 8.1)	
AJCC stage at diagnosis				.72
I	Ref	Ref	Ref	
II	−8.0 (−13.2 to −2.8)	−12.1 (−15.0 to −9.2)	−11.5 (−15.6 to −7.3)	
III	−19.6 (−25.1 to −14.1)	−17.2 (−19.7 to −14.7)	−19.8 (−23.1 to −16.5)	
IV	−32.6 (−37.7 to −27.5)	−27.1 (−29.2 to −25.0)	−31.0 (−33.9 to −28.1)	
Other/unknown	−13.7 (−21.1 to −6.3)	−14.8 (−18.4 to −11.1)	−18.7 (−23.4 to −14.0)	
Histology				.008
NSCLC/other	Ref	Ref	Ref	
Adenocarcinoma	3.6 (−0.1 to 7.3)	3.3 (1.4 to 5.1)	2.5 (0.1 to 4.8)	
Large cell	−7.3 (−17.9 to 3.4)	−5.1 (−11.8 to 1.6)	0.8 (−5.6 to 7.3)	
Squamous	−7.2 (−12.9 to −1.5)	0.9 (−1.2 to 3.0)	−2.8 (−5.5 to −0.2)	
Small cell	−6.7 (−12.7 to −0.7)	−3.6 (−5.8 to −1.4)	−1.8 (−4.5 to 0.9)	
Carcinoids	6.1 (1.02 to 11.2)	3.5 (−0.6 to 7.7)	3.9 (−3.9 to 11.6)	
Clinical conditions				.34
No previous non-lung cancer	Ref	Ref	Ref	
Previous non-lung cancer	−3.4 (−7.1 to 0.4)	−0.3 (−2.2 to 1.6)	−2.6 (−5.1 to −0.1)	
Modified Charlson Comorbidity Index[c]				.15
0-1 condition	Ref	Ref	Ref	
2 or more conditions	−1.3 (−4.4 to 1.7)	−3.2 (−4.8 to −1.6)	−0.3 (−2.1 to 1.5)	
Receipt of other first course therapy[d]				
No radiation	Ref	Ref	Ref	
Radiation	−0.8 (−4.2 to 2.7)	2.8 (1.3 to 4.3)	2.5 (0.6 to 4.3)	.64
No surgery	Ref	Ref	Ref	
Surgery	8.1 (3.3 to 12.8)	16.8 (14.6 to 19.0)	15.0 (12.0 to 18.0)	.045
No systemic therapy	Ref	Ref	Ref	
Systemic therapy	7.8 (4.6 to 11.0)	7.9 (6.3 to 9.4)	9.3 (7.4 to 11.1)	.79
BMI status at diagnosis				.60
<25 (underweight/normal)	Ref	Ref	Ref	
25-29 (overweight)	0.2 (−3.0 to 3.3)	2.2 (0.7 to 3.7)	−0.3 (−2.2 to 1.6)	
30+ (obese)	2.2 (−1.1 to 5.4)	2.9 (1.2 to 4.6)	0.8 (−1.5 to 3.1)	
Unknown	3.2 (−11.3 to 17.7)	−6.9 (−13.9 to 0.1)	−7.0 (−12.7 to −1.2)	

[a] RUCA = Rural-Urban Commuting Area; AJCC = American Joint Committee on Cancer; Ref = Reference group in multivariable model. Results mutually adjusted for year of diagnosis and health-care system in addition to all variables listed in the table. BMI = body mass index; CI = confidence interval; NSCLC = non–small-cell lung cancer.

[b] The coefficient value represents the number of additional months of survival gained or lost if the corresponding characteristics were present relative to the reference group for that covariate.

[c] Modified Charlson Comorbidity Index excludes HIV/AIDS diagnoses.

[d] First-course therapy as documented in tumor registry data.

literature, with proportions at 54%-93% (4,6,9-11,13,24). In contrast to previous studies, we found patients who never smoked had a higher proportion of early-staged lung cancers (9,10,13,24,25). This may be explained by our insured cohort that may be clinically and demographically different from those who were diagnosed in other countries (9,10,13,24,25) and/or were diagnosed in years prior to our study (9,25).

Supporting the large and robust literature on smoking as a primary mortality risk factor, we found overall survival was higher in patients who never smoked (9,10,13,14,25). However, our survival estimates were longer than those previously reported in some studies (9,10,25), with a median survival for patients who never, formerly, and currently smoked of 29.0, 16.1, and 13.0 months, respectively. Although we adjusted for receipt of systemic therapy, longer survival may be partly explained by the shift since 2015 in systemic therapy from platinum-based chemotherapy to new immunotherapy and targeted therapies that have shown improved survival in clinical trials (51). Targeted therapies have shown prolonged survival, particularly among patients who never smoked, females, and/or Asian patients with *EGFR* driver mutations. New immunotherapy treatments have shown improved survival among patients with smoking-related cancers (28,52).

