HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2018 August 15.

Published in final edited form as:

Int J Cancer. 2017 August 15; 141(4): 744–749. doi:10.1002/ijc.30779.

Particulate Matter Air Pollution and Liver Cancer Survival

Huiyu Deng, MA[1], **Sandrah P Eckel, PhD**[1], **Lihua Liu, PhD**[1], **Frederick W Lurmann, MS**[2], **Myles Cockburn, PhD**[1], and **Frank D Gilliland, MD PhD**[1]

[1]Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA

[2]Sonoma Technology Inc., Petaluma, CA, USA

Abstract

Particulate air pollution (PM) exposure has been associated with cancer incidence and mortality especially with lung cancer. The liver is another organ possibly affected by PM due to its role in detoxifying xenobiotics absorbed from PM. Various studies have investigated the mechanistic pathways between inhaled pollutants and liver damage, cancer incidence, and tumor progression. However, little is known about the effects of PM on liver cancer survival.

20,221 California Cancer Registry patients with hepatocellular carcinoma (HCC) diagnosed between 2000–2009 were used to examine the effect of exposure to ambient PM with diameter less than 2.5μm ($PM_{2.5}$) on HCC survival. Cox proportional hazards models were used to estimate hazard ratios (HRs) relating $PM_{2.5}$ to all-cause and liver cancer-specific mortality linearly and non-linearly— overall and stratified by stage at diagnosis (local, regional, and distant)—adjusting for potential individual and geospatial confounders.

$PM_{2.5}$ exposure after diagnosis was statistically significantly associated with HCC survival. After adjustment for potential confounders, the all-cause mortality HR associated with a 1 standard deviation (5.0 $\mu g/m^3$) increase in $PM_{2.5}$ was 1.18 (95% CI: 1.16 – 1.20); 1.31 (95% CI:1.26 – 1.35) for local stage, 1.19 (95% CI:1.14 – 1.23) for regional stage, and 1.05 (95% CI:1.01 – 1.10) for distant stage. These associations were nonlinear, with substantially larger HRs at higher exposures. The associations between liver cancer-specific mortality and $PM_{2.5}$ were slightly attenuated compared to all-cause mortality, but with the same patterns.

Exposure to elevated $PM_{2.5}$ after the diagnosis of HCC may shorten survival, with larger effects at higher concentrations.

Corresponding author contact information: Sandrah P. Eckel, Department of Preventive Medicine, University of Southern California, 2001 N. Soto Street, MC-9234, Los Angeles, CA 90089, eckel@usc.edu, Phone: (323)-442-2030, Fax: (323)-442-2349.

Author Contributions:

Study concept and design: Gilliland
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Deng
Obtained funding: Gilliland
Administrative, technical, or material support: Liu, Lurmann, Cockburn
Study supervision: Gilliland, Eckel, Liu

Keywords

Air pollution; Hepatocellular carcinoma; $PM_{2.5}$; Survival analysis

Introduction

Air pollution is classified as a carcinogen by the International Agency for Research on Cancer (IARC).[1] While associations between ambient particulate matter with diameter less than 2.5μm ($PM_{2.5}$) and lung cancer have been well documented, associations with cancers at other sites have received less attention.[2] The liver may be a target as $PM_{2.5}$ can induce oxidative stress, inflammation, genotoxicity, and accelerate liver inflammation and steatosis, driving the development and progression of liver cancer.[3] For example, $PM_{2.5}$ exposure has been linked to increased serum levels of hepatic enzymes such as alanine aminotransferase (ALT), which is a marker of liver damage and a predictor of hepatocellular carcinoma (HCC), the most common liver cancer.[4] Long-term $PM_{2.5}$ exposures have recently been linked to an increased incidence of HCC,[4] but the effects of $PM_{2.5}$ exposure on survival of HCC have not been investigated. We hypothesized that $PM_{2.5}$ exposure accelerates the progression of HCC and decreases survival after the diagnosis of liver cancer.

