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Air Pollution Affects Lung Cancer Survival

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Abstract

Rationale—Exposure to ambient air pollutants has been associated with increased lung cancer incidence and mortality but, due to the high case fatality rate, little is known about the impacts of air pollution exposures on survival after diagnosis. This study aimed to determine whether ambient air pollutant exposures are associated with lung cancer patient survival.

Methods—Participants were 352,053 patients with newly diagnosed lung cancer during 1988–2009 in California, ascertained by the California Cancer Registry. Average residential ambient air pollutant concentrations were estimated for each participant's follow-up period. Cox proportional hazards models were used to estimate hazard ratios (HRs) relating air pollutant exposures to all-cause mortality overall and stratified by stage (localized only, regional, and distant site) and histology (squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, and others) at diagnosis, adjusting for potential individual and area-level confounders.

Results—Adjusting for histology and other potential confounders, the HR associated with 1 standard deviation increases in NO₂, O₃, PM₁₀, PM_{2.5} for patients with localized stage at diagnosis were 1.30 (95% CI: 1.28–1.32), 1.04 (95% CI: 1.02–1.05), 1.26 (95% CI: 1.25–1.28), and 1.38 (95% CI: 1.35–1.41), respectively. Adjusted HR were smaller in later stages, and varied by histological type within stage ($p < 0.01$, except O₃). The largest associations were for patients with early stage non-small cell cancers, particularly adenocarcinomas.

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Conclusions—These epidemiological findings support the hypothesis that air pollution exposures after lung cancer diagnosis shorten survival. Future studies should evaluate the impacts of exposure reduction.

Keywords

Air pollution; Lung Cancer; Survival; Particulate matter; Nitrogen dioxide

INTRODUCTION

Lung cancer has been the most common cancer for decades. Worldwide, lung cancer causes nearly one in five cancer deaths, about 1.59 million deaths annually (<http://globocan.iarc.fr>). This heavy burden is largely a result of a high prevalence of cigarette smoking, the leading cause of lung cancer; advanced stage at diagnosis; and poor survival, especially among those with advanced stage disease.^{1,2} Accordingly, interventions have focused on reduction of tobacco use, early-stage diagnosis, and improved treatment. Although progress has been made in each area, lung cancer survival remains stubbornly poor suggesting that novel approaches are needed.^{3–6} A promising approach is identifying and intervening on modifiable determinants of survival; however, little research attention has been directed to determinants beyond smoking. One modifiable determinant of emerging interest is ambient air pollution,⁷ which was recently classified as carcinogenic by the International Agency for Research on Cancer (IARC).⁸

A growing body of evidence indicates that ambient air pollutants are associated with lung cancer incidence and mortality.^{9–12} However, relatively little is known about air pollution effects on survival after any cancer diagnosis.^{13,14} We reasoned that if ambient air pollution is a carcinogen affecting lung cancer development, then inhaled pollutants may also drive tumor progression through the same mechanistic pathways to shorten survival after diagnosis. If ambient air pollution increases both the incidence of lung cancer and shortens survival after diagnosis, then it could have a larger contribution to lung cancer mortality than previously understood.

To determine whether ambient air pollutants are associated with survival in lung cancer patients, we conducted a population-based cohort study of 352,053 California residents with lung cancer newly diagnosed in 1988–2009. We estimated average residential exposures to nitrogen dioxide, ozone, and particulate matter air pollutants from diagnosis to end of follow-up and related these exposures to all-cause mortality and lung cancer specific mortality by stage and tumor histology at diagnosis.

METHODS

Lung cancer cases and individual-level data

Our study population included lung cancer cases (ICD-O-3 site code C34), diagnosed in 1988–2009 and registered by the California Cancer Registry (CCR), the statewide population-based cancer surveillance system (www.ccrca.org). The CCR has collected information on all newly diagnosed cancers (except non-melanoma skin cancer) in

California since 1988 and has received the highest level of data quality certification from the North American Association of Central Cancer Registries.¹⁵ The CCR gathers individual-level data on demographics (age, sex, marital status, race/ethnicity), date of diagnosis, tumor characteristics at diagnosis (stage, anatomical site, histology), treatment occurring < 6 months after diagnosis, and patient vital status (date of death or date last known alive). The CCR routinely updates patient vital status by linking to the electronic death certificate master file from the California Department of Public Health, recording the underlying cause of death for deceased patients, as defined by the Department of Health Services. After excluding patients with diagnoses of *in situ* cancer (N=305) and non-carcinoma histology (N=20,964), there were 352,053 cases remaining for analysis with complete information on follow-up, date of birth, date of diagnosis, and race/ethnicity. We created standard histology groupings¹⁶ using ICD-O-3 morphology codes for carcinoma (8010–8576): squamous cell carcinoma (8050–8078, 8083–8084), adenocarcinoma (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, 8576), small cell carcinoma (8041–8045, 8246), large cell—includes giant cell, clear cell and large cell undifferentiated—carcinoma (8010–8012, 8014–8031, 8035, 8310), and other carcinomas (remaining codes).

No patient contact was conducted for this analysis, so individual patient informed consent was not required. The CCR operates under the annual review of the State of California Committee for the Protection of Human Subjects (i.e. IRB), which provided approval for this analysis.

