The Association between Ambient Fine Particulate Air Pollution and Lung Cancer Incidence: Results from the AHSMOG-2 Study

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BACKGROUND: There is a positive association between ambient fine particulate matter ≤ 2.5 μm in aerodynamic diameter (PM2.5) and incidence and mortality of lung cancer (LC), but few studies have assessed the relationship between ambient PM2.5 and LC among never smokers.

OBJECTIVES: We assessed the association between PM2.5 and risk of LC using the Adventist Health and Smog Study-2 (AHSMOG-2), a cohort of health conscious nonsmokers where 81% have never smoked.

METHODS: A total of 80,285 AHSMOG-2 participants were followed for an average of 7.5 years with respect to incident LC identified through linkage with U.S. state cancer registries. Estimates of ambient air pollution levels at participants’ residences were obtained for 2000 and 2001, the years immediately prior to the start of the study.

RESULTS: A total of 250 incident LC cases occurred during 598,927 person-years of follow-up. For each 10-μg/m3 increment in PM2.5, adjusted hazard ratio (HR) with 95% confidence interval (CI) for LC incidence was 1.43 (95% CI: 1.11, 1.84) in the two-pollutant multivariable model with ozone. Among those who spent > 1 hr/day outdoors or who had lived 5 or more years at their enrollment address, the HR was 1.68 (95% CI: 1.28, 2.22) and 1.54 (95% CI: 1.17, 2.04), respectively.

CONCLUSION: Increased risk estimates of LC were observed for each 10 μg/m3 increment in ambient PM2.5 concentration. The estimate was higher among those with longer residence at enrollment address and those who spent > 1 hr/day outdoors.

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Introduction

Lung cancer (LC) is the leading cause of cancer deaths and the second leading cause of incident cancer among both men and women in the United States with 224,390 new cases and 158,080 deaths expected in 2016 (American Cancer Society 2016). Known risk factors for LC include tobacco smoke (Doll and Hill 1950; Prizment et al. 2014; Weiss 1997), asbestos (Markowitz et al. 2004) and radon (Krewski et al. 2005). According to the International Agency for Research on Cancer (IARC), there is sufficient evidence indicating outdoor air pollution as a cause of LC; the agency has classified outdoor air pollution as well as particulate matter (PM) air pollution, including diesel exhaust (DE), as Group 1 carcinogens (IARC 2013). The findings from several studies, especially the recent results from the European Study of Cohorts for Air Pollution Effects (ESCAPE) (Raaschou-Nielsen et al. 2013), form the basis for the IARC classification. A meta-analysis by Hamra et al. (2014) reported a positive association between ambient PM and LC incidence and mortality, thus supporting the IARC report. The Diesel Exhaust in Miners Study further elucidated the role of PM since DE is dominated by fine PM. A 5-fold increased estimate of LC was found among miners who had spent significant time using diesel power equipment underground compared to workers who had never worked underground (Attfield et al. 2012).

Given the high fatality rate of LC, studies on mortality and incidence have provided similar results. Studies on the association between LC mortality and ambient fine particulate matter ≤ 2.5 μm in aerodynamic diameter (PM2.5) report harmful estimates including a 14% increase in LC mortality in the American Cancer Society (ACS) study (Pope et al. 2002), a 27% increase in LC mortality among women 51–70 years old enrolled in the Oslo Cohort Study (Naess et al. 2007), and a 37% increase in LC mortality in the most versus least polluted cities reported from the Harvard Six Cities Study (Dockery et al. 1993). However, Beelen et al. (2008a) did not find any association with LC mortality in the Dutch Cohort NLCS-AIR Study.