Materials and Methods

To determine whether $PM_{2.5}$ exposure is associated with survival in liver cancer patients, we combined data on patients newly diagnosed with primary HCC (ICD-O-3 site code of C22.0 and morphology codes of 8170–8176[5]) between 2000–2009 from the California Cancer Registry (CCR) (http://www.ccrcal.org) and $PM_{2.5}$ air pollution data collected by the U.S. Environmental Protection Agency's (EPA) Air Quality System (AQS) database[6] for the same time period, using the same methods as described in detail in a previous study.[7] Briefly, the CCR data contain information on patient demographics, routine follow-up on vital status, tumor characteristics (including stage of diagnosis), and first course of treatment within 6 months of diagnosis for all HCC patients diagnosed in California. Cancer records were geocoded by longitude and latitude based on residential address at diagnosis, and then assigned into census tracts and block groups for assignment of area-based estimates of rural-urban commuting area (RUCA) codes and socioeconomic status (SES). Specifically, RUCA codes are census tract-level designations from 1 (metropolitan) to 10 (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).[8] Socioeconomic status was calculated at the census block group level using validated area-level measures based on census 2000 data and American Community Survey 2007–2011 5-year estimates (online supplement).[9–11] Routine CCR follow-up of cancer patients monitored patient vital status through information sharing with reporting hospitals and linkage with a variety of administrative records.[12] There were 20,221 eligible HCC cases with $PM_{2.5}$ exposures included in the analysis. We censored the date of last follow-up to December 31, 2011.

Using hourly measurements of ambient $PM_{2.5}$ (in $\mu g/m^3$) in the AQS database, monthly average $PM_{2.5}$ concentrations were calculated from hourly and daily measurements[6], and spatially interpolated to residence locations from up to four closest air quality monitoring stations using inverse distance-squared weighting.[7,13] $PM_{2.5}$ exposures were not assigned to patient residences with unmatched geocodes or with the nearest monitor located > 25km away. Survival-period exposure summaries were calculated as the average ambient residential monthly $PM_{2.5}$ from date of diagnosis to date of death or loss to follow-up or the end of study.

Kaplan-Meier curves were used to calculate median survival stratified by stage at diagnosis and categorized $PM_{2.5}$ exposure. Cox proportional hazards models were used to estimate the $PM_{2.5}$ exposure (<10 $\mu g/m^3$, 10–25 $\mu g/m^3$, >25 $\mu g/m^3$) and survival association. We considered both all-cause and liver cancer specific mortality, where liver cancer was the underlying cause of death on the death certificate (ICD-10 code C22.0-C22.9).[14] Patient survival was censored due to loss to follow-up or study end (or, for liver cancer specific mortality, censored due to death by another cause). Hazard ratios (HRs)—scaled to a standard deviation (SD) increase in $PM_{2.5}$—were obtained from Cox models that adjusted for predetermined potential confounders: age, sex, race/ethnicity (non-Hispanic white, Hispanic, non-Hispanic black, Asian/Pacific islanders, other/unknown), marital status (single, married, formerly married, unknown), year of diagnosis, month of diagnosis, and initial treatment (surgery, radiation, and/or chemotherapy versus none), SES, dichotomized RUCA (metropolitan core, non-metropolitan core), categorized distance to primary interstate highways and primary US and State Highways (<300m, 300–1500m, >1500m). Adjusted Cox models were stratified by tumor stage at diagnosis (local, regional, distant). Sensitivity analyses were performed by further stratifying the stage-specific Cox models by distance to monitor, geocoding accuracy (street-level matching vs. city-level matching), regions (Los Angeles county, San Francisco Bay Area, San Diego county, and other regions in California), and socioeconomic status. Nonlinear associations with $PM_{2.5}$ were examined using a natural cubic spline with 2 degrees of freedom[2] and Cox models with categorized $PM_{2.5}$.

Analyses were conducted using SAS version 9.4 (SAS Institute Inc.) and R version 3.3.1 (http://www.R-project.org). Hypothesis tests were 2-sided with a 0.05 significance level.