Geocoding

We geocoded residential addresses at the date of diagnosis using the Texas A&M geocoding service (geoservices.tamu.edu). Details of the process, used by cancer registries throughout the U.S., are provided elsewhere.¹⁷ Briefly, address records were geocoded to the centroid of the smallest resolvable area based on the address completeness, ranging from tax assessor parcels to state centroid when no address information was available (in <0.1% of cases). In previous work, this method substantially improved spatial resolution.¹⁸

Area-level covariates

Area-level covariates were assigned to each patient using the geocodes. Rural-urban commuting area (RUCA) codes, based on data from the 2000 decennial census, classify census tracts into ordinal ranks (1–10, from metropolitan to rural) based on the size and direction of primary commuting flows, using measures of population density, urbanization, and daily commuting (www.ers.usda.gov/data-products/rural-urban-commuting-area-codes.aspx). Education index was defined as the average years of schooling in the patient's census tract based on a weighted sum of the distribution of years of schooling.¹⁹ Socioeconomic status, at the patient's census block group, was calculated using validated area-level measures from multiple census years.²⁰

Air Pollution Exposure Assignments

California air pollutant data was obtained from the U.S. Environmental Protection Agency's (EPA) Air Quality System (AQS) database.²¹ Data were available for nitrogen dioxide (NO₂, ppb), ozone (O₃, ppb), particulate matter with diameter < 10 μm (PM₁₀, μg/m³) and 2.5 μm

(PM_{2.5}, µg/m³). Hourly measurements were summarized as 24-hour averages for NO₂, PM₁₀, and PM_{2.5} and average 8-hour daily maximum for O₃. Monthly average concentrations were spatially interpolated to residence locations from the up to 4 closest air quality monitoring stations within a 50 km radius using the well-established method of inverse distance weighting,^{22,23} with the decay parameter equal to the inverse of the square of the distance of the residence from each monitoring site. Interpolation performance is summarized in eTable 1. We excluded exposure assignments when the nearest monitor was located > 25 km away or a geocode match was unavailable. Residential ambient air pollution exposure assignments were calculated as the average of the patient-level interpolated monthly concentrations from the date of diagnosis to the date of last follow-up or death. PM_{2.5} exposure assignments were only available for patients diagnosed in 1998 and later because routine monitoring did not start until 1998. Our primary goal was to evaluate associations with large-scale, regional variation in ambient pollutants, so to account for potential confounding by local traffic, we calculated and adjusted for distance from residential address to primary interstate highways and primary US and state highways.

Outcome

Survival time was calculated from the date of newly diagnosed lung cancer to date of death from any cause (all-cause mortality). For sensitivity analysis, we assessed time to death from an underlying cause of lung cancer (ICD-9 code 1629 for 1988–1998 deaths and ICD-10 code C349 deaths after 1998). The last day of follow-up was December 31, 2011.

Statistical Analysis

Descriptive statistics were calculated for survival, air pollution exposures, and other covariates. Median survival and five-year survival rates were calculated after stratifying patients by stage at diagnosis and categorized air pollution exposures (cutoffs: 25th and 75th percentile and average of the two). Cox proportional hazards models were used to model time to all-cause mortality, allowing for right censoring due to loss to follow up (or study end) or, in the case of time to lung cancer mortality, censoring due to death from another underlying cause. Preliminary analyses determined the following potential confounding variables were predictors of mortality, so all models adjusted for: age, sex, race/ethnicity (non-Hispanic white, Hispanic, non-Hispanic black, other/unknown), marital status (single, married, formerly married, unknown), education index (quartiles), socioeconomic status (quintiles), dichotomized rural-urban community area (metropolitan core (1), non-metropolitan core (>1)), categorized distance to primary interstate highway (<300m, 300–1500m, >1500m, missing), categorized distance to primary US and State highways (<300m, 300–1500m, >1500m, missing), categorized year of diagnosis (1988–1992, 1993–1997, 1998–2002, 2003–2009), calendar month of diagnosis, and initial treatment (surgery, radiation, and/or chemotherapy versus none).

Single pollutant models were used to estimate hazard ratios (HRs) associated with a 1 standard deviation (SD) increase in continuous air pollution exposure, after adjusting for the aforementioned covariates. Initial models also adjusted for stage and histology at diagnosis. We then evaluated evidence for modification of air pollution associations by stage and then by histology. Final single pollutant models were fit separately for each stage and histology.

Sensitivity analyses were performed by further stratifying stage-specific models (adjusted for histology) by: sex, race/ethnicity, year of diagnosis, metropolitan core group, and large urban areas (LA county, Bay area counties, and San Diego County).

Analyses were performed using SAS version 9.4 (SAS Institute Inc.). Select graphical displays were created using R version 3.1.3.²⁴ Hypothesis tests were 2-sided, with a 0.05 type I error rate.