Similarly, for LC incidence, estimates range from 6% to 29% increase with increments of 5–10 μg/m3 in PM2.5 (Beelen et al. 2008b; Hystad et al. 2013; Puett et al. 2014; Raaschou-Nielsen et al. 2013). When limiting their study population to never and past smokers, the Nurses’ Health Study reported a 37% stronger association with LC for each 10 μg/m3 increment in PM2.5 (Puett et al. 2014). A new follow-up to the European Study of Cohorts for Air Pollution
Effects (ESCAPE) analyzed data from 14 of the cohort studies within the ESCAPE study and reported that the positive association between ambient PM and LC can be attributed to various PM components and sources (Raaschou-Nielsen et al. 2016). Few studies have assessed the relationship of ozone (O₃) with LC and most have found no association (Hystad et al. 2013; Vineis et al. 2006). In contrast, in the previous and smaller AHSMOG study, we found an increased LC hazard rate (HR) of 3.56 [95% confidence interval (CI): 1.35, 9.42] for every 100 ppb increment in ambient O₃ among male study participants (Beeson et al. 1998).

Objectives

Never-smoking participants have been underrepresented in previous cohort studies. The aim of the current study was to assess the association between ambient PM₂.₅ and LC incidence in a health conscious nonsmoking, mostly never-smoking population. Because of our previous findings of an association between ambient O₃ and LC mortality (Beeson et al. 1998), we also aimed to study the independent relationship with ambient O₃ in two-pollutant models with PM₂.₅.

Methods

Study Population

The study population is the AHSMOG-2 study, a large, health conscious cohort of nonsmokers. This is a subpopulation of the Adventist Health Study-2 (AHS-2), a cohort study of about 96,000 participants from all 50 U.S. states as well as 5 provinces of Canada (Butler et al. 2008). Exclusions are shown in Figure 1, which identifies participants not linked with cancer registries (including 4,148 Canadians and 1,402 living in two U.S. states where we were not able to obtain permission to link with the state cancer registry); participants with incomplete address information, which made it impossible to estimate residence-specific air pollution concentrations (n = 677); prevalent cancers except non-melanoma skin cancer (n = 7,412); missing values on important confounders: age, sex, education levels, hours per day spent outdoors, race, and the nested smoking covariate: smoking status, years since quitting smoking, average number of cigarettes per day (n = 2,545).

The final analytic study population consisted of 80,285 participants (Figure 1). Written informed consent was obtained from all participants upon enrollment into the parent study (AHS-2) and this included subsequent analyses using de-identified data. The study was approved by the Loma Linda University Institutional Review Board (IRB) and by the IRBs of participating cancer registries, as required.

Outcome Assessment

LC cases were identified by ICD-O-3 codes C34.0-C34.9 (WHO 2013) through computer-assisted record linkage of each study participant with state cancer registries (2002–2011). Participants also completed a questionnaire that was mailed biennially regarding newly diagnosed cancers. If such self-reported cancers were not verified through the cancer registry linkage, medical records were obtained to verify such cases (Butler et al. 2008). LC subtypes assessed in this study included squamous cell carcinoma, adenocarcinoma, small cell carcinoma, unspecified carcinoma, and large cell carcinoma. LC cases with histology classification of “other specified” such as lymphoma, carcinoid, and malignant mesothelioma (n = 11) were not considered true incident LC and were censored at the time of diagnosis (Figure 1). Thus, the total number of incident LC cases in this study was 250.

Estimation of Ambient Air Pollution Concentrations

Ambient concentrations of criteria pollutants are measured over a network of hundreds of monitoring stations owned and operated mainly by state environmental agencies. As part of the AHSMOG-2 study, ambient air pollution data were obtained from the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) for the fixed time period from January 2000 through December 2001: the 2 years immediately prior to the start of the AHSMOG-2 study. Using the U.S. EPA AQS data and inverse distance weighted (IDW) interpolations methods, monthly pollution surfaces were created for PM₂.₅ and O₃ across the United States using ArcGIS (ArcMap, version 10.1; ESRI, Redlands, CA). Monthly exposure averages were based on 24-hr O₃ and daily PM₂.₅ measurements. To minimize errors, the IDW interpolation parameters were selected by assessing the goodness of fit of alternative model configurations through mean prediction error and root-mean-square error estimates. Only months with at least 75% valid data were included in the exposure estimates. The GIS-derived monthly exposure averages were used to accumulate and assign monthly concentrations of ambient O₃ and PM₂.₅ to the geocoded baseline residential address of the participants.

