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ORIGINAL PAPER

# Ambient $PM_{2.5}$ air pollution exposure and hepatocellular carcinoma incidence in the United States

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## Abstract

**Purpose** To conduct the first epidemiologic study prospectively examining the association between particulate matter air pollution < 2.5 μm in diameter ($PM_{2.5}$) exposure and hepatocellular carcinoma (HCC) risk in the U.S.

**Methods** Surveillance, Epidemiology, and End Results (SEER) provided information on HCC cases diagnosed between 2000 and 2014 from 16 population-based cancer registries across the U.S. Ambient $PM_{2.5}$ exposure was estimated by linking the SEER county with a spatial $PM_{2.5}$ model using a geographic information system. Poisson regression with robust variance estimation was used to calculate incidence rate ratios and 95% confidence intervals (CIs) for the association between ambient $PM_{2.5}$ exposure per 10 μg/m$^3$ increase and HCC risk adjusting for individual-level age at diagnosis, sex, race, year of diagnosis, SEER registry, and county-level information on health conditions, lifestyle, demographic, socioeconomic, and environmental factors.

**Results** Higher levels of ambient $PM_{2.5}$ exposure were associated with a statistically significant increased risk for HCC ($n = 56{,}245$ cases; adjusted IRR per 10 μg/m$^3$ increase = 1.26, 95% CI 1.08, 1.47; $p < 0.01$).

**Conclusions** If confirmed in studies with individual-level $PM_{2.5}$ exposure and risk factor information, these results suggest that ambient $PM_{2.5}$ exposure may be a risk factor for HCC in the U.S.

**Keywords** $PM_{2.5}$ · Particulate matter · Air pollution · Liver cancer · Hepatocellular carcinoma · Geographic information system

## Introduction

Hepatocellular carcinoma (HCC) is the most common histological type of primary liver cancer, accounting for 85–90% of primary liver cancer cases [1, 2]. Risk factors for HCC vary by geography and include chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, aflatoxin exposure, heavy alcohol consumption, smoking, obesity, and diabetes [3]. Although liver cancer incidence and mortality have been increasing in many regions around the world including the U.S. [4–6], an estimated 40.5% of HCC cases in the U.S. are unexplained by known risk factors including HCV, HBV, alcohol consumption, diabetes, and obesity [7]. Primary prevention of HCC is essential as the five-year relative survival rate remains low (< 12%) [8].

Recent evidence suggests that exposure to fine particulate matter air pollution < 2.5 μm in diameter ($PM_{2.5}$) may increase the risk of liver cancer [9, 10]. $PM_{2.5}$ is a ubiquitous environmental exposure produced from combustion sources such as motor vehicles and power plants [11]. PM,

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and outdoor air pollution in general, is classified as an International Agency for Research on Cancer (IARC) Group 1 human carcinogen largely based on evidence of positive associations with lung cancer in epidemiologic and experimental studies [12]. Humans are primarily exposed to $PM_{2.5}$ via inhalation; its relatively finer particle size fraction allows for deposition deep in the lung (e.g., alveoli) through sedimentation and diffusion processes [13]. In addition, $PM_{2.5}$ has been shown to induce oxidative damage, inflammation, and genotoxicity in the liver [14], promote HCC cell invasion and migration [15], and promote collagen deposition in the liver by activating TGF-β signaling [16]. Higher $PM_{2.5}$ exposure has also been associated with reduced liver cancer survival [17] as well as higher prevalence of hepatic steatosis, a risk factor for HCC [18]. Two epidemiologic studies have examined the association between $PM_{2.5}$ exposure and HCC incidence in Taiwan and Europe showing positive associations, although there were temporal mismatches as the date of case diagnoses preceded the exposure time periods [9, 10]. To date, no studies have been conducted in the U.S.

Although $PM_{2.5}$ levels have decreased in the U.S. over the past two decades, $PM_{2.5}$ remains an important environmental concern as urbanization continues to rise in parts of the U.S. and around the world such as in China [19–21]. An estimated 13.6% of the U.S. population resides in areas where $PM_{2.5}$ concentrations exceed the 24-hour Environmental Protection Agency (EPA) National Ambient Air Quality Standards of 35 $\mu g/m^3$ [22, 23]. Further, in 2017, an estimated 19.9 million (6.2% of the population) reside in locations with unhealthy levels of year-round particle pollution in the U.S. [24]. $PM_{2.5}$ exposure is a modifiable risk factor that can be mitigated through reduced time spent outdoors at and during high-traffic locations and times [25]. The objective of this study was to prospectively examine the association between ambient $PM_{2.5}$ exposure and HCC incidence in the U.S.