Results

Characteristics of the study participants are presented in Table 1. Patients were on average 69.3 years old at diagnosis, predominantly non-Hispanic white (77.2%), and most lived in a metropolitan core (85.7%). More than half of lung cancers were diagnosed at an advanced stage (53.0% distant site). During the study period, there were 324,266 deaths (92.1% of 352,053 patients). Of these deaths, 78.3% were assigned an underlying cause of lung cancer. Median survival times for localized, regional, and distant site diagnoses were 3.6, 1.3, and 0.4 years, respectively. For patients with localized stage at diagnosis, median survival was shortest for small and large cell carcinomas patients (1.5 and 1.6 years, respectively) and longest for adenocarcinoma patients (5.1 years). The number of patients with “unknown” stage at diagnosis decreased from 12,573 in 1988–1992 (5 year period) to 4,399 in 2003–2009 (7 year period), likely due to changes in technology, medical practice and/or coding practices. The highest quality geocode match (street address) was obtained for 91.1% of patients.

Average air pollution exposure assignments (average from diagnosis to end of follow-up for each patient 25km from a monitor) across patients were 21.9 ppb for NO₂, 40.2 ppb for O₃, 31.8 µg/m³ for PM₁₀, and 13.7 µg/m³ for PM_{2.5} (Table 2). As expected, PM₁₀, PM_{2.5}, and NO₂ were more highly correlated (Pearson’s R=0.70–0.76) than O₃ and PM₁₀ (R=0.36), O₃ and NO₂ (R=−0.01), or O₃ and PM_{2.5} (R=−0.02). Over the study period, there were long-term downward trends in NO₂, PM₁₀ and PM_{2.5} in California (eFigure 1 and eTable 2). Only 8.7% of patients lived < 300m from a primary interstate highway, while 45.4% were >1500m (eTable 3).

We observed a pattern of shorter median survival and lower five-year survival for patients with local or regional stage at diagnosis who had higher categorized NO₂, PM₁₀, or PM_{2.5} exposures (Table 3). For example, median survival for patients with local stage at diagnosis was 2.4 years for those with high PM_{2.5} exposure (≥ 16 µg/m³) and 5.7 years for those with low PM_{2.5} exposure (< 10 µg/m³). Survival for patients with distant stage at diagnosis was poor and showed little variation with air pollution exposure.

After adjusting for important determinants of survival and potential confounders (including stage and histology), the HR for all-cause mortality associated with a 1 SD increase in each pollutant were 1.13 (95% CI: 1.12, 1.13) for NO₂, 1.02 (95% CI: 1.02, 1.03) for O₃, 1.11 (95% CI: 1.11, 1.12) for PM₁₀, and 1.16 (95% CI: 1.16, 1.17) for PM_{2.5} (eTable 4). As shown in Table 4, these associations varied by stage at diagnosis (all interaction p < 0.01) and were of similar magnitude whether considering all-cause mortality or lung cancer-

specific mortality. For each pollutant, adjusted HR were larger for patients diagnosed at early stages. After stratifying by stage, we found additional variation in the associations by histology (all interaction $p < 0.01$, except O_3). After stratifying by stage and histology, exposure to NO_2 , PM_{10} , and $PM_{2.5}$ remained strongly associated with all-cause mortality, with the largest magnitude adjusted HR for local stage (Figure 1). The adjusted HR for NO_2 , PM_{10} , and $PM_{2.5}$ were generally smaller for small cell carcinoma patients and larger for adenocarcinoma patients (e.g., local stage HR for PM_{10} : 1.16 (95% CI: 1.11, 1.21) vs 1.30 (95% CI: 1.28, 1.33), respectively). O_3 was not statistically significantly associated with all-cause mortality for small and large cell cancer patients, but was modestly associated for squamous cell and adenocarcinoma patients (local stage adjusted HR of 1.04 (95% CI: 1.02, 1.07) and 1.03 (95% CI: 1.01, 1.05), respectively). Dose-response associations were evaluated in adjusted Cox models with categorized air pollution exposures, stratified by stage (data not shown). Results were qualitatively similar to the unadjusted associations in Table 3.

In sensitivity analyses, no substantial heterogeneity in stage-specific adjusted HR was found by sex, race/ethnicity, or distance to air quality monitors (eTables 5ab). There was modest heterogeneity by year of diagnosis, particularly for NO_2 and PM_{10} , but the patterns of larger HR for patients diagnosed at earlier stages remained consistent. Patients with local stage at diagnosis living in a metropolitan core had slightly higher HR for PM_{10} and $PM_{2.5}$ than those living in non-metropolitan core areas (e.g., $PM_{2.5}$ HR of 1.40 vs 1.25), a pattern that was also observed in the subsets of patients diagnosed in Los Angeles county, the San Francisco Bay area, or San Diego county. These findings merit further study.

Discussion

While ambient air pollutants have been associated with lung cancer incidence and mortality,^{7,9-11} their impacts on survival after diagnosis have yet to be fully assessed.¹⁴ In a population-based study of 352,053 patients with newly diagnosed lung cancer in California, we observed reduced survival associated with higher average NO_2 , $PM_{2.5}$ and PM_{10} exposure over the follow-up period after diagnosis. HR associated with these pollutants were largest for early stage cancers and varied by histology, with the largest HR in early stage non-small cell cancers, particularly adenocarcinoma.

