2772-9931
https://doi.org/10.1016/j.atssr.2024.06.010

Lung: Short Report

The Role of Environmental Exposures on Survival After Non-Small Cell Lung Cancer Resection

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ABSTRACT

BACKGROUND Socioeconomic status and pollution exposure have been described as risk factors for poor survival in patients with non-small cell lung cancer (NSCLC). However, the relationship between these factors is complex and inadequately studied. This study aimed to evaluate the relationship between environmental and social factors and their impact on survival after NSCLC resection.

METHODS A prospective database for all patients with NSCLC who underwent primary resection from 2006 to 2021 was analyzed. Ambient fine particulate matter (air pollution smaller than 2.5 μm [$PM_{2.5}$]), greenness, and deprivation index (a measure of neighborhood-level material deprivation composed of 6 factors) were linked to individual patients by geocoding their residential address.

RESULTS A total of 661 patients who underwent pulmonary resection for NSCLC were evaluated. Black patients had increased levels of community deprivation compared with White patients; however, there was no difference in $PM_{2.5}$ exposure or overall survival between races. Increased $PM_{2.5}$ exposure was an independent predictor of worse survival on univariable and multivariable analysis (hazard ratio, 1.06; $P = .003$).

CONCLUSIONS Increased $PM_{2.5}$ exposure is associated with worse overall survival in resected NSCLC and was a more significant factor than race and material deprivation in this population. Interventions to reduce environmental air pollution could improve lung cancer survival.

(Ann Thorac Surg Short Reports 2024;2:618-623)

Patients with socioeconomic disadvantage have a greater incidence of non-small cell lung cancer (NSCLC) and worse survival.[1] Socioeconomic disadvantage predisposes an individual to adverse conditions of living, notably, increased air pollution exposure.[1,2] Air pollution is a major factor contributing to an increasing incidence of non-smoking-related lung cancer.[3]

Ambient fine particulate matter, which has a diameter less than 2.5 μm ($PM_{2.5}$), is a Group 1

IN SHORT

- There is a complex interplay between environmental and social factors in determining lung cancer physiology, access to treatment, and survival outcomes.
- Increased exposure to particulate matter smaller than 2.5 μm and decreased community greenness are associated with worse survival for patients with resected non-small cell lung cancer.
- Interventions to reduce environmental air pollution could improve lung cancer survival.

Accepted for publication Jun 4, 2024.
Presented at the One-hundred-third Annual Meeting of the American Association for Thoracic Surgery, Los Angeles, CA, May 6-9, 2023.
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carcinogen shown to increase lung cancer incidence and mortality.[3,4] However, the impact of air pollution on lung cancer patients after resection is not well studied.

This study aimed to investigate the relationship between environmental and social factors on survival for patients with NSCLC. Particularly, we sought to determine the influence of neighborhood-level deprivation and $PM_{2.5}$ exposure on survival for patients who have undergone surgical resection for NSCLC.

PATIENTS AND METHODS

STUDY DESIGN. Data from the prospectively collected University of Cincinnati Lung Cancer Database from 2006-2021 was analyzed. Adults with NSCLC who underwent resection with curative intent were included. This study was approved by the University of Cincinnati institutional review board on July 30, 2021 (IRB#: 2021-0628).

Variables collected included demographics, medical and surgical history, and lung cancer-specific factors. Patients' addresses at treatment were geocoded using the Decentralized Geomarker Assessment for Multi-Site Studies (DeGAUSS) platform. DeGAUSS uses geocoding software to match street addresses to street ranges provided by the U.S. Census Bureau.[5] Factors produced include daily average exposure to ambient fine particulate matter ($PM_{2.5}$), greenness within a 500-meter radius, proximity to major roadways, and deprivation index. $PM_{2.5}$ is obtained from a model that incorporates Environmental Protection Agency data on meteorology, aerosol density, population density, emissions, and traffic from 2000-2020; levels <5 $\mu g/m^3$ are recommended by the World Health Organization.[6] Greenspace is a satellite-based measure based on the Enhanced Vegetation Index, which is provides values from -1 to 1 with values closer to 1 representing healthy levels of vegetation.[5] Deprivation index is a validated score from 0 to 1 which measures the socioeconomic disadvantage of a neighborhood based on 6 unique factors including poverty levels, assisted income, high school education, median income, health insurance, and vacant housing. Increasing scores represent increased socioeconomic disadvantage.[5]

