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Ambient PM$_{2.5}$ exposure and risk of lung cancer incidence in North America and Europe

Marya Ghazipura$^{1,2}$, Eric Garshick$^{3,4,5}$ and Kevin Cromar$^{1,2}$

1 Marron Institute of Urban Management, New York University, New York, NY, United States of America
2 New York University Langone School of Medicine, Department of Population Health, New York, NY, United States of America
3 Pulmonary, Allergy, Sleep, and Critical Care Medicine section, Medical Service, VA Boston Healthcare System, Boston, MA, United States of America
4 Channing Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital, Boston, MA, United States of America
5 Harvard Medical School, Boston, MA, United States of America

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E-mail: kevin.cromar@nyu.edu

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Abstract

Regulatory analysis in the US has not previously identified lung cancer incidence as an adverse health outcome of fine particle air pollution (PM$_{2.5}$). In an effort to provide the latest scientific knowledge in support of the pending scientific evaluation of PM$_{2.5}$ by the US Environmental Protection Agency (EPA), a systematic review and meta-analysis was conducted to examine the relationship between long-term PM$_{2.5}$ exposure and lung cancer incidence. We extracted data from four studies based on North American study populations and two studies based on European study populations in accordance with PRISMA guidelines. The results of the meta-analysis indicate a 25% increased risk of lung cancer incidence per 10 $\mu$g m$^{-3}$ increase in PM$_{2.5}$ concentrations ($RR = 1.25, 95\% CI: 1.12–1.40$), which is higher than previously published risks for lung cancer mortality. These effects were observed at concentrations relevant to current US standards. It is recommended that the EPA identifies lung cancer incidence, in addition to previous evidence for lung cancer mortality, as an adverse effect of long-term PM$_{2.5}$ exposures.

Introduction

Regulatory analysis in the United States (US) has not previously identified lung cancer incidence as an adverse health outcome of ambient air pollution. The most recent Environmental Protection Agency (EPA) integrated science assessment for particulate matter (PM), completed in 2009, notes that studies available at that time had not generally reported or even addressed associations between long-term exposure to PM and lung cancer incidence [1]. As the EPA assembles an updated science assessment for PM air pollution, it is required by the Clean Air Act that they ‘accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health…which may be expected from the presence of [criteria] pollutant[s] in the ambient air’ [2]. The latest scientific knowledge now includes North American and European studies investigating the potential impact of air pollution on lung cancer incidence, and, as such, should be evaluated and taken into consideration as part of future scientific assessments.

Lung cancer is the second most common cancer in the US after breast cancer and before prostate cancer [3]. However, it is responsible for more deaths annually than both breast and prostate cancer combined [3, 4]. In 2018, an estimated 154,050 deaths were attributed to lung cancer, making up 25.3% of all cancer deaths [4]. In addition to its high mortality rate, there were an estimated 234,030 incident cases of lung cancer in 2018, accounting for 13.5% of all new cancer cases in the US, and ranking it second to only breast cancer [4].

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Although cigarette smoking is the single biggest risk factor for the development of lung cancer, anywhere from 10%–25% of lung cancer cases develop in those who never smoked. Consequently, lung cancer in never smokers is ranked as the seventh leading cause of cancer mortality. The most recent literature on non-small cell lung cancer indicates that the overall incidence of lung cancer within this non-smoking population is increasing [5–9]. While there is some conflicting evidence on lung cancer rates in non-smokers [10–14], it is becoming increasingly important to understand the risk factors, other than smoking, that contribute to incident lung cancer [8, 15].

Prior reviews and meta-analyses assessing the link between ambient air pollution exposure and lung cancer have included studies investigating lung cancer mortality, not exclusively lung cancer incidence, and have also included studies with ambient pollution concentrations that far exceed those observed in the US [16, 17]. Also, more studies investigating the impacts of particle pollution on lung cancer incidence on lung cancer incidence have been published since the publication of these prior reviews. As a result, this is the most up-to-date review and meta-analysis that specifically evaluates the effects of ambient PM$_{2.5}$ on lung cancer incidence at concentrations relevant to the regulatory process in the US, as well as other locations with similar levels of ambient pollution.