Study Covariates

Covariates for the model were selected a priori based on published studies and suspected relationships and included sex, race, smoking status, years since participant quit smoking, average number of cigarettes per day during all smoking years, and education level. Additional candidate covariates included calendar time, alcohol consumption, family income, body mass index (BMI), physical activity, and marital status.

In addition, three variables were identified a priori as either confounders or effect modifiers: hours per day spent outdoors, years of pre-study residence length at enrollment address, and moving distance from enrollment address during follow-up.

Statistical Analysis

Baseline characteristics of cases and noncases were compared using chi-square test for categorical and Student’s t-test for continuous variables. Cox proportional hazards regression modeling, with attained age as the time variable with left truncation by age at study entry, was used for multivariable analyses. The Cox regression was augmented by adding

| AHS-2 subjects (n=96,469) |
|-------------------------|
| n=90,919 |
| Missing air pollution data (n=677) |
| n=90,242 |
| Prevalent cancer except non-melanoma skin cancer (n=7,412) |
| n=82,830 |
| Missing important confounders (n=2,545) |
| n=80,285 |

Non-cases (n=80,035) Total LC cases (250)

Figure 1. Study flowchart for the final analytic population.
The multivariable model (Model 1) was specified based on the pollutant(s) and the \textit{a priori} selected covariates. Smoking was used as a nested covariate \cite{i.e., smoke status \times years since quit smoking} + \textit{years since quit smoking} \times current years). Pollutants were entered into the model as continuous variables and HRs were calculated for an increment of 10 μg/m³ for PM$_{2.5}$ and 10 ppb for average 24-hr O$_3$. The increment for PM$_{2.5}$ started with the lowest increment of ambient air pollution registered for this particular cohort.

The three \textit{a priori} potential effect modifiers (time spent outdoors, residence length, and moving distance) were found to modify the association between PM$_{2.5}$ and LC. However, for those spending > 1 hr/day outdoors, there was a 68% increase in the estimate for LC \cite{[HR = 1.68 (95% CI: 1.28, 2.22)] (Table 3). Similarly for those who had moved < 5 years within 10 mi (16 km) of their enrollment address, there was no association between PM$_{2.5}$ and LC. However, among those having lived > 5 years at or close to their enrollment address, the estimate for incident LC increased to 54% \cite{[HR = 1.54 (95% CI: 1.17, 2.04)]. For those who had moved > 30 km during follow-up, the estimate was somewhat higher \cite{[HR = 1.68 (95% CI: 0.94, 2.98)] compared to those who had not moved or moved < 30 km from their enrollment address \cite{[HR = 1.38 (95% CI: 1.04, 1.83)]).

### Sensitivity and Subgroup Analyses

When we excluded the very small group of current smokers (2 cases of LC among 241 current smokers), the HR remained unchanged. When we excluded 33 cases with unspecified carcinoma of the lung, the HR became slightly stronger at 1.45 (95% CI: 1.10, 1.92). Finally, when comparing never and ever smokers, the HRs associated with each 10 μg/m³ were comparable at 1.32 (95% CI: 0.90, 1.93) and 1.49 (95% CI: 1.02, 2.18), respectively.

