Ambient particulate matter and lung cancer incidence and mortality: a meta-analysis of prospective studies

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Background: Chronic exposure to ambient particulate matter (PM) has been suggested to be associated with an increased risk of lung cancer, but the results were inconsistent. We performed a systematic review and meta-analysis of prospective studies to assess the association between exposure to PM and the incidence and mortality of lung cancer in adults. Methods: We searched PUBMED and EMBASE databases for prospective cohort studies that evaluated the association between PM\textsubscript{2.5} (diameter < 2.5\textmu m), PM\textsubscript{10} (diameter < 10\textmu m) and lung cancer incidence and mortality. Relative risks (RRs) and 95% confidence interval (CI) were calculated using fixed-effect or random-effects models when appropriate. Results: We initially identified 1987 citations, and 19 prospective cohort studies were finally included in our meta-analysis. The pooled adjusted RRs for lung cancer mortality were 1.09 (95% CI: 1.06–1.11; \textit{I}\textsuperscript{2} = 18.3%, \textit{P} = 0.26) for 10\textmu g/m\textsuperscript{3} increase in the concentration of PM\textsubscript{2.5} (12 studies), and 1.05 (95% CI: 1.03–1.07; \textit{I}\textsuperscript{2} = 41.9%, \textit{P} = 0.11) for 10\textmu g/m\textsuperscript{3} increase in the concentration of PM\textsubscript{10} (seven studies). The increased risk of lung cancer mortality associated with PM\textsubscript{2.5} and PM\textsubscript{10} was consistent across most subgroups. PM\textsubscript{10} (three studies) and PM\textsubscript{2.5} (two studies) were not found to be significantly associated with lung cancer incidence. Conclusions: Ambient PM\textsubscript{2.5} and PM\textsubscript{10} pollutions are prospectively associated with a significantly increased risk of lung cancer mortality. More studies addressing the association between PM and lung cancer incidence are required.
Introduction

For decades, lung cancer has been the most common cancer with poor prognosis around the world, with ~1.8 million new cases in 2012, accounting for 12.9% of all cancer cases. Ambient particulate matter (PM) pollution was listed as 1 of the 10 leading risk factors for the global burden of disease in 2010. With the increasing pace in economic growth, urbanization and industrialization, more people were exposed to higher concentrations of PM, which accounted for >3 million deaths worldwide, and lung cancer is one of the most important diseases associated with PM.

A number of studies have assessed the association between PM and subsequent risks of lung cancer incidence and mortality, suggesting that PM air pollution could be a risk factor for lung cancer. A previous meta-analysis that focused on ambient PM2.5 exposure pooled results from six cohort studies before 2007 and reported a positive association [relative risk (RR) = 1.21; 95% confidence interval (CI): 1.10–1.32] between PM2.5 and risk of lung cancer mortality. However, very few studies were carried out to assess the effects of PM10 and the report did not evaluate the association about lung cancer incidence and PM. The prospective analysis from the European Study of Cohorts for Air Pollution Effects, which used data from 17 cohort studies based in nine European countries, assessed the association between long-term exposure to ambient air pollution (including PM2.5 and PM10) and lung cancer incidence, but the results could not represent the global ambient air pollution. Therefore, we conducted a systematic review and a meta-analysis of prospective cohort studies to evaluate the association between PM air pollution and the risk of lung cancer.

Methods

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline.

Search strategy

Two investigators (Song and Cui) independently searched Embase and PubMed using the following two groups of key words: (i) lung cancer, lung carcinoma, lung tumour, lung tumour, lung neoplasm and lung adenocarcinoma; (ii) air pollution, PM2.5 and PM10. In the PubMed database, all keywords were searching with Medical Subject Headings (Mesh). In addition, we manually searched the bibliographic reference lists of all identified relevant publications and reviews. We included only cohort studies, and which were published in peer-review literature up to 31 October 2013. The language of the publication was limited to English.

Selection criteria

Two investigators (Song and Cui) independently assessed literature eligibility, and conflicts were adjudicated by consensus. Only data from original peer-reviewed cohort studies (i.e. not case-control studies including nested case-control studies or case-cohort studies, reviews or meeting abstracts, etc) were considered for inclusion in the systematic review. Extended inclusion criteria were used for studies, including all types of lung cancer (total, squamous cell, adenocarcinoma, small cell and large cell). We identified articles eligible for further review by performing an initial screen of identified titles or abstracts, followed by a full-text review, and the reasons of exclusion were recorded.