STATISTICAL ANALYSIS. Continuous variables were compared using *t* tests or analysis of variance. Categorical variables were compared using Pearson χ^2 or Fisher's exact tests. Overall survival (OS) was compared using Kaplan-Meier analysis. Median levels of $PM_{2.5}$ and deprivation index were used in Kaplan-Meier analysis as cutoff points, while these variables

TABLE 1 Characteristics by Vital Status at Last Follow-Up

Characteristic	Total (N = 657)	Status at Last Follow-Up: Alive (n = 488)	Dead (n = 169)	*P* Value
Demographics				
Age, y	63.1 (62.3-63.9)	62.9 (62.0-63.8)	63.7 (62.3-65.1)	.385
Female	353 (53.7)	281 (57.6)	72 (42.6)	<.001
Race				1.000[a]
Black	107 (16.3)	79 (16.2)	28 (16.6)	
White	531 (80.8)	394 (80.7)	137 (81.1)	
Smoking status				
Pack-years	43.9 (41.3-46.5)	41.5 (38.7-44.4)	50.8 (45.3-56.4)	.002
Smoking history				.11
Current smoker	233 (35.5)	167 (34.2)	66 (39.0)	
Ever smoker	358 (54.5)	265 (54.3)	93 (55.0)	
Lung function				
DLCO, % of predicted	74.7 (73.1-76.3)	76.3 (74.4-78.3)	69.9 (67.1-72.8)	<.001
FEV_1, % of predicted	82.1 (80.5-83.7)	82.9 (81.1-84.8)	79.5 (76.7-82.3)	.065
Follow-up				
Length of follow-up, mo	47.9 (45.4-50.4)	51.2 (48.3-54.1)	38.1 (33.3-42.9)	<.001
Length of hospital stay, d	6.1 (5.6-6.6)	5.5 (5.1-5.9)	7.9 (6.5-9.3)	<.001
Recurrence	165 (25.1)	82 (16.8)	83 (49.1)	<.001

[a]Exact test. Values are presented as mean (95% CI) or n (%). DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second.

TABLE 2 Environmental Factors by Status at Last Follow-Up and Race

Factor	Total (N = 657)	Status at Last Follow Up: Alive (n = 488)	Status at Last Follow Up: Dead (n = 169)	*P* Value
Deprivation index	0.37 (0.36–0.38)	0.36 (0.35–0.37)	0.39 (0.36–0.41)	0.048
Predicted $PM_{2.5}$	8.72 (8.31–9.13)	8.16 (7.68–8.65)	9.87 (9.13–10.61)	<.001
Greenness	0.44 (0.44–0.45)	0.45 (0.44–0.45)	0.43 (0.42–0.45)	0.045

Factor	Total (N = 492)	High vs Low $PM_{2.5}$ Exposure (Above or Below Median of 8.282): $PM_{2.5} \leq 8.282$ (n = 245)	High vs Low $PM_{2.5}$ Exposure (Above or Below Median of 8.282): $PM_{2.5} > 8.282$ (n = 247)	*P* Value
Deprivation index	0.37 (0.36–0.38)	0.38 (0.36–0.39)	0.35 (0.34–0.36)	0.52
Greenness	0.44 (0.44–0.45)	0.44 (0.44–0.45)	0.44 (0.43–0.45)	0.88

Values are presented as mean (95% CI). $PM_{2.5}$, particulate matter smaller than 2.5 μm.

were analyzed as continuous variables in the remaining analyses. Univariable Cox proportional hazard regression was performed to identify potential predictors of OS, and factors with $P < .2$ or those considered clinical predictors were utilized as starting covariates for multiple regression analysis. To identify factors independently associated with OS, a backwards selection method was used. All analyses were performed with SAS statistical software (SAS Institute, 2003). Heatmaps were produced using R statistical software (R Foundation for Statistical Computing, 2020).

