Brief Original Contribution

Interactions Between Cigarette Smoking and Fine Particulate Matter in the Risk of Lung Cancer Mortality in Cancer Prevention Study II


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The International Agency for Research on Cancer recently classified outdoor air pollution and airborne particulate matter as carcinogenic to humans. However, there are gaps in the epidemiologic literature, including assessment of possible joint effects of cigarette smoking and fine particulate matter (particulate matter less than or equal to 2.5 µm in diameter) on lung cancer risk. We present estimates of interaction on the additive scale between these risk factors from Cancer Prevention Study II, a large prospective US cohort study of nearly 1.2 million participants recruited in 1982. Estimates of the relative excess risk of lung cancer mortality due to interaction, the attributable proportion due to interaction, and the synergy index were 2.19 (95% confidence interval (CI): −0.10, 4.83), 0.14 (95% CI: 0.00, 0.25), and 1.17 (95% CI: 1.00, 1.37), respectively, using the 25th and 75th percentiles as cutpoints for fine particulate matter. This suggests small increases in lung cancer risk among persons with both exposures beyond what would be expected from the sum of the effects of the individual exposures alone. Although reductions in cigarette smoking will achieve the greatest impact on lung cancer rates, these results suggest that attempted reductions in lung cancer risk through both tobacco control and air quality management may exceed expectations based on reducing exposure to either risk factor alone.

additive interaction; air pollution; cigarette smoking; lung cancer mortality; particulate matter

Abbreviations: AP, attributable proportion due to interaction; BME, Bayesian maximum entropy; CI, confidence interval; CPS-II, Cancer Prevention Study II; LUR, land use regression; PM2.5, particulate matter less than or equal to 2.5 µm in diameter; RERI, relative excess risk due to interaction; RR, relative risk; S, synergy index.

Editor’s note: An invited commentary on this article appears on page 1150.

Increasing evidence links long-term exposure to ambient particulate matter with an aerodynamic diameter less than or equal to 2.5 µm (PM2.5), also called fine particulate matter, to elevated risk of lung cancer (1). Pope et al. (2) reported that each 10-µg/m³ increase in average PM2.5 concentration (1979–1983) was associated with an 8% (95% confidence interval (CI): 1, 16) increase in the risk of lung cancer mortality in the American Cancer Society’s Cancer Prevention Study II (CPS-II). Krewski et al. (3) reported similar results using an extended 18-year follow-up period (an 8% increase in risk per 10-µg/m³ increase in PM2.5 (95% CI: 3, 14)). Results from other recent studies also support a PM2.5-lung cancer association (4, 5). Based on current observational and mechanistic evidence, the International Agency for Research on Cancer (Lyon, France) recently classified both outdoor air pollution and airborne particulate matter as carcinogenic to humans (Group 1) (6).

This conclusion notwithstanding, there remain important gaps in the epidemiologic literature on the role of air pollution in lung cancer risk, including the assessment of possible joint effects of cigarette smoking and PM2.5 exposure on lung cancer risk. Such information is useful from a public health perspective to better understand the total burden of disease associated with these highly prevalent lung cancer risk factors.
factors and the impact of interventions designed to reduce exposure to either risk factor. Although some earlier studies suggested that the joint effects of smoking and air pollution may be greater than additive, to our knowledge no major cohort study has provided estimates of interaction between smoking and air pollution on the additive scale, which is most relevant for population health risk assessment (7, 8).

In this analysis, we examined interactions on the additive scale between 2 major lung cancer risk factors, cigarette smoking and PM\textsubscript{2.5}, exposure, in CPS-II. This large-scale cohort study has been instrumental in increasing understanding of the main effects of both risk factors and afforded us a unique opportunity to examine their possible interaction.

METHODS

Study population

CPS-II is a prospective cohort study of nearly 1.2 million participants enrolled by over 77,000 volunteers in 1982. Ethics approval for CPS-II was obtained from the Emory University School of Medicine (Atlanta, Georgia) Human Investigations Committee. Participants were recruited in all 50 US states as well as the District of Columbia and Puerto Rico. Participants were largely friends and family members of the volunteers. For inclusion in CPS-II, participants had to be at least 30 years of age and have at least 1 family member aged 45 years or older. A 4-page self-administered questionnaire completed at the time of enrollment collected data on a range of demographic, lifestyle, medical, and other factors, including place of residence.