## Methods

### Study population

The Surveillance, Epidemiology, and End Results (SEER) database is a U.S. National Cancer Institute program collecting individual-level information on cancer incidence, survival, and treatment from population-based cancer registries covering 28% of the U.S. population [26]. The following 16 registries were included in the analysis: Atlanta (metropolitan); Greater California; Connecticut; Detroit (metropolitan); Greater Georgia; Iowa; Kentucky; Los Angeles; Louisiana (excluding July–December 2005 cases due to Hurricanes Katrina and Rita); New Jersey; New Mexico; Rural Georgia; San Francisco–Oakland; San Jose–Monterey; Seattle (Puget Sound); and Utah. The study area included all 607 counties located in the catchment areas captured by these 16 SEER registries that did not restrict coverage to specific populations and that were located in the 48 contiguous U.S. states with available $PM_{2.5}$ exposure data. To protect patient confidentiality, the SEER database does not include personal identifiers. This study was exempt from Institutional Review Board review.

### Outcomes

The following criteria were used to define HCC cases: International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography code C22.0 for primary liver cancer and ICD-O-3 histology codes 8170 to 8175 [27]; diagnostic confirmation (e.g., positive histology) excluding clinical diagnosis only [28]; sequence number of one primary only; diagnosis between 2000 and 2014; and not reported via autopsy or death certificate only [29]. As conducted in previous SEER-based epidemiologic studies, counts of HCC cases were stratified by age at diagnosis ($<65$ years, $\geq 65$); sex (male, female); race (white, black, Asian/Pacific Islander/American Indian/Alaska Native); and year of diagnosis (2000–2007, 2008–2014) for each county [30–32]. Each county was associated with one SEER registry.

### Exposure assessment

Ambient $PM_{2.5}$ exposure was estimated for each county in the study area using a spatial $PM_{2.5}$ exposure model. The model was created by applying inverse distance weighting (IDW) spatial interpolation to $PM_{2.5}$ concentrations ($\mu g/m^3$) in 2000 measured at 1,082 monitoring sites located across the contiguous U.S. provided by the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) database annual summary file [33, 34]. $PM_{2.5}$ data from 2000 were selected as the first year cases were diagnosed was 2000; further, few $PM_{2.5}$ monitoring data were available prior to 1999 [35]. IDW was used to create a spatial raster prediction surface of $PM_{2.5}$ exposure levels for the entire contiguous U.S., where the predicted value for $PM_{2.5}$ at any given location is the distance-weighted average of sample points (i.e., monitors) in a surrounding neighborhood [36]. The IDW neighborhood was defined using the 12 nearest monitors, resulting in an approximately $10 \times 10$ km spatial model, similar in spatial resolution to $PM_{2.5}$ exposure models used in previous studies [37, 38]. In sensitivity analyses, visual inspection of prediction surfaces created using neighborhoods including between 5 and 20 monitors yielded similar results. Monitors outside of the contiguous U.S. were excluded from IDW modeling as they exert relatively minimal influence on $PM_{2.5}$ concentrations at prediction points in

the contiguous U.S. (the closest non-contiguous U.S. monitor was 899 km in distance to the nearest contiguous U.S. boundary) [39]. Using 2000 U.S. county boundaries [40], the $PM_{2.5}$ model was aggregated to the county level in a geographic information system (GIS) (i.e., $PM_{2.5}$ raster cell centroids intersecting a county were averaged to calculate a mean county $PM_{2.5}$ value). Annual average ambient $PM_{2.5}$ values were linked with each county in the study area, using the county at diagnosis that was available for each case from SEER. In secondary analyses, ambient $PM_{2.5}$ exposure was estimated using the EPA AQS Annual Air Quality Statistics Report, which provided county-level $PM_{2.5}$ estimates in 2000 for the weighted annual mean (weighted by the calendar quarter) [41]. $PM_{2.5}$ estimates from the secondary analyses are available for a total of 687 counties (150 of the 607 counties in the study area; Supplementary Fig. 1), while $PM_{2.5}$ estimates from the primary IDW exposure metric are available for 3,109 counties (all 607 counties in the study area). All spatial analyses were conducted in ArcGIS 10.5.1 (Esri, Redlands, CA) using the contiguous U.S. Albers equal area conic coordinate system (NAD83 datum; USGS version).

## Additional covariates

The following individual- and county-level information on known and suspected HCC risk factors and variables known to be associated with the exposure were evaluated as potential confounders. From the SEER database, we acquired individual-level data on age at diagnosis, sex, race, year of diagnosis, and SEER registry. We acquired the following county-level socioeconomic and demographic information from the 2000 U.S. Census Bureau Summary Files (SFs) that were available through SEER: educational attainment (percentage with a Bachelor's degree or higher), poverty (percentage of individuals below the poverty level), percentage unemployed, median household income, and percentage foreign born (a proxy for HBV prevalence as HBV is endemic in parts of Asia and Africa [1]). We also acquired information on county-level urbanicity (a proxy for HCV prevalence as rural–urban differences in HCV have been observed [42]) using U.S. Department of Agriculture Rural–Urban Continuum Codes [43].