RESULTS

POPULATION CHARACTERISTICS. Of the 661 patients evaluated, 112 (16.9%) identified as Black and 549 (83.1%) as White. Mean age was 63.1 years and 53.7% were female. At the time of resection, 35.4% were current smokers, and mean pack-years was 43.9. Mean follow-up was 47.9 months, and 74.3% were alive at last follow-up (Table 1).

There was no difference in age or race between those alive and deceased at last follow-up. Mean pack-years of smoking was greater for the deceased group compared with the alive group. Patients who were alive at last follow-up were more likely to have stage 1 disease at diagnosis, lower pathologic T and N stages, lower rates of lung cancer recurrence, and be female (Supplemental Table 1).

Black patients were more likely to be active smokers at the time of lung cancer resection (47.3% vs 33%, $P = .011$) (Supplemental Table 2). There was no difference between pretreatment clinical stage of disease, pathologic stage, or recurrence between races.

ENVIRONMENTAL FACTORS. The mean deprivation index of our study population was 0.37. Those who

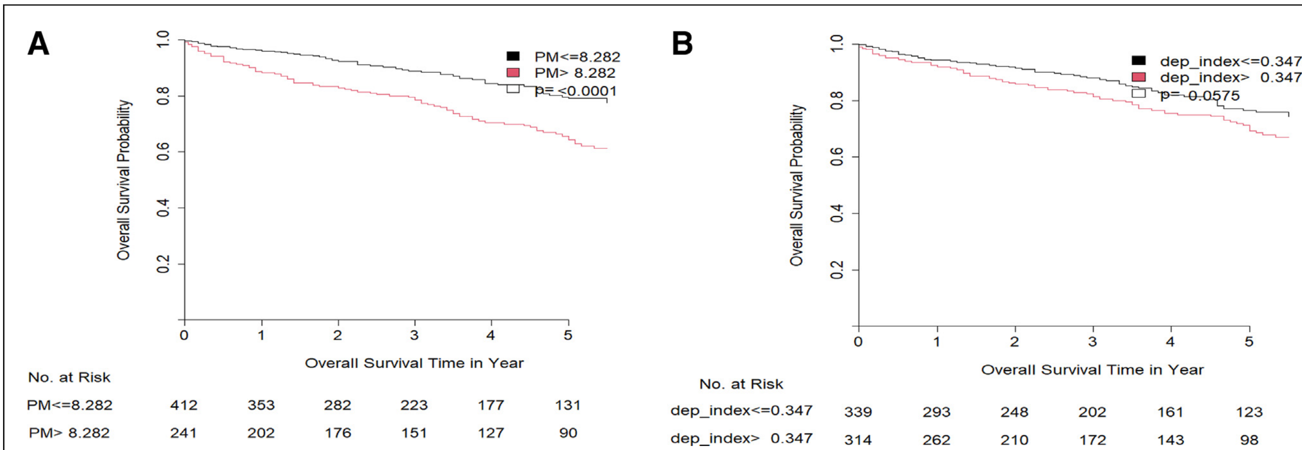

FIGURE (A) Kaplan-Meier survival curve by $PM_{2.5}$ exposure (pm_pred_C). Survival comparing $PM_{2.5}$ level ≤8.282 (median) vs >8.282. (B) Kaplan-Meier survival curve by deprivation index (dep_index_C). Survival comparing deprivation index level ≤0.347 (median) vs >0.347. ($PM_{2.5}$, particulate matter smaller than 2.5 μm.)

were alive at follow-up had slightly lower overall deprivation index score (0.36 vs 0.39, $P = .048$), higher levels of greenness (mean Enhanced Vegetation Index, 0.45 vs 0.43, $P = .045$), and lower $PM_{2.5}$ exposure (mean $PM_{2.5}$, 8.16 vs 9.87, $P < .001$) (Table 2). Pearson's correlation coefficient for $PM_{2.5}$ and greenness and $PM_{2.5}$ and deprivation index were not significant (-0.034, $P = .45$, and -0.011, $P = .80$, respectively). Heatmaps generated showed the distribution of $PM_{2.5}$ in our patient population surrounding the city of Cincinnati (Supplemental Figure 1).