#### Table 1. Incident lung cancers by type, during the 7.5 years of follow-up.

| Histology                  | Total | Women | Men | Women | Men |
|----------------------------|-------|-------|-----|-------|-----|
| Adenocarcinoma             | 166   | 65    | 24  | 45    | 32  |
| Squamous cell carcinoma    | 32    | 2     | 1   | 10    | 17  |
| Small cell carcinoma       | 17    | 4     | 0   | 7     | 6   |
| Large cell carcinoma       | 2     | 0     | 0   | 1     | 1   |
| Unspecified carcinoma      | 33    | 9     | 8   | 5     | 11  |
| Total                      | 250   | 79    | 72  | 68    | 67  |
Lung cancer and ambient particulate air pollution

For each 10 ppb increase in O₃ (Hystad et al. 2013), the HR = 1.06 (95% CI: 0.91, 1.25) for each 10 μg/m³ increment in PM₂.₅ (95% CI: 0.95, 1.29) to 1.29 (95% CI: 0.95, 1.76) for each 10-μg/m³ increment in PM₂.₅ and 9% increase in LC incidence was reported with a 29% [OR = 1.29 (95% CI: 0.95, 1.76)] increase for assessment of ambient air pollution, 1975–1994, and spatio-temporal models study using LC cases accrued between a Canadian cancer registry-based case–control study and this is higher than the other studies on ambient concentrations of PM₂.₅ (Hystad et al. 2013). Depending on the full meta-estimate of all studies included in the meta-analysis, and RR = 1.18 (95% CI: 1.00, 1.39) for never smokers, for each 10 μg/m³ increment in ambient concentrations of PM₂.₅ (Hamra et al. 2014). Also, in a Canadian cancer registry-based case–control study using LC cases accrued between 1975–1994, and spatio-temporal models for assessment of ambient air pollution, a 29% [OR = 1.29 (95% CI: 0.95, 1.76)] increase in LC incidence was reported with each 10-μg/m³ increment in PM₂.₅ and 9% [OR = 1.09 (95% CI: 0.85, 1.39)] increase for each 10 ppb increase in O₃ (Hystad et al. 2013). The results of the present study are in agreement with the weight of prior evidence and the recent determinations by the IARC Working Group classifying outdoor air pollution and particulate matter as carcinogenic (Group 1) (IARC 2013). Depending on the model, our HR estimates range from 1.43 (95% CI: 1.11, 1.84) to 1.68 (95% CI: 1.11, 1.84) per 10 μg/m³ increment in PM₂.₅ and this is higher than the other studies on LC incidence.

Smoking seems to modify the association of ambient air pollution with LC incidence. The Nurses’ Health Study, in a follow-up from 1994 through 2010, found a positive, but weak, association with incident LC with HR = 1.06 (95% CI: 0.91, 1.25) for each 10-μg/m³ increment in PM₂.₅. However, the HR was 1.37 (95% CI: 1.06, 1.77) and closer to our findings when limiting analyses to never smokers and those who had quit smoking ≥ 10 years ago (Puett et al. 2014).

The Netherlands Cohort Study on Diet and Cancer did not find an association between LC and ambient PM₂.₅ levels. It is unclear why the Netherlands Cohort Study on Diet and Cancer reported null findings, but it could possibly be due to the high prevalence of current and past smokers, which would be in line with the weak findings in the Nurses’ Health Study before smokers were excluded. However, the Netherlands Cohort Study on Diet and Cancer reported stronger associations between black smoke exposure estimates and incident LC among never smokers as compared to former and...
current smokers with HR = 1.47 (95% CI: 1.01, 2.16), HR = 0.91 (0.68, 1.23) and HR = 0.85 (95% CI: 0.70, 1.03), respectively (Beelen et al. 2008b). Hystad, on the other hand, found stronger associations of PM$_{2.5}$ among former [HR = 1.45 (95% CI: 0.96, 2.19)] and current smokers [HR = 1.17 (95% CI: 0.75, 1.84)] than among never smokers [HR = 0.95 (0.38–2.34)] (Hystad et al. 2013). In our study, the association between PM$_{2.5}$ and LC incidence among former and never smokers was comparable, although slightly stronger among former smokers, HR = 1.49 (95% CI: 1.02, 2.18) and HR = 1.32 (95% CI: 0.90, 1.93), respectively. The similar estimates probably reflect the fact that our past smokers had quit smoking on average 24 years ago and thus there is less residual confounding by smoking.