The following county-level data were acquired from the Institute for Health Metrics and Evaluation (IHME), created by applying small area models to data from the U.S. Behavioral Risk Factor Surveillance System and U.S. National Health and Nutrition Examination Survey: sex-specific age-adjusted prevalence of heavy alcohol consumption in 2005 (average > 1 drink per day for women or > 2 drinks per day for men in the past 30 days) [44]; diabetes in 2000 (percentage of adults aged ≥ 20 years who reported a previous diabetes diagnosis and/or have a fasting plasma glucose ≥ 126 mg/dL and/or hemoglobin A1c ≥ 6.5%) [45, 46]; physical activity in 2001 (participation during the past month in any physical activities/exercises outside of work); obesity in 2001 (body mass index [BMI] ≥ 30 kg/m$^2$) [47]; and current smoking in 2000 (currently smoking daily or nondaily cigarettes) [48].

County-level age-adjusted drug poisoning-related mortality rates, defined using ICD-10 underlying cause-of-death codes X40–X44, X60–X64, X85, or Y10–Y14, were estimated using two-stage hierarchical models applied to the U.S. National Vital Statistics System multiple cause-of-death mortality files [49, 50]. Drug poisoning mortality was considered as a proxy for HCV prevalence as a substantial proportion of drug poisoning deaths are due to injection drug use, which is the predominant route of HCV transmission in the U.S. [51]. County-level population density (population per mi$^2$), which is associated with higher traffic concentrations and thus other sources and types of air pollution, was downloaded from the 2000 U.S. Census Bureau SF1 [52, 53]. We created a variable for region of residence, which is associated with differences in $PM_{2.5}$ chemical composition, by grouping all counties into the four U.S. Census Bureau-defined regions: Northeast, Midwest, South, and West [54, 55]. Vitamin D has been shown to be associated with a reduced risk for HCC [56]. Ultraviolet (UV) radiation exposure is the primary source of vitamin D for most individuals [57, 58]. We estimated ambient UV exposure using a spatiotemporal exposure model created by applying geostatistical methods to known predictors of UV including ozone, aerosol optical depth, cloud cover, and elevation [59]. UV raster cell centroids were intersected with county boundaries and aggregated to the county level using GIS. County-level data were compiled using unique U.S. Federal Information Processing Standard (FIPS) codes.

## Statistical analysis

Poisson regression with robust variance estimation was used to calculate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the association between ambient $PM_{2.5}$ exposure and HCC risk. $PM_{2.5}$ exposure was examined continuously per 10 μg/m$^3$ increase. Restricted cubic regression splines were used to test for deviations from linearity. All models were a priori-determined to include the following variables on known and suspected HCC risk factors: age, sex, race, year, SEER registry, urbanicity, heavy alcohol consumption, smoking, obesity, diabetes, socioeconomic status (median household income, Bachelor's degree education or higher, unemployment, and poverty), foreign born, and ambient UV exposure. Population density and SEER registry (used as a more granular variable for region) were also included in the final model to account for other types of outdoor air pollution and differences in $PM_{2.5}$ constituents. We evaluated potential confounding by physical activity and

drug poisoning mortality. As adjustment for these variables did not substantially change the IRR for $PM_{2.5}$ exposure and HCC risk, they were not included in the final model. The natural logarithm of the population size, stratified by county, age (<65 years, ≥65), sex (male, female), race (white, black, Asian/Pacific Islander/American Indian/Alaska Native), and year (annual average from 2000 to 2007; annual average from 2008 to 2014) was used as the offset in all models. Population data were acquired from the National Center for Health Statistics (NCHS) Bridged-Race Resident Population Estimates 1990–2014 online database downloaded from the Centers for Disease Control and Prevention (CDC) WONDER [60].