In multivariable analyses, we found 6 factors associated with longer survival across all smoking statuses: female sex, decreased age, earlier AJCC stage, adenocarcinoma or carcinoid histology, first-course systemic therapy, and first-course surgery. This is consistent with some studies but is in contrast with others. Clement-Duchene did not observe a significant longer survival with respect to sex, age, and adenocarcinoma histology (9). We also found that BMI categories of overweight (BMI = 25-30) and obese (BMI > 30) provided a protective survival effect for patients who formerly smoked.

Our findings show that although never smoking is best, quitting smoking as early as possible is still beneficial relative to current smoking, as suggested by the reduced survival times (53). This reinforces the call for enhanced smoking cessation efforts as a key strategy for increasing survival among lung cancer patients. Our cohort consisted of insured patients with access to high-quality health-care services; therefore, our findings suggest that much of the survival deficit observed among non-White persons as shown in other studies can potentially be alleviated with access to insurance and high-quality health care. We observed a slight survival advantage among Black patients who formerly smoked relative to White patients. This finding aligns with the previous literature that found often Black patients who do smoke tend to smoke fewer cigarettes per day and start later in life (54).

A key strength of this study is the large, population-based cohort from which we obtained our data. The PROSPR-Lung cohort is racially, ethnically, and geographically diverse and speaks to the generalizability of our results. The calculation of survival in terms of a more clinically relevant measure split out by specific demographic, and clinical factors associated with survival is rarely reported.

Although we report novel survival estimates across multiple factors, it is not without limitations. We did not have access to individual-level SES data but reported Census tract–level data (55,56). However, area-level variables themselves are informative because they capture structural effects of SES inequities and are a widely used and accepted proxy (57). We did not have access to molecular marker mutation data, nor did we stratify by specific type of first-course systemic therapy (eg, cytotoxic, targeted, or immunotherapy), which could have affected our survival measures; however, we did adjust our model for stage, histology, and receipt of first-course therapy. Receipt of first-course therapy had large impacts on increased survival; however, this finding is difficult to interpret because there is little surgery among patients with stage IIIB/IV and systemic therapy is not standard treatment for stage I. We did not model small cell and non–small cell cancers separately. However, our subanalysis analyzing adenocarcinoma cancers covered 54.4% of all non–small cell cancers (58). Changes in smoking status after cancer diagnosis were not ascertained, which could have affected survival. Lastly, smoking status was collected as documented by providers in the electronic health record. Smoker misclassification is generally thought to be small (59-62), and our estimate of the proportion of those who never smoke is consistent with other reported proportions (1,4-6,10,14,24). However, the true smoking prevalence may be underestimated in our cohort.

This study supported prior findings showing statistically significantly longer unadjusted and adjusted survival among patients who never smoke, while finding potentially actionable and observed non–tobacco-related risk factors. Illuminating targets for interventions and advancing evidence and awareness on rates and predictors of survival within different patient groups may be key to optimizing survival as evidence emerges that lung cancer increasingly becomes a heterogeneous disease with increased availability of novel therapeutics.

Data availability

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions

Nikki M Carroll, MS (Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Software; Validation; Visualization; Writing—original draft; Writing—review & editing), Andrea N. Burnett-Hartman, PhD (Conceptualization; Methodology; Writing—review & editing), Katharine A. Rendle, PhD, MSW, MPH (Methodology; Writing—review & editing), Christine M. Neslund-Dudas, PhD (Methodology; Writing—review & editing), Robert T. Greenlee, PhD, MPH (Methodology; Writing—review & editing), Stacey A. Honda, MD, PhD (Methodology; Writing—review & editing), Anil Vachani, MD, MS (Methodology; Writing—review & editing), Debra P. Ritzwoller, PhD (Conceptualization; Methodology; Writing—original draft; Writing—review & editing).

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Conflicts of interest

NMC and DPR report research support from Pfizer paid to their institution outside of the submitted work. KAR reports research support from Pfizer and AstraZeneca paid to her institution and personal fees as a scientific advisor to Merck, all outside of the submitted work. ABH reports research support from Biodesix paid to her institution outside of the submitted work. AV reports personal fees as a scientific advisor to the Lung Cancer Initiative

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