A growing number of large cohort studies have found evidence for associations between air pollution exposures and lung cancer mortality using either incident lung cancer or death from lung cancer.⁹⁻¹² Meta-analysis estimates of the relative risk of lung cancer incidence/death (not stratified by stage) were slightly smaller than those observed in our study [1.04 (95% CI: 1.01, 1.08) for a 10 ppb increase in NO_2 ,¹¹ 1.08 (95% CI: 1.00, 1.17) for a 10 $\mu g/m^3$ increase in PM_{10} ,¹⁰ and 1.04 (95% CI: 1.02, 1.07) for a 5 $\mu g/m^3$ increase in $PM_{2.5}$] and showed some evidence for heterogeneity by histology.¹⁰ For the two most common histologies, relative risks associated with a 5 $\mu g/m^3$ increase in $PM_{2.5}$ were 1.18 (95% CI: 1.03, 1.35) for adenocarcinoma and 1.05 (95% CI: 0.85, 1.31) for squamous cell carcinoma.¹⁰

Few studies have attempted to disentangle determinants of lung cancer incidence from determinants of lung cancer survival due to the high case fatality rate.^{10,25} To our knowledge, only one study has related air pollution exposures to survival in patients diagnosed with lung cancer.¹⁴ Xu *et al* studied white respiratory cancer patients in Honolulu and Los Angeles between 1992–2008 and found adjusted HR—slightly larger than we observed—for all-cause mortality [1.48 (95% CI: 1.44, 1.52) for a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} ; 1.57 (95% CI: 1.53, 1.61) for a 5 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$; 1.04 (95% CI 1.03, 1.06) for a 10 ppb change in O_3] and slightly larger PM associations when restricting the analysis to Los Angeles cases only.¹⁴ Key differences include that we interpolated ambient exposures to residence locations (rather than using county-level exposures) and that we considered only lung cancer cases and stratified by stage and histology. Xu *et al* considered all respiratory cancer cases and adjusted for primary cancer site and stage. By fully conditioning on disease type and severity at diagnosis, we more effectively target inference about air pollution exposure associations with survival after diagnosis by limiting carry-over effects from differences at diagnosis potentially caused by earlier air pollution exposures.

Our observed associations were clinically significant (~38% increased risk of death depending on stage and pollutant) suggesting that reductions in exposure have the potential to improve lung cancer survival. As expected, we observed a substantially larger association with survival in local compared to distant stage at diagnosis. As lung cancer screening becomes widely implemented, a shift to diagnosis at earlier stages is likely to occur. This is the stage at which air pollutants appear to have the most impact on survival. To maximize the effectiveness of lung cancer screening, interventions targeting modifiable determinants of survival for early stage diagnoses are needed. Our findings suggest that future work should investigate the impact of interventions to reduce air pollution exposures (e.g., avoidance, relocation, home filtration systems) on lung cancer survival.

The pathophysiologic mechanism underlying the relationship between NO_2 , $\text{PM}_{2.5}$ and PM_{10} and lung cancer survival is uncertain. Ambient air pollution has been classified as a carcinogen and therefore may affect cancer progression after diagnosis via the same well described pathways including oxidative stress, DNA damage, cell proliferation, or epigenetic modifications. We observed some of the largest air pollution hazard ratios for adenocarcinoma, the only common histological subtype of lung cancer that develops in a significant number of nonsmokers.^{26,27} More generally, air pollution may reduce survival in the susceptible subpopulation of patients with cancer, for example, by impairing respiratory function.

Strengths of our study include the population-based, large sample size drawn from all cases diagnosed in California, minimizing selection bias and avoiding the survivorship bias in standard cohort studies. Using standardized methods, the CCR collects detailed clinical data and individual-level information on important determinants of survival (histology, stage, age, and year of diagnosis; first course of treatment, sex, race/ethnicity, and marital status). Our study focused on California, which has one of the most extensive and longest-running air quality monitoring networks in the US.

Several limitations of our study should be considered. The CCR collects information only on first course treatments, but residual confounding by subsequent treatments is unlikely since treatment is determined primarily by stage at diagnosis and we stratify by stage. Follow-up in the CCR is passive, but nearly complete (> 95%) for cancers with short survival. Individualized residential ambient air pollution exposure assignments offer a refinement over area-level exposure assignments (e.g., reducing spatial exposure misclassification, which can attenuate associations),^{10,28,29} but are subject to standard limitations, including inability to account for individual behavior (e.g., cancer patients may spend even more time indoors than the general population), changes of residence, or potentially long periods of time at medical facilities located in an area with different air pollution levels. We focused on air pollution exposures with large-scale, regional variability using spatial interpolation of air quality monitoring data, which does not capture the effects of traffic-related pollution (TRP) that varies over a finer spatial scale. We accounted for potential confounding by a crude measure of local traffic (distance to highways). Future investigation of the effects of TRP on lung cancer survival requires the development of highly spatially-resolved TRP exposure metrics (e.g., using land-use regression or line-source dispersion models) to directly evaluate TRP associations. The air pollution monitoring network is less dense in rural areas, so exclusion of patients living > 25km from a monitor differentially excludes patients in rural areas. Long-term downward trends in NO₂, PM₁₀ and PM_{2.5} in California during the study period have been recognized previously.³⁰ The lack of consistent long-term temporal trend for O₃ likely reduced variability in O₃ exposure across participants. Note that because survival is relatively short in lung cancer patients, we expected short-term (seasonal) variability to dominate long-term variability during each patient's follow-up period. We adjusted for month of diagnosis in our models to account for potential confounding by short-term temporal factors. Results were robust to sensitivity analyses stratifying by categorized year of diagnosis, suggesting that long-term trends did not induce spurious associations (particularly of concern for early stage diagnosis adenocarcinoma cases with longer median survival). Finally, we lacked individual-level data on important potential confounders/effect modifiers and risk factors (e.g., smoking, diet, alcohol use, education, access to care, obesity, previous lung disease and occupational exposures). These omitted factors could have spuriously induced the observed associations only if they were strongly associated with the spatio-temporal distribution of ambient air pollution exposures, which seems unlikely. Previous studies have suggested that nonsmokers may be at greater risk for air pollution related lung cancer incidence/mortality than current smokers.¹⁰ While smoking is an important risk factor, previous data suggests that, at diagnosis, only 39% of lung cancer patients are current smokers (drops to 14% at 5 months after diagnosis).³¹