Using stratified analyses, we explored potential effect modification by factors that may be associated with differential time spent outdoors and thus $PM_{2.5}$ exposure, or associated with disparities in HCC incidence rates: age, sex, race, urbanicity, physical activity, obesity, diabetes, heavy alcohol consumption, and median household income. We further stratified by population density and region of residence, which influence ambient levels and/or chemical constituents of $PM_{2.5}$, and by smoking, which has been associated with decreased lung deposition of $PM_{2.5}$ and competition for metabolic activation [61]. To examine potential exposure misclassification due to migration, we stratified by residential mobility using data from the SEER-provided 2000 U.S. Census Bureau SF1 on the percentage of the county population that stayed in the same house (no migration from 1995 to 2000). Movers were defined as those residing in counties in which at least 51.9% (20th percentile of all counties) of the population did not migrate. We stratified by year of diagnosis to examine the effect of a potential exposure lag. Tests for interaction were conducted by adding an interaction term to the model and using likelihood ratio tests to determine statistical significance ($p<0.05$). We performed sensitivity analyses using the secondary ambient $PM_{2.5}$ exposure measure from the EPA AQS Annual Air Quality Statistics Report; using Poisson models with a random intercept for county to determine if there was potential county-level clustering; and using scaled Poisson models applying the Pearson and deviance methods to account for overdispersion [62]. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

## Results

A total of $n=56{,}245$ HCC cases diagnosed between 2000 and 2014 were included in the analysis. HCC cases were on average 62.4 years of age at diagnosis, mostly male (77.1%), white (68.5%), and/or resided in the Western region of the U.S. (61.5%) (Table 1). Using county-level data from the underlying population from which HCC cases were sampled, HCC cases at the time of diagnosis resided in counties where annual average ambient $PM_{2.5}$ levels were 14.6 ± 3.1 μg/m$^3$ (Table 1). HCC cases resided in counties where 23.9% of the population smoked cigarettes, 25.7% were obese

**Table 1** Population characteristics of $n=56{,}245$ hepatocellular carcinoma cases in the U.S. (SEER 2000–2014)

| Characteristic | Cases *n* (%) |
|---|---|
| Individual level | |
| Age at diagnosis (years) (mean ± SD) | 62.4 ± 11.6 |
| Sex | |
| Male | 43,357 (77.1) |
| Female | 12,888 (22.9) |
| Race | |
| White | 38,546 (68.5) |
| Black | 7,737 (13.8) |
| Asian or Pacific Islander | 9,305 (16.5) |
| American Indian or Alaskan Native | 657 (1.2) |
| Region of residence at diagnosis | |
| Northeast | 7,596 (13.5) |
| South | 9,995 (17.8) |
| Midwest | 4,084 (7.3) |
| West | 34,570 (61.5) |
| Year of diagnosis | |
| 2000–2007 | 23,589 (41.9) |
| 2008–2014 | 32,656 (58.1) |
| County level | |
| $PM_{2.5}$ (μg/m$^3$) (mean ± SD)[a] | 14.6 ± 3.1 |
| UV (mW/m$^2$) (mean ± SD)[a] | 214.4 ± 36.1 |
| Percent heavy alcohol consumption (mean ± SD)[a] | 8.3 ± 2.2 |
| Percent smoking status (mean ± SD)[a] | 23.9 ± 4.8 |
| Percent physical activity (mean ± SD)[a,b] | 76.9 ± 5.8 |
| Percent obese (mean ± SD)[a,b] | 25.7 ± 4.1 |
| Percent diabetes (mean ± SD)[a] | 11.4 ± 1.7 |
| Median household income ($10,000) (mean ± SD)[a] | 47.1 ± 11.1 |
| Percent bachelor's degree or higher (mean ± SD)[a] | 26.1 ± 9.2 |
| Percent unemployed (mean ± SD)[a] | 6.5 ± 2.3 |
| Percent poverty (mean ± SD)[a] | 13.1 ± 5.3 |
| Population density (population/mi$^2$) (mean ± SD)[a] | 1,750.9 ± 2,883.5 |
| Percent foreign born (mean ± SD)[a] | 17.9 ± 12.1 |
| Urbanicity[a] | |
| Rural | 460 (0.8) |
| Urban | 55,785 (99.2) |

*HCC* hepatocellular carcinoma, *$PM_{2.5}$* particulate matter < 2.5 μm, *SD* standard deviation, *SEER* Surveillance, Epidemiology, and End Results, *UV* ultraviolet radiation

[a]County-level information was based on the county at diagnosis for cases from SEER

[b]Sex-specific physical activity and obesity prevalence rates were averaged to estimate a total prevalence

(BMI ≥ 30 kg/m$^2$), 8.3% consumed a heavy amount of alcohol (i.e., an average of more than 1 drink per day for women and more than 2 drinks per day for men in the past 30 days), and 11.4% had diabetes. HCC cases resided in densely populated counties (average 1,750.9 population/mi$^2$) that were characterized by an average median household income of $47,100, where less than 30% of the population had a Bachelor's degree education or higher, 13.1% were living below the poverty level, and 17.9% were foreign born. Figure 1 shows annual average ambient $PM_{2.5}$ exposure in 2000 categorized by quintiles calculated using all 607 counties included in the study. Annual average ambient $PM_{2.5}$ levels ranged between 5.5 and 19.8 μg/m$^3$. Higher $PM_{2.5}$ concentrations were observed in the Southern U.S. (counties in the Kentucky and Georgia registries), as well as parts of the Northeast (New Jersey) and West (California), consistent with the higher levels typically observed in these regions during the 2000s [35].