Results

Overall, median survival was 0.64 years and only 324 patients were lost to follow-up (i.e., not known to be dead and with a last follow-up date 15 months or longer before the study end). HCC patients were on average 63.7 years old at diagnosis, racially diverse (38.9% non-Hispanic white, 25.9% Hispanic white, 26.1% Asian/Pacific islander) and predominantly male (75.0%), and living in metropolitan core areas (90.6%) (Table 1). The most common stage at diagnosis was local (44.8%) followed by: regional (27.5%), distant (17.6%), and unknown (10.0%). The number of patients diagnosed at local stage increased from 533 (5.9%) in 2000 to 1347 (14.9%) in 2009 while the number decreased from 548 (15.4%) to 395 (11.1%) in distant stage (data not shown). The most common initial treatments were chemotherapy (32.4%) and surgery (21.9%). In general, patients who lived in areas with

high $PM_{2.5}$ tended to have lower socio-economic status and were more likely to be diagnosed with advanced stage disease (eTable1).

Median all-cause mortality times were higher in low $PM_{2.5}$ areas for patients diagnosed at either local or regional stage (Table 2). For example, median survival times for patients diagnosed at local stage living in lowest and highest $PM_{2.5}$ exposure areas were 2.16 and 0.07 years, respectively. After adjusting for potential confounders, $PM_{2.5}$ level was inversely associated with all-cause mortality with statistical significance. Allowing for nonlinear associations using splines or categorized exposure, the adjusted $PM_{2.5}$ HR for all-cause mortality were significantly higher in high exposure areas in both overall and in stage-specific models (Figure 1, Table 2). In stage-specific models using a linear term for continuous $PM_{2.5}$ exposure, the HRs associated with a 1 SD increase in $PM_{2.5}$ were 1.31 (95% CI: 1.26 – 1.35) for local stage, 1.19 (95% CI: 1.14 – 1.23) for regional stage, and 1.05 (95% CI: 1.01 – 1.10) for distant stage. This indicates the damaging effect of $PM_{2.5}$ is most substantial for patients with local disease and diminishes with worsened stage, which likely reflects the shortened survival/exposure time for patients with late stage disease. The associations between liver cancer specific survival and exposure to $PM_{2.5}$ were slightly attenuated, but the pattern that adjusted $PM_{2.5}$ HR was larger for patients diagnosed at early stage remained (eTable 2). Sensitivity analyses show that stage-stratified HRs were robust to stratification by distance to monitor, geocoding accuracy, and socioeconomic status (eTable 3). Stratification by various metropolitan areas (LA county, San Diego county, San Francisco Bay Area) showed a consistent pattern of larger $PM_{2.5}$ HR for patients with local stage at diagnosis as compared to patients with more advanced stage at diagnosis.

Discussion

Our study provides the first evidence that exposure after HCC diagnosis to a major ambient air pollutant, $PM_{2.5}$, is associated with shortened survival. These associations were strongest for patients diagnosed at local stage and showed larger adverse effects at higher $PM_{2.5}$ levels. To our knowledge, no study has related $PM_{2.5}$ to liver cancer survival, but several have examined other $PM_{2.5}$-liver cancer associations.[2,4] For instance, in a large cohort study (n=66,820) Wong *et al* found that $PM_{2.5}$ was associated with mortality from accessory organ cancers (liver, gall bladder, and pancreas) (overall: 1.35 (95% CI: 1.06–1.71), in males: 1.28 (95% CI: 0.83–1.96), in females: 1.37 (95% CI: 1.05–1.80), and in female never smokers: 1.36 (95% CI: 1.01–1.84)).[2] A key difference between our study and the Wong *et al* study is that we calculated the average $PM_{2.5}$ exposure after diagnosis, addressing the hypothesis that $PM_{2.5}$ exposure after diagnosis adversely affects survival. Wong *et al* assigned exposures based on the subjects' recruitment year average (between 1998 and 2001). Our study specifically targeted HCC and conducted stage-specific analysis, which limits carry-over effects at diagnosis.