Follow-up for vital status has been conducted every 2 years. In 1984, 1986, and 1988, information on vital status was obtained from the study volunteers, and deaths were confirmed by obtaining death certificates. Since 1989, computerized linkage to the National Death Index has been used for follow-up (9). For the present analysis, however, follow-up was truncated at the first 6 years in order to classify participants by cigarette smoking status, because updated information on cigarette smoking status was not collected after enrollment (10). Over 99% of all known deaths have been assigned an underlying cause. Lung cancer deaths were classified according to the underlying cause of death using the International Classification of Diseases, Ninth Revision (11), coding system (code 162).

Of the 1,184,588 CPS-II participants, we excluded persons with invalid address information (n = 385,422) and persons with missing data on vital status or other individual-level covariates of interest (n = 130,119), as well as former cigarette smokers (n = 172,690) and persons who had ever smoked a pipe or cigars (n = 66,951). A total of 429,406 participants were retained for analysis. A total of 1,921 lung cancer deaths were observed in 2,509,717 person-years of follow-up.

Exposure to PM\textsubscript{2.5}

Estimated ambient PM\textsubscript{2.5} concentrations were linked to the geocoded home addresses of CPS-II participants at enrollment in 1982 using a national-level hybrid land use regression (LUR) and Bayesian maximum entropy (BME) interpolation model (12). Monthly PM\textsubscript{2.5} data were available from 1999 to 2008 for a total of 1,464 monitoring locations. In the first stage, a LUR model using a deletion/substitution/addition algorithm predicted PM\textsubscript{2.5} concentrations based on 2 variables: vehicular traffic at 1,000 m (based on modeled traffic counts) and green space at 100 m cubed. In the second stage, a BME interpolation model was used to capture residual spatiotemporal variation in PM\textsubscript{2.5} concentrations that was not characterized by the LUR model in the first stage. Cross-validation indicated an R\textsuperscript{2} value of 0.79. Monthly values from 1999 to 2004 were averaged and assigned to study participants. Estimated PM\textsubscript{2.5} exposure concentrations ranged from 1.38 µg/m\textsuperscript{3} to 27.94 µg/m\textsuperscript{3}, with a mean of 12.61 (standard deviation, 2.85) µg/m\textsuperscript{3}.

Statistical analysis

Cox proportional hazards regression models were used to obtain adjusted hazard ratios and 95% confidence intervals for associations with lung cancer mortality. The proportional hazards models were stratified by age (1-year categories), sex, and race (white, black, or other). Follow-up time since enrollment (1982) was used as the time axis. Survival times of persons who were still alive at the end of follow-up were censored. Dichotomous indicators for cigarette smoking (current smoker at enrollment vs. never smoker at enrollment) and PM\textsubscript{2.5} exposure (>50th percentile (>12.56 µg/m\textsuperscript{3}) vs. ≤50th percentile (≤12.56 µg/m\textsuperscript{3}); >66th percentile (>13.81 µg/m\textsuperscript{3}) vs. ≤33rd percentile (≤11.24 µg/m\textsuperscript{3}); and >75th percentile (>14.44 µg/m\textsuperscript{3}) vs. ≤25th percentile (≤10.59 µg/m\textsuperscript{3})) were assessed.

Estimated hazard ratios and 95% confidence intervals were adjusted for the following individual-level risk factors: education; marital status; body mass index (weight (kg)/height (m)\textsuperscript{2}); body mass index squared; secondhand smoke exposure (“passive smoking”; hours/day); quintiles of vegetable, fruit, fiber, and fat intake; alcohol consumption (beer, wine, and liquor); occupational exposures (asbestos, chemicals/ solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, and diesel engine exhaust); and a previously developed “occupational dirtiness index” (13).

On the additive scale, effect modification was assessed according to the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S). The REPI is defined as relative risk (RR)\textsubscript{11}− RR\textsubscript{10}− RR\textsubscript{01}+ 1, the AP as REPI/RR\textsubscript{11}, and the S as (RR\textsubscript{11}− 1)/(RR\textsubscript{10}+RR\textsubscript{01}− 2). These variables were calculated according to the “MOVER” method for the analysis of 4 × 2 tables with associated 95% confidence intervals (14). REPI and AP values of 0 and S values of 1 indicate no interaction. On the multiplicative scale, interaction terms for interaction between cigarette smoking and PM\textsubscript{2.5} concentrations were entered into the proportional hazards regression models. Two-sided P values were calculated to assess the significance of the interaction term using the likelihood ratio statistic. All statistical tests were 2-sided. Analyses were conducted using SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina) (15). Ethics approval for the statistical analysis was obtained from the Ottawa Hospital (Ottawa, Ontario, Canada) Research Ethics Board.