The present study has assessed possible effect modification of time spent outdoors on the association between ambient air pollution and incident LC. Besides the strength of studying a nonsmoking and mostly never-smoking population, our ability to include effect modification by both time spent outdoors and length of residence at enrollment address can possibly explain our stronger findings. When limiting our analyses to those who had lived within 10 mi of their enrollment address for > 5 years, our estimates increased substantially from HR = 1.43 (95% CI: 1.11, 1.84) to HR = 1.54 (95% CI: 1.17, 2.04) (Table 3). This is in line with the Nurses’ Health Study that also found that the HR increased when limiting their study population to those who had not moved between 1976 and 1994, the years immediately prior to the start of the LC follow-up from 1994 through 2007 (Puett et al. 2014). Given the long latency period for cancers, this result would be expected. Similarly, the Danish study reported an increase in HR of total LC incidence from HR = 1.18 (95% CI: 0.96, 1.46) to HR = 1.33 (95% CI: 0.98, 1.80) when excluding those who had moved during the 12.8 years follow-up (Raaschou-Nielsen et al. 2013). In our study, however, such an association was less clear, possibly due to our relatively short follow-up and the long latency time for LC.

Our study participants are health conscious, mostly nonsmokers, about 50% adhere to plant-based diets, and engage in medium to high physical activity. Nonetheless, we found similar associations of known risk factors for LC as other studies have reported. Specifically, we found that HR of incident LC decreased with increasing number of years since study participants quit smoking (Figure 3). A similar monotonic association has been reported with increments of cigarettes per day in the ACS Cancer Prevention Study II (Pope et al. 2011).

| Model | Pollutant | Cases | Single pollutant | Two pollutant$^a$ | Two pollutant$^{a,b}$ |
|-------|-----------|------|------------------|-------------------|----------------------|
| Model 1 | PM$_{2.5}$ | 250  | 1.42 (1.02, 1.98) | 1.43 (1.03, 2.00) | 1.43 (1.11, 1.84) |
| Model 1 | O$_3$ |                  | 1.07 (0.78, 1.48) | 1.07 (0.78, 1.47) |                      |
| Model 2 | PM$_{2.5}$ | 250  | 1.45 (1.04, 2.03) | 1.46 (1.05, 2.05) | 1.46 (1.13, 1.89) |
| Model 2 | O$_3$ |                  | 1.08 (0.78, 1.49) | 1.08 (0.79, 1.47) |                      |

Note: Models based on data of 80,285 AHSMOG-2 participants (LC cases: n = 250).

$^a$Model (1–5)–adjusted for O$_3$ (ozone) with increments of 10 ppb.

$^b$Model (1–5)–with Sandwich variance estimate.

Model 1–Adjusted for sex, education level, race, and nested covariates: smoking status, years since quitting smoking, and average number of cigarettes per day.

Model 2–Model 1 + outdoors, residence length, moving distance.

Model 3–Model 1 + PM$_{2.5}$ × outdoors (2 levels of outdoors: < 1 and ≥ 1 hr/day).

Model 4–Model 1 + residence + PM$_{2.5}$ × residence (2 levels of residence: < 5 and ≥ 5 years).