Our population-based study design—consisting of all Californian HCC cases between 2000–2009—minimizes selection and survivorship bias. California also has one of the largest and longest running air pollution monitoring networks and a wide range of $PM_{2.5}$ exposures allowing large valid scale exposure assessment using standard methods. Residential addresses were available only at the date of diagnosis, so there could be exposure

misclassification due to patients relocating. However, patients with HCC were less likely to relocate after diagnosis as the survival times were very short. An important limitation of our registry-based design is that personal-level data (e.g., alcohol consumption, Hepatitis A/B status, weight, and residential histories after diagnosis) were not available in the CCR. We did control for area-level SES and rural/urban factors, major confounders to the $PM_{2.5}$-HCC survival associations, and believe that factors other than SES and residential location were unlikely to be associated with the spatio-temporal distribution of ambient air pollution exposures. Thus, the associations could not have spuriously induced with the adjustment of these omitted factors. Nevertheless, future studies should consider additional personal-level factors.

Previous studies have suggested exposure-response relationships for $PM_{2.5}$ that were linear for lung cancer mortality or steeply increasing at low exposure levels and flattening out at higher exposures for cardiovascular mortality.[15–16] On the one hand, our finding of nonlinear (concave upward, quadratic curved) $PM_{2.5}$-HCC survival associations has significant public health implications, providing evidence that relatively small reductions in high pollution levels could have substantial health impacts. On the other hand, the magnitude of the hazard ratios at the high pollution levels were large. While these findings were plausible and consistent with the results from the analysis on the linear association, we recognize there might be unmeasured risk factors such as those personal-level confounders that are not available in our data. Future research is needed to confirm this finding.

In summary, we found adverse effects of $PM_{2.5}$ exposure after diagnosis on liver cancer survival. Not only were such effects more profoundly for those diagnosed with early stage, but they also increased strongly with concentration, suggesting that reductions in high $PM_{2.5}$ exposure could increase survival for a non-respiratory system cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This work was supported by the Southern California Environmental Health Sciences Center (grant P30ES007048) funded by the National Institute of Environmental Health Sciences; and the Hastings Foundation. The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 5NU58DP003862-04/DP003862; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