Data extraction

We extracted the following data for each study: study characteristics (study name, authors, publication year, study location, follow-up years and number of events and participants), participants' characteristics (mean age or range of age and source of the cohorts), main exposure PM (pollutants, mean concentration or range of concentration and increment for analysis), main outcome lung cancer (incidence or mortality and diagnostic criteria), analysis strategy (statistical models and covariates included in the models) and the risk estimates [RRs/Hazard Ratios (HRs)] and their 95% CIs, without contacting authors for further information of their original researches. Study quality was evaluated systematically by using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses.

Statistical analysis

Assuming the response function was linear, as most authors do, a standardized increment in pollutant concentration was used to pool RRs: 10 μg/m³ for PM2.5 and PM10. We calculated standardized risk estimates for each study using the following formula:

$$RR_{(standardized)} = \frac{RR_{(increment)}}{RR_{(original)}}$$

The RRs were used as the common effect measure of association across cohort studies, and HRs were considered equivalent to RRs. We produced forest plots to visually assess the RRs and corresponding 95% CI. Heterogeneity of RRs across studies was evaluated by the Cochrane Q statistic ($P < 0.10$ was considered indicative of statistically significant heterogeneity) and the I² statistic (values of 25, 50 and 75% were considered to represent low, medium and high heterogeneity, respectively). We used the fixed-effect model to pooled RRs and 95% CIs if there was no heterogeneity, otherwise, the DerSimonian and Laird random-effects model, and the weights were equal to the inverse variance of each study's effect estimation. The possibility of publication bias was evaluated using the Begg test and inspected the visual of asymmetry of a funnel plot in our meta-analysis. Moreover, subgroup and sensitivity analyses were performed to evaluate the influences of selected study and participant characteristics on study results. The analyses were performed with Stata statistical software version 11.0. P values were taken as two-sided with a significance level of <0.05.

Results

Literature search

We assessed the abstracts of 1987 citations (1193 from PubMed and 794 from Embase) and 93 potentially relevant studies underwent a further review, with 19 cohort studies included in our meta-analysis. The workflow of the search and selection process was showed in figure 1.

Among the 19 cohort studies, 912–20 were about PM2.5, 521–25 about PM10 and 5,26–29 for both. Overall, 12 and 7 studies, respectively, reported on PM2.5, PM10 and the risk of lung cancer mortality. In the investigation of the association about PM and risk of lung cancer incidence, we identified only 113 about PM2.5, 221,24 about PM10 and 17 for both.

Study characteristics

We listed characteristics of the 19 selected studies in table 1. The total number of participants included in this meta-analysis was 4,992,425, with 36,031 reported lung cancer mortality outcomes (one study did not report the number of lung cancer cases14). The studies varied in the presentation of the results: one study reported by age groups27 two studies stratified by smoking status15,17 and one study assessed in the cohort of never smokers16 three studies stratified by sex.15,22,27 Most of the studies comprised both men and women, while one study28 investigated only in males and one25 only in females. The study follow-up durations ranged from...
1 to 35 years. All studies reported overall lung cancers except for one study that reported lung adenocarcinomas and squamous-cell carcinomas. 6 With regard to study location, most of the studies were from the USA or European countries, only one study was conducted in Japan, 15 one in New Zealand, 23 two for all European, 12 Cao J and his colleagues 30 conducted a cohort study reported the crude results without adjustment. 12 Most of the results were from the USA or European countries, only one study was conducted in Japan, 15 one in New Zealand, 23 two for all European, 12 Cao J and his colleagues 30 conducted a cohort study in China, finding an increase of 10 μg/m² of PM100 corresponded to 1.1% (95%CI: −0.1%, 2.3%) increase of lung cancer mortality. However, we aimed to evaluate PM10 or PM2.5, but not PM100.

Adjusted RRs could be found for all studies, except that one study reported the crude results without adjustment. 12 Most of the results were adjusted for age, sex, pack-years of past smoking, smoking status, education and socio-economic status.

**PM and risk of lung cancer mortality and incidence**

From the 12 reports of exposure to PM2.5 and lung cancer mortality, seven studies reported a positive association, five studies reported RRs/HRs of >1.00 but these values were not statistically significant. Low heterogeneity was detected with an I² = 18.3% (Cochrane Q statistic = 74.76, P = 0.264), the pooled RR from fixed-effects model was 1.09 (95% CI: 1.06–1.11, per 10 μg/m³ increase) (figure 2a).

Association between PM10 and lung cancer mortality were available from seven studies with a pooled RR of 1.05 (95% CI: 1.03–1.07) from fixed-effect model (figure 2a). A modest heterogeneity was found with an I² = 41.9% (Cochrane Q statistic = 74.76, P = 0.111).