In summary, we found evidence for associations between all-cause and lung cancer specific mortality and NO₂, PM_{2.5} and PM₁₀, robust to a number of sensitivity analyses. Future studies should evaluate the impacts of ambient air pollution exposure reduction since controlling patients' exposures could offer a novel approach to improve lung cancer outcomes, especially among patients diagnosed at early stages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Messages

What is the key question?

Does exposure to ambient air pollution after diagnosis of lung cancer affect survival?

What is the bottom line?

Lung cancer patients with higher average ambient NO₂, PM_{2.5} and PM₁₀ exposures since diagnosis had shorter survival, with the largest differences in survival for patients with early stage non-small cell cancers (particularly adenocarcinomas).

Why read on?

This is the first study to link individual-level estimates of air pollution exposures after lung cancer diagnosis to survival, and the study population was the population-based sample of 352,053 patients with newly diagnosed lung cancer during 1988–2009 in California as ascertained by the California Cancer Registry.

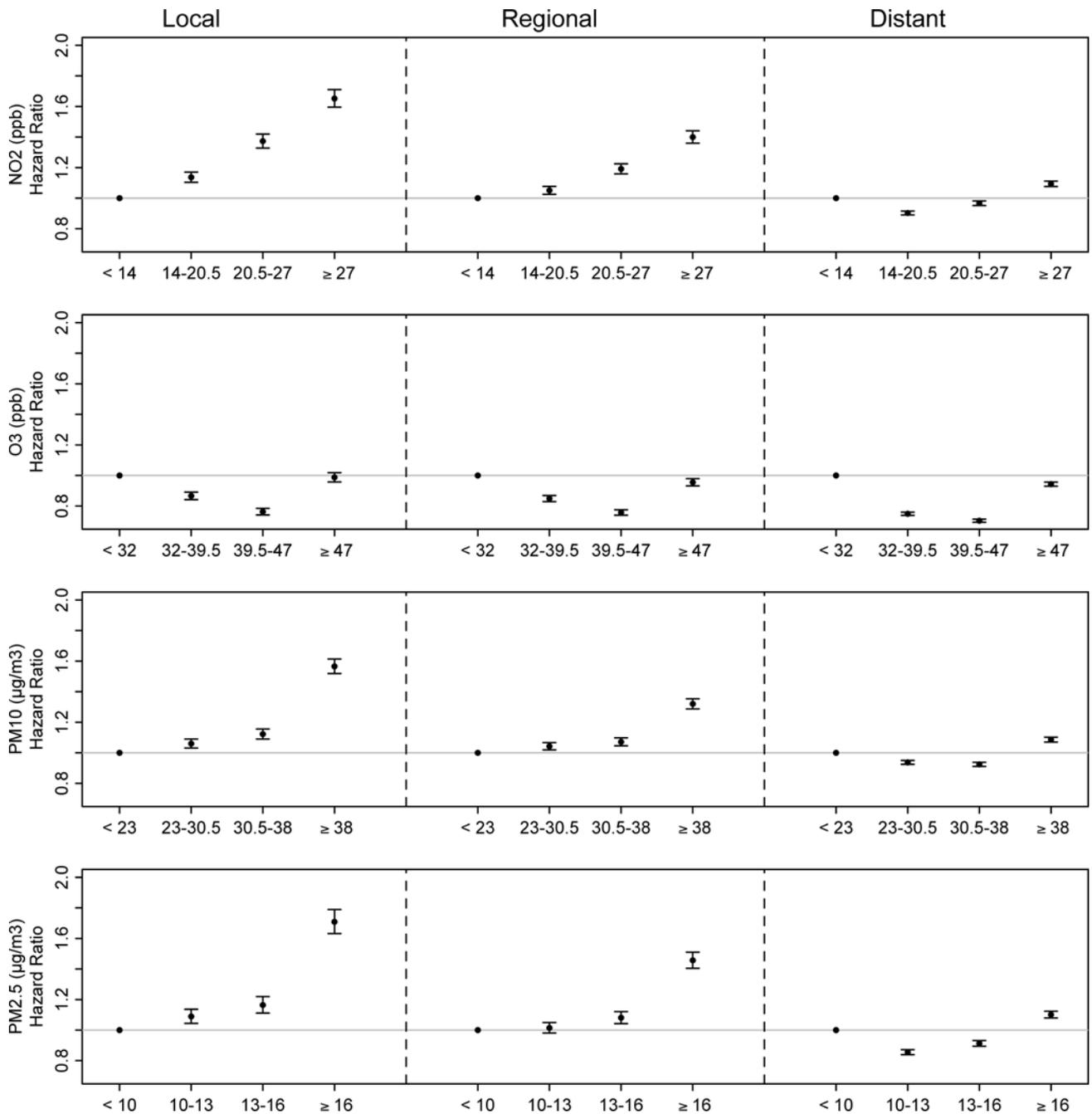


Figure 1. Adjusted^a hazard ratios and 95% confidence intervals for all-cause mortality associated with a standard deviation (SD) increase in air pollutant exposure,^{bc} stratified by stage and histology at diagnosis

^aAdjusted for age, sex, race/ethnicity, marital status, education index, SES, RUCA, distance to primary interstate highway, distance to primary US and State highways, month of diagnosis, year of diagnosis, and initial treatment

^bSD values: 10.2 ppb for NO₂, 11.9 ppb for O₃, 12.1 µg/m³ for PM₁₀, and 5.3 µg/m³ for PM_{2.5}

^cPM_{2.5} results are only for the subset of patients whose cancer was diagnosed in 1998 or later