References

1. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K. The carcinogenicity of outdoor air pollution. Lancet Oncol. 2013; 14:1262–3. [PubMed: 25035875]
2. Wong CM, Tsang H, Lai HK, Thomas GN, Lam KB, Chan KP, Zheng Q, Ayres JG, Lee SY, Lam TH, Thach TQ. Cancer Mortality Risks from Long-term Exposure to Ambient Fine Particle. Cancer Epidemiol Biomarkers Prev. 2016; 25:839–45. [PubMed: 27197138]
3. Kim JW, Park S, Lim CW, Lee K, Kim B. The role of air pollutants in initiating liver disease. Toxicol Res. 2014; 30:65–70. [PubMed: 25071914]
4. Pan WC, Wu CD, Chen MJ, Huang YT, Chen CJ, Su HJ, Yang HI. Fine Particle Pollution, Alanine Transaminase, and Liver Cancer: A Taiwanese Prospective Cohort Study (REVEAL-HBV). J Natl Cancer Inst. 2016; 108
5. Egevad, L., Heanue, M., Berney, D., Fleming, K., Ferlay, J. Histological groups. In: Curado, M.Edwards, B.Shin, H.Strom, H.Ferlay, J.Heanue, M., Boyle, P., editors. Cancer incidence in five continentsed. Vol. IX. Lyon, France: IARC Press; 2007. p. 61-6.IARC Scientific Publications No. 160
6. US Environmental Protection Agency. Air Quality System Data Mart. 2007; 2012
7. Eckel SP, Cockburn M, Shu YH, Deng H, Lurmann FW, Liu L, Gilliland FD. Air pollution affects lung cancer survival. Thorax. 2016; 71:891–8. [PubMed: 27491839]
8. Rural Urban Commuting Area Codes Data. 2016; 2015
9. Yost K, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control. 2001; 12:703–11. [PubMed: 11562110]
10. Yin D, Morris C, Allen M, Cress R, Bates J, Liu L. Does socioeconomic disparity in cancer incidence vary across racial/ethnic groups? Cancer Causes Control. 2010; 21:1721–30. [PubMed: 20567897]
11. Yang J, Schupp C, Harrati A, Clarke C, Keegan T, Gomez S. Developing an area-based socioeconomic measure from American Community Survey data. Cancer Prevention Institute of California. 2014
12. CALIFORNIA SO, Health DoP. CANCER REPORTING IN CALIFORNIA SYSTEM STANDARDS: ABSTRACTING AND CODING PROCEDURES FOR HOSPITALS (Rev. 2.0, April 2012). California Cancer Registry Data Standards and Quality Control Unit (12). 2012; 1
13. Wong CM, Tsang H, Lai HK, Thomas GN, Lam KB, Chan KP, Zheng Q, Ayres JG, Lee SY, Lam TH, Thach TQ. Cancer Mortality Risks from Long-term Exposure to Ambient Fine Particle. Cancer Epidemiol Biomarkers Prev. 2016; 25:839–45. [PubMed: 27197138]
14. The Web's Free 2016/17 ICD-10-CM/PCS Medical Coding Reference. 2016; 2016
15. Pope CA 3rd, Burnett RT, Krewski D, Jerrett M, Shi Y, Calle EE, Thun MJ. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. Circulation. 2009; 120:941–8. [PubMed: 19720932]
16. Pope CA 3rd, Burnett RT, Turner MC, Cohen A, Krewski D, Jerrett M, Gapstur SM, Thun MJ. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. Environ Health Perspect. 2011; 119:1616–21. [PubMed: 21768054]

Novelty & Impact Statements

This is the first registry-based study to link individual-level estimates of air pollution exposures after liver cancer diagnosis to survival on a population-based sample of 20,221 patients with newly diagnosed liver cancer during 2000–2009 in California. We found adverse effects of $PM_{2.5}$ exposure after diagnosis on liver cancer survival increased strongly with concentration, suggesting that reductions in high $PM_{2.5}$ exposure could increase survival for a non-respiratory system cancer.

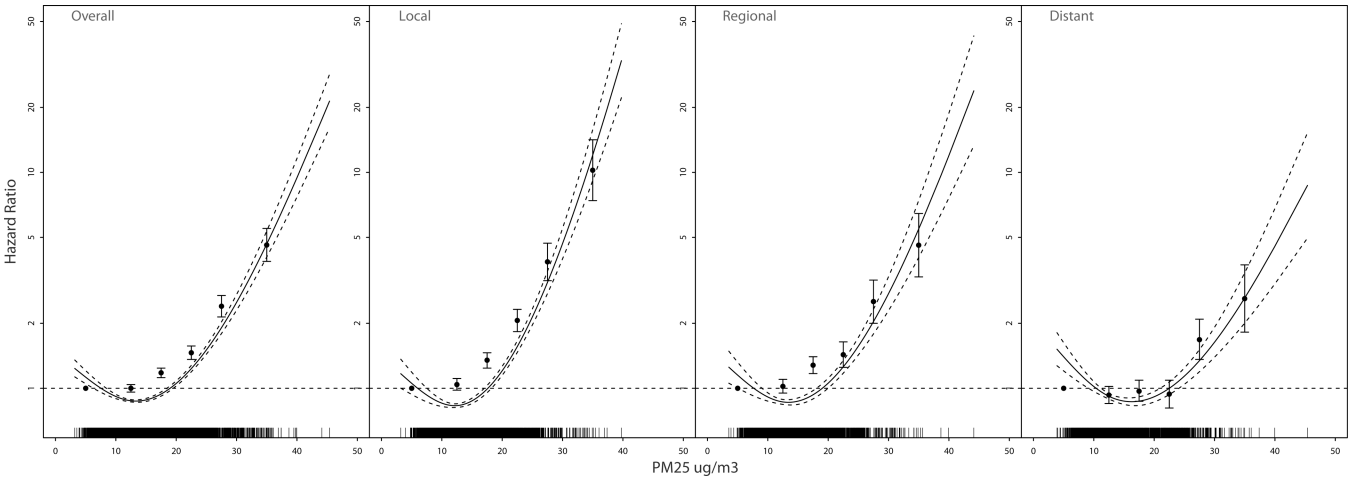

Figure 1.