Methods

A systematic review and meta-analysis of studies that specifically examines the relationship between long-term fine particulate matter (PM$_{2.5}$) and lung cancer incidence was conducted in order to assess whether ambient PM$_{2.5}$ air pollution at concentrations relevant to current US levels is associated with increased risk of incident lung cancer. Long-term exposures refer to exposures to occur over several months to several years, as opposed to short-term exposures which generally corresponded exposures that occur from days up to several weeks. A comprehensive literature review was conducted for all relevant sources using Pubmed, Ovid MEDLINE, Ovid EMBASE, the Centre for Reviews and Dissemination database Cumulative Index to Nursing & Allied Health Literature (CINAHL Plus), and the Wiley Cochrane Library from January 1985 to June 2017.

A separate grey literature search was conducted using Open Grey, Grey Literature Report, and Proceedings of the National Academy of Sciences. To help refine the search strategy, we referred to the systematic review on lung cancer by the World Health Organization International Agency for Research on Cancer (IARC) [17] and also used PubMed ReMiner to ensure any additional relevant search terms were captured.

Medical Subject Heading (MeSH) terms included ‘particulate matter’ OR ‘particulate air’ OR ‘air pollution’ OR ‘pm2.5’ AND ‘cancer’ OR ‘neoplasms’ with results restricted to English language only and human studies. All available studies pertaining to lifetime lung cancer incidence were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used to ensure thorough and transparent evaluation of all included literature [18].

It was determined a priori that studies would be included if: they provided quantitative estimates of exposure levels of PM$_{2.5}$; they quantitatively measured changes in lifetime lung cancer incidence risk as a result of this exposure; and their study population was in Europe, North America or other study locations with similar levels of ambient pollution concentrations (e.g., Australia, New Zealand, etc.). Examples of reasons that studies were excluded include: if they only reported on lung cancer mortality as an outcome, studies that combined and mortality results (studies that report separate effect estimates for incidence and mortality would not be excluded); and studies that based exposures on measured concentrations of PM$_{10}$ or PM$_{2.5–10}$ instead of PM$_{2.5}$. Studies were not excluded based on the choice of statistical models. For studies including overlapping cohorts with updated findings based on extended follow up, we included the most recently published results as these had the longest follow up times.

Using Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration, 2014), a meta-analysis was conducted to pool the results from all included studies pertaining to risk of lung cancer incidence for every 10 $\mu$g m$^{-3}$ increase of PM$_{2.5}$ exposure. Relative risks (RR) with corresponding 95% confidence intervals were computed using a random effects model to account for the between-study variance and a forest plot was created to graphically depict the results. Additional analysis based on smoking status was also investigated. We assessed statistical heterogeneity among studies using the chi-squared test, and we quantitatively assessed it using $I^2$, which measures the degree of inconsistency across studies in the meta-analysis. We further checked for publication bias by assessing the presence of funnel plot asymmetry via Egger’s test [19].

Risk of bias for all the included studies was assessed using the updated Cochrane Collaboration Risk of Bias Tool (RoB V.2.0) [20], which was used to evaluate the quality of the body of evidence incorporated in the meta-analysis in accordance to the Grading of Recommendations Assessment, Development and Evaluation
(GRADE) Working Group [21]. Using this tool, the result of the meta-analyses for each outcome was graded as high, moderate, low, or very low quality based on the methodology reported in the individual studies. Risk of bias, inconsistency, indirectness, imprecision, and publication bias were considered, and any limitations in these fields resulted in downgrading the quality of evidence. Presence of a dose-response relationship would result in upgrade considerations. All data extraction was conducted by one author and reviewed independently for accuracy by a second author.