In the assessments of PM and the incidence of lung cancer (figure 2b), the pooled RR from random-effects model was 1.03 (95%CI: 0.48–1.58, per 10 μg/m³ increase) with moderate heterogeneity (I² = 68.7%, P = 0.074) for PM2.5 and 1.45 (95%CI: 0.87–2.03, per 10 μg/m³ increase) with modest heterogeneity (I² = 36.6%, P = 0.207) for PM10.

**Subgroup analyses**

We did additional analyses by geographical location (USA vs. non-USA), year of publication (before 2010 vs. after 2010), gender (male vs. female), smoking status (smoking vs. never smoking), events (<1000 vs. >1000; <1500 vs. >1500 (only for PM2.5)), pollutants concentration (<20 μg/m³ vs. >20 μg/m³) and duration of exposure (<5 years vs. ≥5 years). Most of the results from the subgroup analysis showed an increased risk of lung cancer mortality from PM2.5 and PM10 (Supplementary figures SE1 and SE2). Nevertheless, moderate to high heterogeneities were observed in part of the subgroups.

**Sensitivity analysis**

After omitting one study in each turn, the sensitivity analysis showed that the primary results were not affected much.

**Analysis of publication bias**

Publication bias was not noted for PM2.5 and PM10, the asymmetry was visually inspected by the funnel plot (figure 3), and the Begg test was not significant: PM2.5 (z = 0.62; P = 0.54) or PM10 (z = 1.80; P = 0.08).

**Discussion**

The results of this meta-analysis demonstrate that both PM2.5 and PM10 are prospectively associated with a significantly increased risk of lung cancer mortality. Furthermore, the association still remained statistically significant across several subgroups stratified by study and participant characteristics. However, there is no significant association with PM2.5/PM10 and lung cancer incidence. Because we

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**Table 1 Details of the cohort studies included in meta-analysis**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Nation</th>
<th>Year published</th>
<th>Follow-up period</th>
<th>Age of population</th>
<th>Pollutants</th>
<th>Number of events</th>
<th>Outcome</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beeson et al.¹⁷</td>
<td>USA</td>
<td>1998</td>
<td>1977–92</td>
<td>27–79 years</td>
<td>PM10</td>
<td>36</td>
<td>Incidence</td>
<td>9</td>
</tr>
<tr>
<td>Abbey et al.²²</td>
<td>USA</td>
<td>1999</td>
<td>1977–92</td>
<td>27–79 years</td>
<td>PM10</td>
<td>29</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>McDonnell et al.²⁶</td>
<td>USA</td>
<td>2000</td>
<td>1977–92</td>
<td>≥10 years</td>
<td>PM10, PM10</td>
<td>13 (males only)</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Boldo et al.¹²</td>
<td>Europe</td>
<td>2006</td>
<td>2002–03</td>
<td>≥20 years</td>
<td>PM2.5, PM10</td>
<td>1296</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Naess et al.²⁷</td>
<td>Norway</td>
<td>2007</td>
<td>1992–98</td>
<td>51–90 years</td>
<td>PM10</td>
<td>1453</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Beelen et al.¹³</td>
<td>Nether</td>
<td>2008</td>
<td>1986–97</td>
<td>55–69 years</td>
<td>PM2.5</td>
<td>2183</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Brunekreef et al.⁷⁹</td>
<td>Nether</td>
<td>2009</td>
<td>1986–97</td>
<td>55–69 years</td>
<td>PM2.5, PM10</td>
<td>1935</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Krewski et al.⁷⁸</td>
<td>USA</td>
<td>2009</td>
<td>1982–2000</td>
<td>≥30 years</td>
<td>PM2.5, PM10</td>
<td>N/A</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Ori Eitan, et al.²⁴</td>
<td>Israel</td>
<td>2010</td>
<td>1995–99</td>
<td>≥30 years</td>
<td>PM2.5, PM10</td>
<td>460</td>
<td>Incidence</td>
<td>9</td>
</tr>
<tr>
<td>Katanoda et al.¹⁵</td>
<td>Japan</td>
<td>2011</td>
<td>1985–95</td>
<td>≥40 years</td>
<td>PM2.5</td>
<td>421</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Turner et al.¹⁶</td>
<td>U.S.</td>
<td>2011</td>
<td>1982–2008</td>
<td>≥30 years</td>
<td>PM2.5, PM10</td>
<td>1100</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Hart et al.²⁶</td>
<td>USA</td>
<td>2011</td>
<td>1985–2000</td>
<td>42.1 years</td>
<td>PM2.5, PM10</td>
<td>800 (males only)</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Lepelis et al.¹⁷</td>
<td>USA</td>
<td>2012</td>
<td>1974–2009</td>
<td>25–74 years</td>
<td>PM2.5, PM10</td>
<td>351</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Hales et al.¹³</td>
<td>New Zealand</td>
<td>2012</td>
<td>1996–99</td>
<td>30–74 years</td>
<td>PM2.5, PM10</td>
<td>1686</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Cesaroni et al.⁸⁰</td>
<td>Italy</td>
<td>2013</td>
<td>2001–10</td>
<td>≥30 years</td>
<td>PM2.5</td>
<td>12208</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Heinrich et al.⁵²</td>
<td>Germany</td>
<td>2013</td>
<td>1990-2008</td>
<td>50–59 years</td>
<td>PM2.5, PM10</td>
<td>41 (females only)</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Carey et al.²⁹</td>
<td>UK</td>
<td>2013</td>
<td>2003–07</td>
<td>40–89 years</td>
<td>PM2.5, PM10</td>
<td>5244</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Jarrett et al.²⁰</td>
<td>USA</td>
<td>2013</td>
<td>1982–2000</td>
<td>≥30 years</td>
<td>PM2.5, PM10</td>
<td>1481</td>
<td>Mortality</td>
<td>9</td>
</tr>
<tr>
<td>Raaschou-Nielsen et al.⁶</td>
<td>European</td>
<td>2013</td>
<td>Mean of 12.8 years</td>
<td>44–73 years</td>
<td>PM2.5, PM10</td>
<td>2095</td>
<td>Incidence</td>
<td>9</td>
</tr>
</tbody>
</table>
identified only two studies for PM$_{2.5}$ and three for PM$_{10}$, the RR for the association between PM$_{10}$ and lung cancer incidence is 1.45, higher than the RR for PM and lung cancer mortality, but not statistically significant as the number of studies was only three. Researches about evaluation of ambient PM pollution and risk of lung cancer incidence are badly needed in the future.