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Demographic, tumor, and treatment characteristics of lung cancer patients in California by stage of diagnosis, 1988–2009.

Table 1

| Characteristics (Mean ± SD or %) | Localized Only (n=59,609) | Regional (n=73,513) | Distant Site(s) (n=186,496) | Unknown ^c (n=32,435) | Total (n=352,053) |
|--------------------------------------|------------------------------|------------------------|--------------------------------|------------------------------------|----------------------|
| Age (years) | 69.9 ± 10.5 | 68.8 ± 10.5 | 68.7 ± 11.3 | 72.5 ± 10.7 | 69.3 ± 11.0 |
| % Male | 49.8 | 54.7 | 56.1 | 54.8 | 54.6 |
| Race/ethnicity, % | | | | | |
| Non-Hispanic white | 81.0 | 78.7 | 75.0 | 79.2 | 77.2 |
| Hispanic | 6.5 | 7.1 | 8.8 | 7.4 | 7.9 |
| Non-Hispanic black | 6.2 | 7.2 | 7.9 | 6.9 | 7.4 |
| Other/Unknown | 6.2 | 7.0 | 8.3 | 6.5 | 7.5 |
| Marital Status, % | | | | | |
| Single | 9.4 | 9.6 | 11.9 | 9.6 | 10.8 |
| Married | 56.2 | 57.1 | 53.7 | 47.9 | 54.3 |
| Formerly married | 32.5 | 31.5 | 32.1 | 37.6 | 32.6 |
| Unknown | 1.8 | 1.8 | 2.3 | 4.9 | 2.4 |
| Education index ^a , % | | | | | |
| Low | 22.3 | 23.6 | 25.6 | 29.6 | 25.0 |
| Low-medium | 24.5 | 25.0 | 24.8 | 27.4 | 25.0 |
| Medium-high | 25.4 | 25.4 | 24.9 | 24.2 | 25.0 |
| High | 27.9 | 26.1 | 24.7 | 18.8 | 25.0 |
| Rural-urban commuting area (RUCA), % | | | | | |
| Non-Metropolitan core | 13.8 | 14.1 | 13.8 | 18.7 | 14.3 |
| Metropolitan core | 86.2 | 85.9 | 86.2 | 81.3 | 85.7 |
| Unknown | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 |
| Socioeconomic Status (SES), % | | | | | |
| Lowest | 14.0 | 15.0 | 16.6 | 18.8 | 16.1 |
| Lower-middle | 20.3 | 20.7 | 20.9 | 23.6 | 21.0 |
| Middle | 21.6 | 22.1 | 22.0 | 22.2 | 22.0 |
| Higher-middle | 21.8 | 21.3 | 20.8 | 19.8 | 21.0 |
| Highest | 21.1 | 19.6 | 18.2 | 15.2 | 18.7 |
| Unknown | 1.3 | 1.3 | 1.4 | 0.5 | 1.3 |