RESULTS

The majority of participants were 40–69 years of age at enrollment, were female, and had attained a level of education
Examining interactions among environmental exposures, even 2 well-characterized carcinogens assessed in a large study, we examined the interaction between cigarette smoking and PM$_{2.5}$ for lung cancer mortality on the additive scale in CPS-II. This scale is generally considered to be most appropriate for purposes of population health risk assessment (8). Small increases in risk among persons with both exposures were observed beyond what would be expected from the sum of the individual exposures alone. Estimates of the RERI, AP, and S also generally increased when using the 25th and 75th percentiles as cutpoints for PM$_{2.5}$ in men (RERI = 4.64, 95% CI: −2.18, 14.75; AP = 0.17, 95% CI: 0.00, 0.31; S = 1.22, 95% CI: 1.00, 1.48), participants reporting less than 3 hours of daily exposure to secondhand tobacco smoke (RERI = 3.09, 95% CI: −0.50, 7.24; AP = 0.18, 95% CI: −0.03, 0.35, S = 1.24, 95% CI: 0.97, 1.58), and heavy (≥20 pack-years) cigarette smokers (RERI = 2.68, 95% CI: −0.17, 6.02; AP = 0.14, 95% CI: 0.00, 0.26; S = 1.17, 95% CI: 1.00, 1.37).

On the multiplicative scale, estimates of interaction ranged from 0.81 (95% CI: 0.59, 1.10) to 0.93 (95% CI: 0.65, 1.33), indicating a joint effect somewhat smaller than the product of the individual exposures, but these estimates were imprecise (Table 2; Web Table 1). Similar results were obtained when adjusting for mean county-level residential radon concentrations or 1980 sociodemographic ecological covariates (16, 17).

**DISCUSSION**

Greater than high school (Table 1). Lung cancer mortality rates varied according to cigarette smoking status and PM$_{2.5}$ exposure (Appendix Table 1). The difference in lung cancer mortality between never cigarette smokers and current cigarette smokers was greater with higher PM$_{2.5}$ concentrations.

Hazard ratios for current cigarette smokers as compared with never smokers ranged from 13.53 (95% CI: 10.21, 17.93) to 14.48 (95% CI: 11.31, 18.52) among subjects exposed to low PM$_{2.5}$ concentrations (Table 2; also see Web Table 1, available at http://aje.oxfordjournals.org/). Hazard ratios for current cigarette smokers exposed to high levels of PM$_{2.5}$, when compared with never smokers exposed to low levels of PM$_{2.5}$, ranged from 15.00 (95% CI: 12.34, 18.25) to 16.48 (95% CI: 12.91, 21.05).

Estimates of the RERI ranged from 0.66 (95% CI: −0.92, 2.20) to 2.19 (95% CI: −0.10, 4.83) (Table 2, Web Table 1), depending on the categorical indicator of cigarette smoking and PM$_{2.5}$ concentration, indicating small increases in risk among persons with both exposures compared with that expected based on the sum of the individual exposures alone. The AP ranged from 0.04 (95% CI: −0.06, 0.13) to 0.14 (95% CI: 0.00, 0.25), and S ranged from 1.05 (95% CI: 0.94, 1.17) to 1.17 (95% CI: 1.00, 1.37).

In sensitivity analyses, the RERI, AP, and S also generally increased when using the 25th and 75th percentiles as cutpoints for PM$_{2.5}$ in men (RERI = 4.64, 95% CI: −2.18, 14.75; AP = 0.17, 95% CI: 0.00, 0.31; S = 1.22, 95% CI: 1.00, 1.48), participants reporting less than 3 hours of daily exposure to secondhand tobacco smoke (RERI = 3.09, 95% CI: −0.50, 7.24; AP = 0.18, 95% CI: −0.03, 0.35, S = 1.24, 95% CI: 0.97, 1.58), and heavy (≥20 pack-years) cigarette smokers (RERI = 2.68, 95% CI: −0.17, 6.02; AP = 0.14, 95% CI: 0.00, 0.26; S = 1.17, 95% CI: 1.00, 1.37).

On the multiplicative scale, estimates of interaction ranged from 0.81 (95% CI: 0.59, 1.10) to 0.93 (95% CI: 0.65, 1.33), indicating a joint effect somewhat smaller than the product of the individual exposures, but these estimates were imprecise (Table 2; Web Table 1). Similar results were obtained when adjusting for mean county-level residential radon concentrations or 1980 sociodemographic ecological covariates (16, 17).