Nonlinear patterns of adjusteda associations between $PM_{2.5}$ exposure and all-cause mortality (solid line) and 95% confidence interval (dashed line) estimated using a natural cubic spline with 2 degrees of freedom. Points with confidence intervals are hazard ratios and 95% confidence intervals for all-cause mortality from pooled and stage-specific Cox proportional hazard models with categorized $PM_{2.5}$ exposure.b The distribution of $PM_{2.5}$ exposures are demarcated using ticks above the x-axis.c

[a] Adjusted for age, sex, race/ethnicity, marital status, socioeconomic status, rural–urban commuting area, distance to primary interstate highway, distance to primary US and state highways, month of diagnosis, year of diagnosis and initial treatments.

[b] The categories of $PM_{2.5}$ exposure were 0–10, 10–15, 15–20, 20–25, 30+ $\mu g/m^3$. The hazard ratios for all-cause mortality from pooled and stage-specific Cox proportional hazard models with categorized $PM_{2.5}$ exposure are presented in Table 2 and plotted at 5, 12.5, 17.5, 22.5, and 35 $\mu g/m^3$ in the Figure 1.

[c] Three patients with $PM_{2.5}$ exposure > 50 $\mu g/m^3$ were excluded from the plot (but not the model).

Table 1

Summary of demographic, clinical, treatment characteristics, and distances of residential addresses at diagnosis from highways and $PM_{2.5}$ exposures for liver cancer patients newly diagnosed in California from 2000–2009, by stage at diagnosis.

Characteristics (Mean ± SD or %)	**Local n=9,064 (44.8%)**	**Regional n=5,570 (27.5%)**	**Distant n=3,565 (17.6%)**	**Unknown[a] n=2,022 (10.0%)**	**Total n=20,221**
Age at diagnosis (years)	64.1±11.9	62.9±12.3	62.8±13.3	66.0±12.7	63.7±12.4
Male	72.7	78.2	77.2	72.8	75.0
Race (%)					
Non-Hispanic whites	39.1	37.9	38.5	41.5	38.9
Hispanic	26.2	25.6	25.9	25.5	25.9
Non-Hispanic blacks	6.9	8.7	9.1	6.7	7.8
Asian/Pacific islanders	26.8	26.2	25.2	24.2	26.1
Others/Unknown	1.0	1.5	1.2	2.0	1.3
Marital status (%)					
Single	16.9	20.8	21.3	16.7	18.7
Married	57.2	55.8	53.5	50.2	55.5
Formerly married	23.7	20.9	22.5	29.0	23.3
Unknown	2.1	2.4	2.7	4.1	2.5
Rural-urban commuting area (%)					
Metropolitan core	91.0	90.9	90.4	87.7	90.6
Non-metropolitan core	9.0	9.1	9.6	12.3	9.4
Socioeconomic status (SES, %)					
Lowest	19.0	20.9	23.0	24.0	20.7
Lower-middle	21.8	22.0	22.1	22.2	22.0
Middle	20.8	21.0	21.0	20.3	20.8
Higher-middle	19.9	19.6	19.6	18.9	19.7
Highest	17.5	16.1	14.2	14.2	16.2
Unknown	0.9	0.4	0.1	0.3	0.6
First-course treatment types (%)					
Surgery	36.0	16.6	4.5	4.3	21.9
Radiation	2.2	1.7	10.0	0.7	3.3