| Characteristics (Mean ± SD or %) | Localized Only (n=59,609) | Regional (n=73,513) | Distant Site(s) (n=186,496) | Unknown ^c (n=32,435) | Total (n=352,053) |
|-------------------------------------|------------------------------|------------------------|--------------------------------|------------------------------------|----------------------|
| Year of diagnosis, % | | | | | |
| 1988–1992 | 22.2 | 22.4 | 19.8 | 38.8 | 22.5 |
| 1993–1997 | 23.1 | 22.3 | 21.6 | 29.0 | 22.7 |
| 1998–2002 | 23.0 | 22.9 | 23.9 | 18.7 | 23.0 |
| 2003–2009 ^b | 31.7 | 32.4 | 34.7 | 13.6 | 31.8 |
| Histology at diagnosis, % | | | | | |
| Squamous cell | 26.1 | 27.2 | 15.2 | 22.3 | 20.2 |
| Adenocarcinoma | 45.0 | 35.4 | 35.4 | 23.1 | 35.9 |
| Small cell | 5.7 | 13.2 | 18.1 | 13.8 | 14.6 |
| Large cell | 12.1 | 14.3 | 20.8 | 35.7 | 19.3 |
| Other | 11.2 | 9.9 | 10.5 | 5.2 | 10.0 |
| Treatment types | | | | | |
| Surgery, % | | | | | |
| No | 32.5 | 59.6 | 94.6 | 92.8 | 76.6 |
| Yes | 67.4 | 40.3 | 5.2 | 4.5 | 23.0 |
| Unknown | 0.1 | 0.1 | 0.2 | 2.7 | 0.4 |
| Radiation, % | | | | | |
| No | 81.3 | 52.1 | 56.7 | 72.8 | 61.4 |
| Yes | 18.7 | 47.9 | 43.3 | 26.8 | 38.6 |
| Unknown | <0.1 | <0.1 | <0.1 | 0.5 | 0.1 |
| Chemotherapy, % | | | | | |
| No | 87.0 | 59.2 | 55.1 | 76.2 | 63.3 |
| Yes | 11.3 | 38.0 | 41.2 | 19.8 | 33.5 |
| Unknown | 1.6 | 2.8 | 3.7 | 4.0 | 3.2 |
| Geocode match quality, % | | | | | |
| Street address match | 91.5 | 91.5 | 91.5 | 89.1 | 91.3 |
| Area level match | 8.5 | 8.5 | 8.5 | 10.8 | 8.7 |
| Other or missing | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 |
| Median survival time (years) | | | | | |
| | 3.6 | 1.3 | 0.4 | 0.7 | 0.7 |

| Characteristics (Mean \pm SD or %) | Localized Only (n=59,609) | Regional (n=73,513) | Distant Site(s) (n=186,496) | Unknown ^c (n=32,435) | Total (n=352,053) |
|---|------------------------------|------------------------|--------------------------------|------------------------------------|----------------------|
| Median survival time (years), by histology at diagnosis | | | | | |
| Squamous cell | 2.6 | 1.1 | 0.4 | 0.7 | 0.8 |
| Adenocarcinoma | 5.1 | 1.9 | 0.4 | 0.8 | 0.9 |
| Small cell | 1.5 | 1.0 | 0.4 | 0.8 | 0.6 |
| Large cell | 1.6 | 0.8 | 0.2 | 0.6 | 0.4 |
| Other | 6.1 | 1.3 | 0.4 | 1.0 | 0.8 |

^a Categorized by quartiles.

^b Most recent year of diagnosis category includes 7 years, while the other categories each include 5 years.

^c Insufficient evidence available to assign a stage (e.g., patient dies before workup is complete, patient refuses diagnostic procedure, or limited workup is performed due to patient's age or simultaneous contraindicating condition).

Table 2

Air pollution exposure assignments based on residence at diagnosis, by stage at diagnosis.

| Air pollution exposures (Mean \pm SD or %) | Localized Only (n=59,609) | Regional (n=73,513) | Distant Site(s) (n=186,496) | Unknown (n=32,435) | Total (n=352,053) |
|---|------------------------------|------------------------|--------------------------------|-----------------------|----------------------|
| NO ₂ (ppb) | 20.6 \pm 9.3 | 21.4 \pm 9.7 | 22.0 \pm 10.4 | 24.5 \pm 11.3 | 21.9 \pm 10.2 |
| % available ^a | 87.6 | 86.8 | 87.3 | 83.0 | 86.8 |
| O ₃ (ppb) | 40.3 \pm 9.7 | 40.3 \pm 10.8 | 40.0 \pm 12.8 | 41.2 \pm 12.8 | 40.2 \pm 11.9 |
| % available ^a | 93.6 | 93.2 | 93.3 | 89.9 | 93.0 |
| PM ₁₀ (μ g/m ³) | 30.5 \pm 10.7 | 31.4 \pm 11.6 | 31.9 \pm 12.4 | 35.0 \pm 13.5 | 31.8 \pm 12.1 |
| % available ^a | 91.7 | 91.3 | 91.4 | 88.6 | 91.2 |
| PM _{2.5} (μ g/m ³) ^b | 13.0 \pm 4.5 | 13.4 \pm 4.9 | 13.9 \pm 5.6 | 14.6 \pm 5.7 | 13.7 \pm 5.3 |
| % available ^a | 86.5 | 84.3 | 82.6 | 76.8 | 83.3 |

^a% of patients with exposure assignment available (requires a monitor for that pollutant 25 km from residential address and non-missing geocode)

^bPM_{2.5} data are reported only for the subset of patients whose cancer was diagnosed in 1998 or later

Table 3

Median survival and five-year survival rate, by stage at diagnosis and air pollution exposure.