Dealing with multiple publications, our meta-analysis used data from the studies with recently published, longer follow-up time and largest samples: (i) Beelen et al.$^{31}$ published the results about PM$_{2.5}$ initially in 2008, these data were later published in 2009, we have therefore used data published in 2009. (ii) Dockery et al.$^{32}$, Laden et al.$^{33}$, and Lepeule et al.$^{17}$ used the same cohort Harvard six cities, as the follow-up time was 1974–91, 1974–98 and 1974–2009, respectively, we extracted data from Lepeule et al.$^{17}$ (iii) Pope et al.$^{34,35}$ and Krewski et al.$^{14}$ collected data from American Cancer Society nationwide, the follow-up time was 1982–89, 1982–98 and 1982–2000, respectively, we included the last one.$^{14}$ Although Jerrett et al.$^{36}$ reported the results from the same period 1982–2000, the participants were only from Los Angeles, not from nationwide, and were excluded in the end.

Comparing with previous meta-analysis published in 2008,$^5$ our results were consistent with previous results (RR = 1.21; 95% CI: 1.10–1.32) and have lower heterogeneity. However, previous study found only two studies about lung cancer mortality and PM$_{10}$, and did not analyse this association. A global assessment that did not meet the inclusion criteria for the meta-analysis also found a positive association between PM$_{2.5}$ and lung cancer mortality, from which the investigators reported that global fraction of adult mortality attributable to the anthropogenic component of PM$_{2.5}$ was 12.8% (5.9–18.5) for lung cancer.$^{37}$

The biological mechanisms underlying the association between PM and lung cancer have not yet been fully elucidated. PM represents a complex mixture of organic and inorganic chemicals, such as heavy and transition metals, polycyclic aromatic hydrocarbons and other genotoxic chemicals. The composition and size of these particles determine the potential of deposition in the

Figure 2 Association between PM and lung cancer (a) mortality and (b) incidence
In conclusion, this meta-analysis provides strong evidence that PM (PM$_{2.5}$ and PM$_{10}$) is a significant risk factor for lung cancer mortality. Given the large number of people exposed to particulate air pollution and high mortality rate of lung cancer in the general population, more high-quality scientific research and worldwide scientific network are needed to explore the underlying mechanisms and elucidate the causal pathways that link particulate air pollution and lung cancer.

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**Conflicts of interest:** None declared.

**Key points**

- We included 19 cohort studies for PM and lung cancer incidence and mortality.
- PM$_{2.5}$ and PM$_{10}$ are associated with increased risk of lung cancer mortality.
- More studies are needed to explore the mechanisms that link PM and lung cancer.
- More high-quality scientific research and worldwide scientific network are needed to explore the underlying mechanisms and elucidate the causal pathways that link particulate air pollution and lung cancer.

**References**