Characteristics (Mean ± SD or %)	Local n=9,064 (44.8%)	Regional n=5,570 (27.5%)	Distant n=3,565 (17.6%)	Unknown[a] n=2,022 (10.0%)	Total n=20,221
Chemotherapy	36.6	36.8	25.7	13.4	32.4
Geocode match quality (%)					
Street address	91.8	90.8	91.4	91.2	91.4
Area-level	8.2	9.1	8.5	8.8	8.6
Other or missing	<0.1	0.1	0.1	<0.1	<0.1
Distance to primary interstate highway[b]					
< 300 m	10.3	10.4	9.6	10.6	10.2
300 – 1500 m	38.4	38.8	40.0	37.5	38.7
>1500 m	42.0	40.8	41.0	42.6	41.5
% missing	9.3	10.1	9.4	9.2	9.5
Distance to primary US and State highways[b]					
< 300 m	4.0	4.5	3.8	4.1	4.1
300 – 1500 m	15.1	14.0	13.9	13.3	14.4
>1500 m	71.6	71.5	72.9	73.4	71.9
% missing	9.3	10.1	9.4	9.2	9.5
$PM_{2.5}$ ($\mu g/m^3$)	12.9±4.6	13.3±5.0	14.0±5.5	14.3±5.6	13.3±5.0
% missing[c]	9.0	9.3	9.9	12.0	9.5

[a] 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).

[b] Distance values are primarily missing for participants with poor geocode matches (worse than street address match).

[c] Exposure assignments were excluded when the nearest monitor was located > 25km away or a geocode match was absent.

Table 2

Median all-cause mortality time stratified by stage at diagnosis and categorized fine particulate matter ($PM_{2.5}$) exposure, and adjusted[a] hazard ratios for all-cause mortality from pooled and stage-specific Cox proportional hazard models with categorized $PM_{2.5}$ and continuous $PM_{2.5}$[b].

			Median survival (years)			
		Number of patients	**Local**	**Regional**	**Distant**	**Overall**
Categorized $PM_{2.5}$ ($\mu g/m^3$)	< 10	5364	2.16	0.61	0.18	0.83
	10–15	7431	1.92	0.59	0.23	0.87
	15–20	3794	1.07	0.36	0.21	0.49
	20–25	1393	0.65	0.33	0.27	0.42
	25–30	386	0.25	0.15	0.12	0.19
	≥30	140	0.07	0.06	0.09	0.08
Overall			1.52	0.48	0.20	0.64
Hazard Ratio[a] (95% confidence interval)						
Categorized $PM_{2.5}$ ($\mu g/m^3$)	< 10		REF	REF	REF	REF
	10–15		1.04 (0.98 – 1.11)	1.02 (0.95 – 1.10)	0.93 (0.85 – 1.02)	1.00 (0.96 – 1.04)
	15–20		1.35 (1.24 – 1.46)	1.28 (1.17 – 1.40)	0.97 (0.87 – 1.09)	1.18 (1.12 – 1.24)
	20–25		2.06 (1.83 – 2.32)	1.43 (1.25 – 1.64)	0.94 (0.81 – 1.09)	1.46 (1.36 – 1.57)
	25–30		3.85 (3.15 – 4.70)	2.52 (2.00 – 3.17)	1.68 (1.36 – 2.09)	2.40 (2.14 – 2.69)
	≥30		10.24 (7.40 – 14.16)	4.60 (3.28 – 6.45)	2.60 (1.82 – 3.73)	4.61 (3.87 – 5.50)
Continuous $PM_{2.5}$[b]			1.31 (1.26 – 1.35)	1.19 (1.14 – 1.23)	1.05 (1.01 – 1.10)	1.18 (1.16 – 1.20)

[a] Adjusted for age, sex, race/ethnicity, marital status, socioeconomic status, rural–urban commuting area, distance to primary interstate highway, distance to primary US and state highways, month of diagnosis, year of diagnosis and initial treatments.

[b] Hazard ratios are scaled to a 1 standard deviation increase in $PM_{2.5}$ (equivalent to 5.0 $\mu g/m^3$).