Higher ambient $PM_{2.5}$ exposure was not associated with HCC risk in basic models adjusting for age, sex, race, year, and SEER registry (IRR = 0.99 per 10 μg/m$^3$ increase, 95% CI 0.87, 1.14; $p = 0.93$) (Table 2). After additional adjustment for county-level heavy alcohol consumption, smoking, obesity, diabetes, population density, median household income, Bachelor's degree education, unemployment, poverty, foreign born, urbanicity, and ambient UV exposure, we observed a statistically significant positive association between ambient $PM_{2.5}$ exposure and HCC risk. A 10 μg/m$^3$ increase in ambient $PM_{2.5}$ exposure was associated with a 26% higher risk of HCC (adjusted IRR = 1.26, 95% CI 1.08, 1.47; $p < 0.01$) (Table 2). Model building is shown in Supplementary Table 1. The strongest confounders were population density, socioeconomic factors, and ambient UV.

We observed statistically significant interactions between ambient $PM_{2.5}$ exposure and population density ($p$ for interaction = 0.02), smoking ($p = 0.03$), and residential mobility ($p = 0.02$) (Table 2). $PM_{2.5}$ exposure was positively associated with HCC risk in areas with high population density (adjusted IRR = 1.32, 95% CI 1.11, 1.58), but was not associated with HCC risk in areas with low/medium population density. $PM_{2.5}$ exposure was positively associated with HCC risk in areas with low smoking prevalence (adjusted IRR = 1.23, 95% CI 1.01, 1.51). However, the sample size in