| Categorized air pollution exposure | Median survival (years) | | | Five-year survival rate (%) ^a | | |
|---|-------------------------|----------|---------|--|----------|---------|
| | Localized | Regional | Distant | Localized | Regional | Distant |
| NO ₂ (ppb) | | | | | | |
| <14 | 5.4 | 1.6 | 0.3 | 50 | 24 | 4 |
| 14 – 20.5 | 4.2 | 1.4 | 0.4 | 45 | 21 | 4 |
| 20.5 – 27 | 3.2 | 1.2 | 0.4 | 38 | 17 | 3 |
| 27 | 2.2 | 1.0 | 0.3 | 30 | 12 | 2 |
| O ₃ (ppb) | | | | | | |
| <32 | 2.8 | 1.0 | 0.3 | 36 | 16 | 2 |
| 32 – 39.5 | 3.8 | 1.4 | 0.5 | 42 | 19 | 3 |
| 39.5 – 47 | 4.9 | 1.6 | 0.5 | 49 | 23 | 4 |
| 47 | 2.7 | 1.1 | 0.3 | 35 | 15 | 2 |
| PM ₁₀ (µg/m ³) | | | | | | |
| <23 | 4.7 | 1.5 | 0.3 | 47 | 23 | 4 |
| 23 – 30.5 | 4.4 | 1.4 | 0.4 | 45 | 20 | 4 |
| 30.5 – 38 | 3.7 | 1.3 | 0.4 | 43 | 19 | 3 |
| 38 | 2.1 | 1.0 | 0.3 | 27 | 11 | 2 |
| PM _{2.5} (µg/m ³) ^b | | | | | | |
| <10 | 5.7 | 1.9 | 0.3 | 51 | 27 | 4 |
| 10 – 13 | 5.0 | 1.9 | 0.5 | 48 | 25 | 5 |
| 13 – 16 | 4.5 | 1.5 | 0.5 | 46 | 23 | 4 |
| 16 | 2.4 | 1.2 | 0.3 | 31 | 14 | 2 |

^aStandard errors of all five-year survival rates are <1%, with calculations based on >5,800 patients per group

^bPM_{2.5} results are only for the subset of patients whose cancer was diagnosed in 1998 or later

Table 4

Adjusted^a hazard ratios (95% confidence interval) for all-cause and lung cancer mortality associated with one standard deviation (SD) increase in air pollutant exposure,^b stratified by stage at diagnosis.

| Air pollutant | Stage at diagnosis | Sample size | All-cause mortality | Lung cancer mortality |
|--------------------------------|----------------------|-------------|---------------------------------|---------------------------------|
| | | | HR (95% CI) | HR (95% CI) |
| NO ₂ | Localized only | 52,223 | 1.30 (1.28 – 1.32) | 1.31 (1.29 – 1.33) |
| | Regional | 63,777 | 1.18 (1.17 – 1.20) | 1.18 (1.16 – 1.19) |
| | Distant site(s) | 162,816 | 1.07 (1.07 – 1.08) ^c | 1.07 (1.06 – 1.08) |
| | Overall ^d | 305,721 | 1.13 (1.12 – 1.13) ^c | 1.12 (1.11 – 1.12) ^c |
| O ₃ | Localized only | 55,823 | 1.04 (1.02 – 1.05) | 1.05 (1.04 – 1.07) |
| | Regional | 68,504 | 1.03 (1.02 – 1.04) | 1.03 (1.02 – 1.05) |
| | Distant site(s) | 174,022 | 1.01 (1.01 – 1.02) ^c | 1.02 (1.01 – 1.02) ^c |
| | Overall ^d | 327,513 | 1.02 (1.02 – 1.03) ^c | 1.03 (1.02 – 1.03) ^c |
| PM ₁₀ | Localized only | 54,671 | 1.26 (1.25 – 1.28) | 1.27 (1.25 – 1.29) |
| | Regional | 67,108 | 1.16 (1.15 – 1.17) | 1.15 (1.14 – 1.17) |
| | Distant site(s) | 170,415 | 1.07 (1.06 – 1.07) ^c | 1.07 (1.06 – 1.07) ^c |
| | Overall ^d | 320,940 | 1.11 (1.11 – 1.12) ^c | 1.11 (1.10 – 1.11) ^c |
| PM _{2.5} ^e | Localized only | 28,212 | 1.38 (1.35 – 1.41) | 1.39 (1.36 – 1.43) |
| | Regional | 34,223 | 1.26 (1.24 – 1.28) | 1.24 (1.22 – 1.27) |
| | Distant site(s) | 90,243 | 1.10 (1.09 – 1.11) ^c | 1.10 (1.09 – 1.11) |
| | Overall ^d | 160,707 | 1.16 (1.16 – 1.17) ^c | 1.15 (1.14 – 1.16) ^c |

^aAdjusted for age, sex, race/ethnicity, marital status, education index, SES, RUCA, distance to primary interstate highway, distance to primary US and State highways, histology at diagnosis, month of diagnosis, year of diagnosis, and initial treatment

^bSD values: 10.2 ppb for NO₂, 11.9 ppb for O₃, 12.1 µg/m³ for PM₁₀, and 5.3 µg/m³ for PM_{2.5}

^cEstimate and confidence interval bounds appear identical due to rounding

^dOverall analyses do not stratify by stage, but adjust for stage and include patients with unknown stage

^ePM_{2.5} results are only for the subset of patients whose cancer was diagnosed in 1998 or later