Black patients had overall higher mean deprivation index scores (0.47 vs 0.35, $P < .001$) and decreased greenness compared with White patients (mean Enhanced Vegetation Index, 0.41 vs 0.45, $P < .001$); however, no difference was noted in mean $PM_{2.5}$ between groups (Table 2).

SURVIVAL. On Kaplan-Meier survival analysis, those with $PM_{2.5}$ exposure higher than the median of 8.282 had increased mortality ($P < .001$) (Figure). Survival was not different on Kaplan-Meier analysis when comparing groups above or below the median deprivation index of 0.347 ($P = .059$). However, when comparing high vs low $PM_{2.5}$ exposure by stage, those with lower stages of lung cancer were impacted more significantly by $PM_{2.5}$ exposure than those with higher stages ($P < .001$) (Supplemental Figure 2). In addition, we noted when comparing high vs low $PM_{2.5}$ exposure by tumor type, that those with adenocarcinoma were also more significantly impacted by $PM_{2.5}$ exposure and had worse survival ($P < .001$) (Supplemental Figure 2).

On univariable regression, factors associated with higher risk of mortality included male sex (hazard ratio [HR], 1.68; $P = .001$), increasing $PM_{2.5}$ (HR, 1.07; $P < .001$), increasing deprivation index (HR, 4.29; $P = .013$), hospital length of stay (HR, 1.04; $P < .001$), and increasing smoking pack-years (HR, 1.01; $P = .001$) (Table 3). Factors associated with improved survival included increasing greenness (HR, 0.10; $P = .021$) and increasing predicted diffusing capacity of the lung for carbon monoxide (HR, 0.98; $P < .001$). Race was not predictive of mortality.

On multivariable regression, male sex (HR, 1.63; $P = .004$), hospital length of stay (HR, 1.03; $P < .001$), and increasing $PM_{2.5}$ (HR, 1.06; $P \leq .001$) remained associated with increased mortality. Factors associated with improved survival included greenness (HR, 0.06; $P = .006$) and increasing predicted diffusing capacity of the lung for carbon monoxide (HR, 0.98; $P < .001$). Again, race was not noted to be a significant predictor of mortality, and deprivation index was no longer significant.

TABLE 3 Univariable and Multivariable Overall Survival

Characteristic	HR (95% CI)	*P* Value
Univariable		
Male	1.68 (1.23-2.29)	.001
Deprivation index	4.29 (1.35-13.57)	.013
Predicted $PM_{2.5}$	1.07 (1.03-1.10)	<.001
Greenness	0.10 (0.01-0.71)	.021
Race (White)	1.05 (0.70-1.58)	.807
Pack-years	1.01 (1.00-1.01)	.001
DLCO predicted	0.98 (0.97-0.99)	<.001
Received neoadjuvant chemotherapy	2.02 (1.24-3.30)	.005
Hospital LOS	1.04 (1.02-1.05)	<.001
Pathologic N stage		.001
N1 vs N0	2.14 (1.39-3.31)	.001
N2 vs N0	1.78 (1.07-2.96)	.026
Coronary artery disease	1.33 (0.93-1.90)	.115
Prior myocardial infarction	1.69 (1.05-2.73)	.031
Hypertension	1.41 (1.02-1.93)	.035
Chronic renal insufficiency	2.55 (1.30-4.99)	.007
Dialysis preoperatively	5.26 (1.94-14.24)	.001
Liver disease	2.34 (1.21-4.63)	.012
Diabetes	1.76 (1.26-2.46)	.001
Multivariable		
Characteristic	**HR [95% CI]**	***P* Value**
Male	1.61 (1.14-2.26)	.006
Predicted $PM_{2.5}$	1.06 (1.03-1.10)	<.001
Greenness	0.03 (0.004-0.24)	.001
DLCO predicted	0.98 (0.97-0.99)	<.001
Received neoadjuvant chemotherapy	1.92 (1.12-3.28)	.018
Hospital LOS	1.03 (1.02-1.05)	<.001
Pathologic N stage		<.001
N1 vs N0	2.35 (1.42-3.76)	<.001
N2 vs N0	2.02 (1.16-3.76)	.014
Dialysis preoperatively	3.93 (1.17-13.13)	.026
Liver disease	2.68 (1.23-5.82)	.013
Diabetes	1.78 (1.21-2.62)	.003