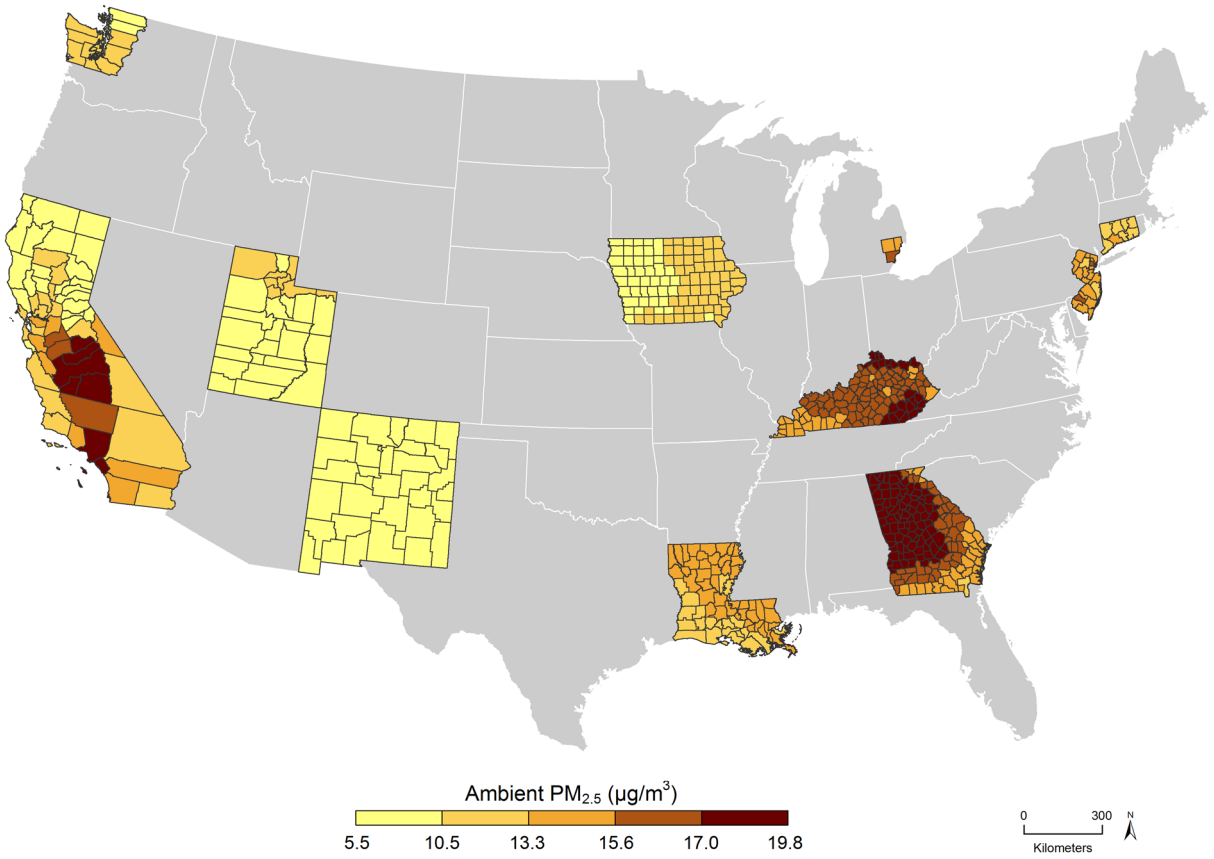


**Fig. 1** Ambient $PM_{2.5}$ exposure (μg/m$^3$) in 2000 by quintiles across 607 counties in the U.S. Higher $PM_{2.5}$ levels are shown in darker colors. The $PM_{2.5}$ quintiles were calculated using all 607 counties captured by the 16 SEER population-based cancer registries included in the study. (Color figure online)

**Table 2** Associations between ambient $PM_{2.5}$ exposure and HCC incidence (SEER 2000–2014)

| $PM_{2.5}$ exposure (per 10 μg/m$^3$ increase) | Cases (*n*) | Basic[a] IRR (95% CI) | *p* | Fully adjusted[b] IRR (95% CI) | *p* |
|---|---|---|---|---|---|
| Overall analysis | | | | | |
| $PM_{2.5}$ | 56,245 | 0.99 (0.87, 1.14) | 0.93 | 1.26 (1.08, 1.47) | < 0.01 |
| Stratified analyses | | | | | |
| Population density[c,d] | | | | | 0.02 |
| Low | 1,850 | | | 0.87 (0.60, 1.28) | |
| Medium | 4,483 | | | 0.78 (0.58, 1.03) | |
| High | 49,912 | | | 1.32 (1.11, 1.58) | |
| Smoking[c,e] | | | | | 0.03 |
| Low | 43,209 | | | 1.23 (1.01, 1.51) | |
| Medium | 7,031 | | | 0.97 (0.67, 1.40) | |
| High | 6,005 | | | 1.19 (0.73, 1.96) | |
| Residential mobility[f] | | | | | 0.02 |
| Non-mover | 31,039 | | | 1.20 (1.01, 1.43) | |
| Mover | 25,206 | | | 1.25 (0.96, 1.63) | |

*CI* confidence interval, *HCC* hepatocellular carcinoma, *IRR* incidence rate ratio, *$PM_{2.5}$* particulate matter < 2.5 μm, *SEER* Surveillance, Epidemiology, and End Results

[a]Adjusted for age at diagnosis, sex, race, year of diagnosis, and SEER registry

[b]Additionally adjusted for the following county-level variables: prevalence of heavy alcohol consumption, smoking, obesity, diabetes; population density; median household income; percentage with a Bachelor's degree or higher; percentage unemployed; percentage of individuals below the poverty level; percentage foreign born; urbanicity; ambient UV exposure

[c]We stratified by tertiles of population density and sex-specific smoking prevalence across all 607 counties included in the analysis

[d]Low population density refers to < 31.9 population/mi$^2$. Medium population density refers to 31.9–83.3 population/mi$^2$. High population density refers to > 83.3 population/mi$^2$

[e]Low smoking prevalence refers to cases residing in a county where < 22.5% of the female population or < 27.7% of the male population smoked cigarettes. Medium smoking prevalence refers to cases residing in a county where 22.5–25.7% of the female population or 27.7–31.7% of the male population smoked cigarettes. High smoking prevalence refers to cases residing in a county where > 25.7% of the female population or > 31.7% of the male population smoked cigarettes

[f]Non-movers were defined as individuals who resided in a county where ≥ 51.9% (20th percentile of all 607 counties) of the population stayed in the same home. Movers resided in a county where < 51.9% of the population stayed in the same home

areas with low/medium population density or low/medium smoking prevalence were relatively smaller than in high population density or high smoking prevalence areas. In general, the association between $PM_{2.5}$ and HCC risk was positive across all strata defined by residential mobility. The association between $PM_{2.5}$ and HCC risk did not vary by age, sex, race, urbanicity, physical activity, obesity, diabetes, heavy alcohol consumption, median household income, and region ($p > 0.05$). In sensitivity analyses among $n = 48{,}187$ HCC cases with $PM_{2.5}$ exposure information available from the EPA AQS Annual Air Quality Statistics Report, we did not observe an association between $PM_{2.5}$ exposure and HCC risk (adjusted IRR = 1.01, 95% 0.88, 1.16) (Supplementary Table 2). We observed a suggestive positive association between $PM_{2.5}$ exposure and HCC risk among cases diagnosed between 2000 and 2007 (adjusted IRR = 1.21, 95% CI 0.98, 1.48); and a statistically significant positive association among cases diagnosed between 2008 and 2014 (adjusted IRR = 1.30, 95% CI 1.13, 1.50) (Supplementary Table 3). Similar results were observed when using Poisson regression with a random intercept for county and scaled Poisson models applying either the Pearson and deviance methods (results not shown).