Results

Figure A1 in the supplementary materials is available online at stacks.iop.org/Environ. Res. Commun. 1 (2019) 015004/1/mmedia represents the Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA) [22] flow diagram for study inclusion. Six studies met the inclusion criteria for the meta-analysis. Four of these were based in North American study populations [23–26] with two studies based in European study populations [27, 28]. The European study by Beelen and colleagues (2008) [29] was excluded, because updated results on that cohort with extended follow-up time was provided in the later published study by Hart and colleagues (2015) [28].

Summaries of the study characteristics, methods, and key findings of each of these studies are shown in table 1. The pollution levels were similar in five of the six included studies with mean concentrations of these five studies ranging from 9.5 ± 3.4 μg m⁻³ to 13.1 ± 3.7 μg m⁻³ [23–26]; the sixth study, one of the European-based study populations, had much higher pollution exposures with a mean of 28.3 ± 2.5 μg m⁻³ [28].

A forest plot of the individual studies and pooled estimate is shown in figure 1. Each of the six studies that met the inclusion criteria reported an increased risk of incident lung cancer associated with PM₂.₅, but only two of the individual studies had statistically significant results at the p < 0.05 level. The pooled result using a random effects model indicates a 25% increased risk of lung cancer incidence per 10-μg m⁻³ increase in PM₂.₅ concentrations (RR: 1.25, 95% CI: 1.12–1.40), based on moderate GRADE quality of evidence (which includes heterogeneity, risk of bias, publication bias, and other forms of quality assessment), as shown in table A1. The pooled results also indicate that when combined, the variability in these studies is negligible as they do not have significant heterogeneity (I² = 15%, p = 0.31).

Positive associations of PM₂.₅ exposure and lung cancer incidence were observed in most subgroups when stratified by smoking status, as noted above and shown in table A1. Since the studies included in the analysis did not use a uniform definition of smoking status, a different combination of studies were used to calculate each of these effect estimates. Effect modification due to smoking status is depicted in figure 2, where the effects among former smokers, whether or not grouped with never smokers or current smokers, are statistically significant at the p < 0.05 level and often found to be consistently higher than the other categories. The results from the random effects meta-analyses indicate a 52% increase in lung cancer incidence from the two studies that assessed effects in former smokers (RR: 1.52, 95% CI: 1.04–2.22), 39% from the three studies that grouped together never smokers and former smokers (RR: 1.39, 95% CI: 1.14–1.70), and 38% from the four studies that grouped together current smokers and former smokers (RR: 1.38, 95% CI: 1.19–1.61). Results from studies that separated out never and current smokers have lower RRs that were not observed to be significant at the p < 0.05 level, with a 21% increase in risk (RR: 1.21, 95% CI: 0.95, 1.56) from the five studies that assessed effects among never smokers and no difference in risk from the three studies that assessed effects among current smokers (RR: 1.00, 95% CI: 0.83, 1.19). However it is important to note that there are insufficient numbers of studies using similar definitions of smoking status to make quantitative determinations regarding whether the effects of PM₂.₅ on lung cancer incidence are quantitatively different between smoking sub-groups.

Similarly, a quantitative analysis comparing histological subtypes was not possible due to the limited data available in the included studies. However, the majority of the studies that reported on this outcome found a consistent increase in risk for adenocarcinomas as compared to other subtypes.

Discussion

Previous analysis by IARC in 2013 concluded that there is sufficient evidence that ambient PM is a risk factor for lung cancer, labeling it as a Group 1 carcinogen [30]. However, the IARC review primarily included studies that assessed lung cancer mortality, with only a small number of the studies reviewed that investigated lung cancer incidence; all of these studies were pooled together in their accompanying meta-analysis [17], thereby assuming homogeneity of outcomes.