DLCO, diffusing capacity of the lung for carbon monoxide; HR, hazard ratio; LOS, length of stay; $PM_{2.5}$, particulate matter smaller than 2.5 μm.

COMMENT

In this study, we utilized the DeGAUSS geocoding system to estimate environmental exposures and community deprivation more precisely. We found that Black patients were more likely to live in communities with increased social deprivation and reduced greenness; however, air pollution exposure was similar between races, and race was not independently associated with survival. Instead, increased exposure to $PM_{2.5}$ and decreased community greenness were associated with worse OS for patients with resected NSCLC.

The importance of environmental factors such as $PM_{2.5}$ in cancer development has been previously reported.[7,8] Recently, Hill and associates[7] reported a proposed mechanism for lung cancer development in never-smokers due to air pollution. Our study found that increased exposure to $PM_{2.5}$ was independently associated with worse OS for patients with resected NSCLC. This finding supports previous literature showing increased lung cancer occurrence and mortality with increased levels of $PM_{2.5}$.[3,4] In addition, prior studies from China have shown the impact of $PM_{2.5}$ on survival after lung cancer resection; however, studies are lacking in the United States. Our study shows that $PM_{2.5}$ also has negative impacts on survival in the United States populations.

Previous studies have also shown that socioeconomic disparities have a negative impact on survival in lung cancer patients, and these have frequently been found to be associated with underrepresented minority patients.[9] Furthermore, it has been demonstrated that patients with higher levels of socioeconomic deprivation are more likely to live in places where exposure to air pollutants is greater, thus leading to higher rates of cancer and mortality.[10] In our study, we found that Black patients were more likely to live in communities with increased social deprivation, though higher levels of deprivation did not produce a significantly increased risk of mortality on multivariable models. There was no difference in $PM_{2.5}$ exposure between Black and White patients, indicating that air pollution could be the primary factor leading to mortality in our population, rather than race or material deprivation levels.

Our study has important limitations. First, estimates of $PM_{2.5}$ determined using the DeGAUSS system were used to represent an individual's exposure to air pollution. This measure provides the daily average exposure of an individual living in this area; however, it is unable to account for cumulative lifetime exposure.[5] We also did not have complete residential history for our patients to determine the length of time they had lived at their residence, which could therefore lead to potential exposure misclassification and bias.[5] We were unable to evaluate data regarding other potential exposures. Next, our study only evaluated patients who underwent surgery, which could have been a confounding factor that decreased the significance of race in our models. Finally, our data is from a single institution therefore limiting generalizability to other centers.

In summary, we demonstrated that $PM_{2.5}$ exposure is associated with worse OS in patients with resected NSCLC while deprivation index and race were not significant in our population. These findings demonstrate the complex interplay between environmental and social factors in determining lung cancer physiology, access to treatment, and survival outcomes. Further studies to evaluate and potentially validate our findings in other settings and patient populations should be performed to further delineate this complex interplay. Interventions to reduce environmental air pollution could improve lung cancer survival, and surgeons should advocate for public policy and patient education to decrease air pollution exposure.

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.atssr.2024.06.010] on http://www.annalsthoracicsurgery.org.

FUNDING SOURCES

The authors have no funding sources to disclose.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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