## Discussion

We observed a statistically significant positive association between county-level ambient $PM_{2.5}$ exposure and HCC risk in the U.S. after adjustment for individual-level age at diagnosis, sex, race, year of diagnosis, and SEER registry, and county-level information on health conditions, lifestyle, demographic, socioeconomic, and environmental factors. To the best of our knowledge, this is the first study examining the association between ambient $PM_{2.5}$ exposure and HCC risk in the U.S.

The results of this study are consistent with the growing body of literature suggesting that exposure to $PM_{2.5}$ impacts hepatocarcinogenesis. Two epidemiologic studies examining individual-level $PM_{2.5}$ exposure (based on geocoded residential addresses) and liver cancer risk have shown generally positive associations. In a prospective cohort study of 464 HCC cases in Taiwan, higher levels of $PM_{2.5}$ exposure were associated with a statistically significant increased risk of HCC in the Taiwan Penghu Islands (HR per 13.1 μg/m$^3$ increase = 1.22, 95% CI 1.02, 1.47) after adjusting for age, sex, hepatitis B surface antigen, hepatitis C antibody, alanine transaminase, alcohol consumption, and smoking [9]. In a prospective cohort study as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) project that included 279 primary liver cancer cases, higher $PM_{2.5}$ exposure was associated with a suggestive but not statistically significant positive association with liver cancer (HR per 5 μg/m$^3$ increase = 1.34, 95% CI 0.76, 2.35) after adjusting for age, sex, smoking, alcohol consumption, occupational exposure, employment status, education, and area-level socioeconomic status [10]. However, neither study considered potential confounding by diabetes, which has been associated with both $PM_{2.5}$ and liver cancer [63, 64]. The ESCAPE study also did not adjust for chronic HBV or HCV infection as potential confounders, although the authors noted that confounding by hepatitis may be unlikely as correlates of HBV and HCV were adjusted for in the models (e.g., education), and prevalence of these viruses is low in the study area. Further, there was a temporal mismatch as $PM_{2.5}$ exposure information was available from 2006 to 2009 for HCC cases diagnosed between 1991 and 2009 in Pan et al. [9], and from 2009 to 2011 for liver cancer cases diagnosed between 1985 and 2012 in Pedersen et al. [10]. The $PM_{2.5}$ exposure assessments used in these studies may not represent long-term exposure relevant to hepatocarcinogenesis, making the interpretation of findings challenging.

In this study, we observed a statistically significant positive association between ambient $PM_{2.5}$ exposure and HCC risk. These results are consistent, in direction and magnitude, with previous research showing positive or suggestively positive associations with liver cancer [9, 10]. We developed an objective measure of ambient $PM_{2.5}$ exposure, linking a spatial $PM_{2.5}$ model, created using $PM_{2.5}$ concentrations measured at EPA monitors spanning the contiguous U.S., with the SEER county at diagnosis for each HCC case. We estimated $PM_{2.5}$ exposure in 2000 as few $PM_{2.5}$ monitoring data were available prior to 1999 [35], which would have provided relatively fewer data points for spatial interpolation of $PM_{2.5}$ before 1999. In addition, 2000 was the first year cases were diagnosed in our study. HCC has been associated with latency periods of up to 20 years; thus, we were primarily interested in estimating historical exposure that may be more relevant to hepatocarcinogenesis compared to recent exposure. We assumed that the county at diagnosis represented the location where cases resided during the period relevant to the development of liver cancer (prior to diagnosis), which is supported by observing that cases in our study resided in counties in which the majority of residents did not move from 1995 to 2000. As expected, compared to cases diagnosed between 2000 and 2007, we observed a stronger positive association between $PM_{2.5}$ exposure and HCC risk among cases diagnosed between 2008 and 2014 (characterized by a potential exposure lag of between 8 and 14 years). Although results in a sensitivity analysis using a $PM_{2.5}$ exposure measure from the EPA AQS Annual Air Quality Statistics Report were null, 457 of the 607 counties in the study were missing these exposure data, resulting in excluding over 14% of HCC cases (many of whom resided in high-exposure areas), and reduced exposure variability.