**DISCUSSION**

In this study, we examined the interaction between cigarette smoking and PM$_{2.5}$ for lung cancer mortality on the additive scale in CPS-II. This scale is generally considered to be most appropriate for purposes of population health risk assessment (8). Small increases in risk among persons with both exposures were observed beyond what would be expected from the sum of the individual exposures alone. Estimates of the RERI, AP, and S were 2.19 (95% CI: −0.10, 4.83), 0.14 (95% CI: 0.00, 0.25), and 1.17 (95% CI: 1.00, 1.37), respectively, using cutpoints of the 25th and 75th percentiles for PM$_{2.5}$. Results suggest a combined effect for lung cancer mortality among cigarette smokers with high PM$_{2.5}$ exposure 2.2 times greater than expected based on the addition of results for cigarette smoking and PM$_{2.5}$ alone. Results also suggest that approximately 14% of lung cancer mortality among cigarette smokers with high PM$_{2.5}$ exposure may be due to interaction of the 2 factors. Previous studies indicated some evidence for departures from additivity (7). On the multiplicative scale, a joint effect somewhat smaller than the product of the individual exposures was observed, but results were imprecise.
We explored various PM2.5 cutpoints for assessing pollution is significantly lower than that from cigarette smoking (20). PM2.5 dose from ambient air pollution is significantly lower than that from cigarette smoking (10). Lung cancer risk is a function of the various carcinogenic substances transported on the particles (21), which may exhibit differential levels of toxicity (22). Results may also be due to chance, differences in timing of exposure, or differences in exposure levels.

In sum, although reductions in cigarette smoking will achieve the greatest impact on lung cancer rates, these results do not rule out the possibility that reductions in lung cancer burden by means of both tobacco control and air quality management may actually be greater than current estimates of the effect of reducing exposure to either risk factor alone. Results are also important for estimates of the global burden of disease, which currently assume independence of PM2.5-related excess mortality across categories of cigarette smoking status (23).

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**Table 2.** Adjusted Hazard Ratiosa for Lung Cancer Mortality in Relation to Categorical Indicators of Cigarette Smoking and PM2.5 Concentration and Measures of Additiveb and Multiplicativec Interaction, Cancer Prevention Study II, 1982–1988

| Level of PM2.5 Exposure | Smoking Status | Never Smoker | | | Current Smoker | | | Smoking in Strata of PM2.5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Category | Mean (SD), µg/m³ | No. of Deaths | No. of Subjects | HR | 95% CI | No. of Deaths | No. of Subjects | HR | 95% CI | No. of Subjects | HR | 95% CI |
| Low (<25th percentile) | | | | | | | | | | | | |
| High (>75th percentile) | | | | | | | | | | | | |
| PM2.5 in strata of smoking | | | | | | | | | | | | |

Abbreviations: AP, attributable proportion due to interaction; CI, confidence interval; HR, hazard ratio; PM2.5, particulate matter less than or equal to 2.5 µm in diameter; RERI, relative excess risk due to interaction; S, synergy index; SD, standard deviation.

a Adjusted for education; marital status; body mass index (weight (kg)/height (m)²); body mass index squared; secondhand smoke exposure (hours/day); quintiles of vegetable, fruit, fiber, and fat intake; alcohol consumption (beer, wine, and liquor); occupational exposures (asbestos, chemicals/ acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, and diesel engine exhaust); and “occupational dirtiness index” (13).

b RERI = 2.19 (95% CI: −0.10, 4.83); AP = 0.14 (95% CI: 0.00, 0.25); S = 1.17 (95% CI: 1.00, 1.37).

c HR = 0.93 (95% CI: 0.65, 1.33).
A.C. is employed by the Health Effects Institute (Boston, Massachusetts). The views expressed in this article do not necessarily represent those of the Health Effects Institute or its sponsors.

Conflict of interest: none declared.

REFERENCES


Appendix Table 1. Lung Cancer Mortality Rates in Relation to Categories of PM2.5 Concentration and Cigarette Smoking Status, Cancer Prevention Study II, 1982–1988

<table>
<thead>
<tr>
<th>Level of PM2.5 Exposure and Smoking Status</th>
<th>No. of Deaths</th>
<th>Person-Years of Follow-up</th>
<th>Mortality per 100,000 Person-Years*</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;25th percentile)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>63</td>
<td>446,447.22</td>
<td>13.39</td>
<td>216.69</td>
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<tr>
<td>Current smoker</td>
<td>346</td>
<td>182,952.46</td>
<td>230.08</td>
<td></td>
</tr>
<tr>
<td>High (&gt;75th percentile)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>81</td>
<td>430,478.22</td>
<td>17.31</td>
<td>271.78</td>
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<tr>
<td>Current smoker</td>
<td>447</td>
<td>195,614.78</td>
<td>289.09</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PM2.5, particulate matter less than or equal to 2.5 µm in diameter.

* Age-standardized.