The rationale for using lung cancer mortality as a surrogate for lung cancer incidence is partly based on the relatively low survival rates for lung cancer. The survival rate of lung cancer varies by stage and type (with a 31% survival rate for stage I lung cancer, dropping to only 2% for stage IV lung cancer) and historically the 5-year survival rate for lung cancer in the US has been 12%–14% [3, 4]. However, as survival rates and treatment
Table 1. Summary of studies used to estimate lung cancer incidence for a 10 \( \mu g \) m\(^{-3} \) change in PM\(_{2.5} \) exposure.

| Study        | No of participants (person-years) | No. of incident cases | PM\(_{2.5} \) Distribution in \( \mu g/m^3 \) Mean ± SD | RR for lung cancer incidence \( ^a \) (95% CI) | Effect estimate by smoking status \( ^b \) (95% CI) | Study design and methods | Other key findings |
|--------------|----------------------------------|----------------------|------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|----------------------|-------------------|
| North America |                                  |                      |                                                      |                                               |                                               |                      |                   |
| Hystad 2013  | 5,418 (108,360)                  | 2,154                | 11.9 ± 3.0                                          | 1.29 (0.95 to 1.76)                          | Never: OR 0.95 (0.38 to 2.34)                | Design: 20-year population-based Canadian case-control (1975–1997), where lung cancer cases were identified through provincial cancer registries. Methods: Spatiotemporal models using exposures from fixed-site air pollution monitors were used to estimate exposure. Hierarchical multivariable logistic regression model used to analyze outcomes. | • Lung cancer incidence increased significantly across increasing percentiles of PM\(_{2.5} \) exposure |
| Puett 2014   | 103,650 (1,510,027)              | 2,155                | 13.1 ± 3.0                                          | 1.06 (0.91 to 1.25)                          | Never: HR 1.25 (0.75 to 2.07)               | Design: 72-month case-control study (1998–2010) assessing long-term residential and traffic related air pollution exposures from the Nurses' Health Study cohort. Methods: Spatiotemporal exposure model based on EPA monthly averages used to assess exposure. Time-varying cox proportional hazard models used for outcomes. | • No clear pattern between exposure and lung cancer histological subtypes |
| Gharibvand 2016 | 80,285 (598,927)              | 250                  | 13.1 ± 3.7                                          | 1.43 (1.11 to 1.84)                          | Never: HR 1.32 (0.90 to 1.93)               | Design: Prospective cohort study using AHSMOG-2 cohort (2002–2011) Methods: Air pollution data from EPA monitors and inverse-distance-weighted interpolation used to assess exposure. Cox proportional hazards in single and two-pollutant models used for outcomes. | • Associations were stronger when only the common subtype, adenocarcinoma, was considered |
| Tomczak 2016 | 89,234 (446,170)                | 932                  | 9.5 ± 3.4                                           | 1.34 (1.10 to 1.65)                          | Never: HR 1.01 (0.56 to 1.80)               | Design: Prospective cohort study of women enrolled in the Canadian National Breast Screening Study between 1980 and 1985. Methods: PM\(_{2.5} \) concentrations were estimated using satellite data. Cox proportional hazards models were used to characterize associations between exposure levels and lung cancer. | • Significantly higher RR if living within 50 m of roads versus >200 m |
|              |                                  |                      |                                                      |                                               | Current: HR 1.49 (1.02 to 2.18)             |                                                    | • Majority of lung cancer cases were adenocarcinomas |