Model 5–Model 1 + distance + PM$_{2.5}$ × distance (2 levels of distance: ≤ 30 and > 30 km).
Biologic Mechanisms

DNA damage and cell cycle alterations are among the biological mechanisms that have been suggested to explain the association between PM$_{2.5}$ and LC (Longhin et al. 2013; Sørensen et al. 2005). Exposing human bronchial epithelial cells in vitro to PM$_{2.5}$, Longhin et al. (2013) observed increased DNA damage that resulted in severe mitotic spindle defects and elevated number of cells having micronuclei, measures that have been reported in other investigations to have a strong correlation with the risk of LC (El-Zein et al. 2008; McHugh et al. 2013). Additionally, PM$_{2.5}$ was also associated with elevated production of reactive oxygen species (Longhin et al. 2013), which previously has been reported to increase cancer risk through oxidative DNA damage, impairment of oncogene suppressor genes and induction of malignancy transformation (Waris and Ahsan 2006). Furthermore, a previous investigation reported that analyzed blood lymphocytes and 24-hr urine samples of participants exposed to PM$_{2.5}$ to assess the role of PM$_{2.5}$ in oxidative stress found that transition metals contained in PM$_{2.5}$, including vanadium and chromium, were responsible for oxidative DNA damage that were independent of other compounds in the mixture (Sørensen et al. 2005). To summarize, it appears that PM$_{2.5}$ causes cell cycle alterations and DNA damage mainly through the production of reactive oxygen species that are inhibited by the presence of antioxidants (Longhin et al. 2013).

Strengths and Limitations of the Study

There are several strengths of this study. The target population is health conscious, and the use of tobacco is very low. This nonsmoking, mostly never smoking, population boosts power to evaluate the association between ambient air pollution and incident LC in the absence of confounding by current or former smoking. Another strength is that this population living across the United States in both urban and rural communities. Because this population seems to reside in areas with relatively low concentrations of ambient PM$_{2.5}$, it provides a unique opportunity to study possible health effects of ambient PM$_{2.5}$ even at relatively low concentrations. The fact that we were able to assess the effect modification of time spent outdoors, length of residence at enrollment address, and moving history during follow-up are strengths that add to our understanding of the role of these variables when assessing the association between ambient air pollution and LC.

We did not have specific information on environmental tobacco smoke (ETS) in our data and this is a potential limitation. However, we believe the prevalence of ETS is very low in this population given the fact that most Adventists live in nonsmoking households with other Adventists. Also, there was no information on how many hours the participants spent traveling in motor vehicles to and from work that would expose them to traffic air pollution, which is known to have higher concentrations of PM$_{2.5}$ than typical residential areas (Brown et al. 2012; Knibs et al. 2010; Mirabelli et al. 2015; Weichenthal et al. 2015). Such information at the individual level could potentially modify the observed associations we have reported. Additionally, residence-specific air pollution estimates were based on air quality monitoring stations and this may result in unknown amounts of misclassification. However, such misclassification is likely to be nondifferential and would thus tend to bias results towards the null. Finally, our data lacked any information regarding the speciation and components of PM$_{2.5}$. In spite of the recent paper from the ESCAPE study (2016), it is still unclear whether the particle size per se or the chemicals coating the particles are the culprit for the observed association with LC. Further studies on the individual effects of various components of PM$_{2.5}$ are needed to better understand the association between air pollution and development of LC.

Conclusions

In summary, this study found increased estimates of incident LC associated with each 10 mg/m$^3$ increment of ambient PM$_{2.5}$ in a study population consisting mainly of never smokers who lived in areas with relatively low concentrations of ambient PM$_{2.5}$. The observed relationship was in line with, or somewhat stronger than, what has been reported by most other studies and was independent of both active smoking and ambient O$_3$ concentrations. There was no independent association between incident LC and ambient 24-hr O$_3$ concentrations. The association between ambient PM$_{2.5}$ and incident LC was comparable among ever and never smokers.

The results of the present study support the conclusions of the IARC in classifying outdoor air pollution and PM as carcinogenic. Furthermore, our findings of substantial positive associations between incident LC and PM$_{2.5}$, even at relatively low ambient concentrations, have important public health implications, especially for never and past smokers, in regards to making informed decisions on place of residence. Also, our findings could have implication for national ambient air quality standards for PM$_{2.5}$ established by the U.S. Environmental Protection Agency.

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