In this analysis, the strongest confounders were population density, socioeconomic factors, and UV, which have been associated with liver cancer. Higher population density has been associated with increased liver cancer risk, and higher socioeconomic status and UV and vitamin D levels have been associated with decreased liver cancer risk [32, 56, 65, 66]. $PM_{2.5}$ concentrations are higher in areas with higher population density, related to sources of $PM_{2.5}$ including combustion from motor vehicles and other anthropogenic sources [12]. Higher socioeconomic status and the ability to choose whether or not to reside near highways and/or improve air quality has generally been associated with lower $PM_{2.5}$ levels [67]. UV is inversely associated with $PM_{2.5}$ as $PM_{2.5}$ particles absorb and scatter UV wavelengths, reducing surface UV levels [68].

We observed statistically significant interactions between $PM_{2.5}$ exposure and population density, smoking, and residential mobility. However, the sample size in low/medium population density areas and low/medium smoking prevalence areas is smaller compared to areas with high population density or high smoking prevalence, and the stratified estimates for residential mobility were generally similar and positive. $PM_{2.5}$ exposure was positively associated with HCC risk in areas with high population density, which have been characterized by higher traffic intensity, decreased driving speeds, and increased emissions, suggesting that densely populated areas may be associated with higher emissions per vehicle [69]. $PM_{2.5}$ exposure was positively associated with HCC risk in areas with low smoking prevalence. Although the mechanisms of action may differ between lung versus liver cancer, several studies have demonstrated stronger adverse effects of $PM_{2.5}$ on lung cancer risk among never-smokers and former smokers compared to current smokers, possibly due to competition for metabolic activation [61, 70].

Limitations of this study include lack of personal $PM_{2.5}$ exposure information and exposure misclassification

associated with using the county at diagnosis provided by SEER. We also lacked information on individual-level factors affecting $PM_{2.5}$ exposure including time spent outdoors. Further, the ecological fallacy cannot be ruled out, as the association between area-level $PM_{2.5}$ and HCC may not represent the individual-level association between $PM_{2.5}$ and HCC risk. However, we applied established spatial interpolation methods to estimate a $PM_{2.5}$ exposure model using a nationwide network of EPA monitors. Ambient $PM_{2.5}$ exposure was assessed using the same methods across all counties in the study. Further, spatially interpolated $PM_{2.5}$ prediction surfaces of similar spatial resolutions, as well as spatiotemporal exposure models created using the EPA monitors used in our study, have been predictive of cancer risk in previous epidemiologic studies [35, 71–73]. Similar positive associations for $PM_{2.5}$ and liver cancer were observed in individual-level epidemiologic studies [9, 10]. Although we did not have information on residential history and could not estimate long-term historical $PM_{2.5}$ exposure, cases lived in counties where the majority of residents stayed in the same home between 1995 and 2000, and results were similarly positive after stratifying by county-level residential mobility. Residual confounding due to lack of information on individual-level risk factors for HCC, such as alcohol consumption and chronic HCV infection, is possible. However, we were able to adjust for individual-level age, sex, race, year of diagnosis, and SEER registry, as well as county-level information on known and suspected HCC risk factors, including heavy alcohol consumption, smoking, obesity, diabetes, and socioeconomic factors. We also adjusted for urbanicity as a proxy for HCV prevalence and percentage of foreign-born individuals as a proxy for HBV prevalence in our analyses. HBV may not be a strong confounder of the association as it was not associated with $PM_{2.5}$ in previous research [9]. Although areas with a high prevalence of HCV, which is the major risk factor for liver cancer in the U.S., have coincided with areas characterized by high $PM_{2.5}$ levels, our results were adjusted for population density and socioeconomic factors, which are associated with HCV prevalence [9, 42]. We also adjusted for county-level obesity and diabetes, major risk factors for HCC in the U.S. that have exhibited rural/urban variations and associations with $PM_{2.5}$ [74, 75].

Strengths of our study include the large sample size of confirmed HCC cases from SEER population-based cancer registries covering a substantial proportion of the U.S. population. We conducted an objective location-based exposure assessment utilizing a spatial $PM_{2.5}$ model incorporating $PM_{2.5}$ concentrations measured at over 1,000 U.S. EPA AQS monitors. The study area includes counties located across the contiguous U.S. characterized by a wide range of $PM_{2.5}$ levels. We also evaluated potential confounding and effect modification using individual- and county-level information from many objective data sources including SEER and the U.S. Census Bureau.

In conclusion, results from the first prospective analysis in the U.S. suggest that higher ambient $PM_{2.5}$ exposure may be an important risk factor for HCC in this country. Future research examining this association using long-term personal $PM_{2.5}$ exposure measures and individual-level HCC risk factors is warranted to confirm these findings.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** To protect patient confidentiality, the SEER database does not include personal identifiers. This study was exempt from Institutional Review Board review. For this type of study, formal consent is not required.

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