\( ^a \) RR for lung cancer incidence. \( ^b \) Effect estimate by smoking status.
| Study                  | No of participants (person-years) | No. of incident cases | PM$_{2.5}$ Distribution in $\mu$g/m$^3$ Mean ± SD | RR for lung cancer incidence$^a$ | Effect estimate by smoking status (95% CI) | Study design and methods | Other key findings                                                                 |
|------------------------|-----------------------------------|-----------------------|---------------------------------------------------|-----------------------------------|---------------------------------------------|--------------------------|------------------------------------------------------------------------------------|
| **Europe**             |                                   |                       |                                                   |                                   |                                             |                          |                                                                                     |
| Raaschou-Nielsen 2013  | (4,013,131)                       | 2,095                 | 13.4 ± 1.2                                        | 1.39 (0.91 to 2.13)               | **Never:** HR 1.46 (0.37 to 5.76)          | Design: Prospective cohort study from 17 European cohorts from ESCAPE in 9 countries (2008–2011) | • Associations were strongest for adenocarcinomas of the lung                   |
| Hart 2015              | 133,977                           | 3,355                 | 28.3 ± 2.5                                        | 1.37 (0.86 to 2.17)               | **Not Available**                          | Design: Case-cohort study using Netherlands Cohort Study (1986–2003)             | • Significant risk for lung cancer with exposure to PM$_{10}$ (HR: 1.22, 95% CI: 1.03 to 1.45 per 10 $\mu$g/m$^3$ increase) |
|                        |                                   |                       |                                                   |                                   |                                             | Methods: Exposure concentrations estimated by land-use regression models. Proportional hazards Cox regression models were fitted for each cohort and random-effects model was used to pool results. | • Elevated lung cancer risk found for all histological subtypes and for black smoke exposure |

$^a$ RRs reported by each study have been adjusted for sociodemographic covariates of gender, race, smoking status, educational level, marital status, and body mass index (BMI). Gharbivand et al. [25] also adjusted for calendar time, alcohol consumption, physical activity. Raaschou-Nielsen et al. [27] also adjusted for indicators of traffic at residence.

Abbreviations: $\mu$g m$^{-3}$, micrograms per cubic meter; AHSMOG-2, Adventist Health and Smog Study-2; CI, confidence interval; EPA, Environmental Protection Agency; ESCAPE, European Study of Cohorts for Air Pollution Effects; HR, hazard ratio; m, meter; №, population; OR, odds ratio; PM$_{2.5}$, particulate matter of aerodynamic diameter ≤ 2.5 micrometers; RR, relative risk; SD, standard deviation.
options continue to improve (from 2006–2013 survival rates increased to 18%), it becomes increasingly important to understand the risks of ambient air pollution on the development of lung cancer separately from the risk of dying from lung cancer. In other words, improvements in air quality, along with other efforts to reduce exposures to air pollution, may reduce the risks of developing new onset lung cancer differentially from reducing the risks of mortality among those with lung cancer.

A previous meta-analysis by Huang and colleagues (2017) looked to differentiate the risk of lung cancer incidence and mortality associated with outdoor air pollution, but several studies included in the current analysis were not available at the time [16]. Additionally, there are some minor differences in which studies were included. For example, while Huang and colleagues (2017) intended to focus on lung cancer incidence in their meta-analysis, a study by Weichenthal and colleagues (2016) which reports on lung cancer mortality, not lung cancer incidence, was erroneously included in their calculations [31]. Also, the current analysis only included results from the most recent update, with the longest follow-up time, if multiple studies were published based on findings within the same cohort while Huang and colleagues included two studies reporting on the same cohort, with one of them serving as an update [28] for the other [29]. While none of these are major issues, they do provide rationale for why the current analysis may be useful in providing the most up-to-date information regarding the associations of ambient PM$_{2.5}$ with increased risk of lung cancer incidence at concentrations relevant to current US policy.

Consequently, this is the first meta-analysis that specifically investigates the associations of PM$_{2.5}$ and lung cancer incidence, which is only possible due to the publication of additional studies since the time of the previous IARC analysis [17]. The result of this meta-analysis, showing increased risk of lung cancer associated with ambient PM$_{2.5}$, is directly relevant to US populations. The average PM$_{2.5}$ exposures in the studies using North American subjects are similar in magnitude to the current federal standard for annual PM$_{2.5}$.

### Figure 1
Risk for lung cancer incidence associated with a 10-μg/m$^3$ change in PM$_{2.5}$ in North American and European populations.

**Abbreviations:** μg/m$^3$, micrograms per cubic meter; CI, confidence interval; SE, standard error.

### Figure 2
Risk for lung cancer incidence associated with a 10-μg/m$^3$ change in PM$_{2.5}$, by smoking status. A different number of studies were available for each of these effect estimates due to a lack of consistent groupings based on smoking status. **Abbreviations:** μg/m$^3$, micrograms per cubic meter; CI, confidence interval; N, number; RR, relative risk. Note: Relevant demographic details and mean PM$_{2.5}$ distribution, by smoking status, are provided in the supplementary material, table A1, along with the GRADE evidence profile for each outcome.
concentrations (12.0 μg m⁻³ averaged over three years). More specifically, ambient concentrations in high pollution locations in the US, such as in Southern California, are currently greater than the average exposures in these studies and many other areas of the US have ambient PM₂.₅ concentrations that are within one standard deviation of the average exposures in these studies [32].

The primary result of this analysis, showing a 25% increased risk of lung cancer incidence per 10 μg m⁻³ increase in PM₂.₅ concentration, suggests that effects of PM₂.₅ on lung cancer incidence in these cohorts may be higher than the results of the IARC associated meta-analysis, which focused primarily on mortality as a measure of cancer risk. Using studies with populations in North America, Europe, and Asia the IARC associated meta-analysis found an overall increase in lung cancer risk of 9% (RR: 1.09, 95% CI: 1.04–1.14) for an increase of 10 μg m⁻³ of PM₂.₅ exposure. Using only studies with populations based in North America, they found an overall increase in lung cancer risk of 11% (RR: 1.11, 95% CI: 1.05–1.16) for the same change in pollution levels [17].

The primary limitation of this current meta-analysis is that only 6 studies fit the criteria and included data on lung cancer incidence in relation to PM₂.₅ exposure. However, regardless of the relatively smaller number of studies included in the analysis, there is a clear trend towards increased lung cancer incidence with exposure to PM₂.₅. Additional investigations into lung cancer incidence as it relates to exposure to air pollution is an area that requires further research attention.

The relative importance of air pollution, and other non-smoking risk factors for lung cancer incidence, would be expected to increase as the prevalence of smoking declines in the US and in some other parts of the world. This is evidenced by the continued rise in the proportion of individuals diagnosed with lung cancer who were never smokers, especially for non-small cell cancers [9]. However, risk factors such as air pollution may be most important for former smokers which may be particularly vulnerable increased risk of lung cancer incidence due to air pollution, as depicted by the higher RRs in the groupings that contained former smokers compared to the overall risk and the risk among current and never smokers.

Lastly, it is important to note that exposure to ambient PM₂.₅ air pollution is not the only risk factor for lung cancer incidence for non-smokers and former smokers. Other important risk factors for lung cancer include exposure to environmental tobacco smoke, radon exposure, diesel exhaust, and certain other occupational exposures that were not the focus of this review [33]. Clinicians, patients, as well as the relevant government agencies, will need to continue to work together to find solutions to mitigate these environmental risk factors, including reducing exposures to ambient air pollution.

Conclusion

Based on the findings of multiple studies identified through this systematic review, it is concluded that exposure to elevated levels of PM₂.₅ is associated with an increased risk of lung cancer incidence at concentrations relevant to current US standards. This finding supplements previous evidence that PM₂.₅ increases the risk of lung cancer mortality. It is recommended that the EPA identifies lung cancer incidence, in addition to the previous evidence of associations with lung cancer mortality, as an adverse effect of long-term PM₂.₅ exposures. This latest scientific evidence on lung cancer incidence should be reflected by the EPA administrator in the scientific and policy assessment for PM₂.₅ NAAQS review and other relevant rulemaking processes. Further reductions in ambient PM₂.₅ concentrations, whether through regulatory action or through other means, would likely result in fewer new cases of lung cancer in the US and other regions with similar levels of outdoor air pollution.

ORCID iDs

Marya Ghazipura © https://orcid.org/0000-0003-4328-6822
Kevin Cromar © https://orcid.org/0000-0002-7745-2780

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