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## Invited Commentary

# Invited Commentary: Epidemiologic Studies of the Impact of Air Pollution on Lung Cancer

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In this issue of the *Journal*, Villeneuve et al. (*Am J Epidemiol*. 2014;179(4):443–451) present epidemiologic evidence supporting the literature on the adverse effects of air pollution on risk of lung cancer. They found that ambient exposure to volatile organic compounds, especially when measured at longer time scales, was associated with increased odds of lung cancer in citizens of Toronto, Ontario, Canada, between 1997 and 2002. Specifically, in fully adjusted models, they observed that an interquartile-range increase in benzene concentration was associated with an odds ratio of 1.51 (95% confidence interval: 1.13, 2.01) using exposure at the time of interview. The odds ratio increased to 1.84 (95% confidence interval: 1.26, 2.68) when time-weighted exposure at all previous addresses was considered. They obtained similar results for exposure to nitrogen dioxide. These findings add weight to the substantial (and rapidly growing) body of literature on the relation of air pollution with lung cancer risk, as well as illustrate important aspects of the effects of different exposure assessment choices and potential sources of key interest.

air pollution; lung cancer; nitrogen dioxide; volatile organic compounds

Abbreviations: CI, confidence interval; ESCAPE, European Study of Cohorts for Air Pollution Effects; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter.

The earliest reference to the keywords "air pollution" and "lung cancer" in the PubMed database is a commentary entitled "Air Pollution and Lung Cancer" (1) that was published in the *British Medical Journal* in 1952. The commentary reviews a number of British studies published in the first half of 1952 (only months before the infamous London Fog event (2)). In addition to detailing the results of a number of studies of occupational exposure to various compounds and lung cancer, the commentary mainly focuses on a study that examined standardized mortality rates for all county boroughs in England (3). The major finding was that the standardized mortality rates for lung cancer tracked highly with the number of dwellings (as a proxy for number of chimneys) and the prevailing winds. The commentary's author speculated that this made a compelling case that chimney smoke may be associated with an increased risk of lung cancer mortality, as the increased rates could not be fully explained by differences in smoking across areas (1). The author concluded that although it was likely that chimney smoke was an important source of risk, car exhaust fumes needed to be considered as well, and it was important for future studies to examine the joint impacts of these environmental sources and active cigarette smoking (1).

In the intervening 61 years, over 1,000 manuscripts have been published on the topic of air pollution and lung cancer. The rate of publication increased dramatically in the last year, probably in anticipation of the new International Agency for Research on Cancer monograph on air pollution and cancer being prepared this fall. However, to date, few if any studies have fully addressed all of the concerns raised in the *British Medical Journal* commentary.

In this issue of the *Journal*, Villeneuve et al. (4) present findings from a Canadian case-control study on the associations of ambient exposure to volatile organic compounds (namely benzene and total hydrocarbons) and nitrogen dioxide with lung cancer mortality. Cases were enrolled from 4 tertiary-care hospitals in Toronto, Ontario, Canada, between 1997 and 2002. Because the risk among never smokers was

of particular interest, the case set was assembled with oversampling of never smokers. A total of 716 eligible cases were identified for the study; however, because of deaths and refusals, only 445 provided information. Two sets of controls were assembled for the study. The first, to allow for genetic comparisons in other work, was assembled from a family medicine practice within one of the hospitals where cases were recruited and included 523 controls. The second, intended to be of more use for environmental analyses, was assembled from property tax assessment files and included 425 controls. The rates of participation of the cases and population-based controls were similar (62% and 59%, respectively), while the participation rate among clinic-based controls was higher (85%). Questionnaires were administered to all cases and controls to collect information on a variety of potential confounders, as well as residential history. Exposures were predicted at the participant's address at the time of study enrollment, at the participant's address 10 years prior to enrollment, and at all addresses up to the time of enrollment. Exposures for the study were predicted on the basis of land-use regressions described elsewhere, but they were based on extensive monitoring campaigns in the city of Toronto, and therefore were spatially varying but time-invariant and could not be estimated for addresses outside of Toronto (5–8). Overall, results were stronger in analyses restricted to the population-based controls and in models using time-weighted exposures averaged over the participant's full residential history. In models adjusted for personal characteristics and neighborhood-level socioeconomic status, interquartile-range increases in nitrogen dioxide, benzene, and total hydrocarbon levels were associated with odds ratios of 1.59 (95% confidence interval (CI): 1.19, 2.12), 1.84 (95% CI: 1.26, 2.68), and 1.43 (95% CI: 1.08, 1.89), respectively.

The Villeneuve et al. study (4) adds 2 important pieces to the literature on this topic. First, in addition to a commonly examined pollutant, nitrogen dioxide, Villeneuve et al. examined volatile organic hydrocarbons, which are more closely tied to sources such as traffic and industry and are more likely to be etiologically relevant pollutants. Their findings of stronger results for benzene than for nitrogen dioxide or total hydrocarbons were probably due to reductions in exposure misclassification. Second, they estimated the levels of each exposure at 3 different time points, allowing for some important insights into the etiologically relevant windows in which air pollution may affect the risk of lung cancer. Future studies on this topic should attempt to address these 2 exposure assessment issues more directly, especially given their clear impact on the associations observed.

As in all investigations, there are some issues that Villeneuve et al. were unable to address. The assessments of exposure in the various time periods were all based on land-use regressions from monitoring campaigns conducted after the last participant was enrolled in the study. Therefore, there is no way to know whether there were substantial changes in the spatial patterns of exposure even between the time periods during which the participants were enrolled, and definitely not for exposures predicted 10 years earlier or over the full residential history of participants (who were in their 50s and 60s at enrollment). For nitrogen dioxide, the authors were able to validate the predictions using historical monitoring information from 1982–2002, and they argue that the high correlations indicate that the major variability in nitrogen dioxide over time in Toronto was probably due to spatial, not temporal, variability. In the absence of spatially and temporally varying predictions, this is an essential check for most exposure predictions, although the information needed is often not available historically.

Another issue that this and many other studies have not been able to address is the association between air pollution and the various histological subtypes of lung cancer. In the literature on active and passive smoking, there is clear heterogeneity in risk of the various histological subtypes with exposure (9), and it is likely that this is also the case for the impacts of air pollution. It may also be the case that different mixes of pollutants from different sources have varying associations with each subtype. However, to date, only a few studies have had sufficient numbers of cases to examine subtype-specific associations. In another Canadian case-control study (covering the full country), Hystad et al. (10) examined the associations of air pollution (specifically particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide, and ozone) with the overall odds of lung cancer, as well as odds for specific histological subtypes. For lung cancer incidence, they observed an odds ratio of 1.11 (95% CI: 1.00, 1.24) for each 10-ppb increase in nitrogen dioxide concentration and concluded that there were no clear patterns by histological subtype. However, the odds did appear to be strongest for adenocarcinoma, which is the most common subtype among never smokers. In a recent analysis of multiple cohorts included in the European Study of Cohorts for Air Pollution Effects (ESCAPE), there was also a suggestion that associations with $PM_{2.5}$ were strongest for the adenocarcinoma subtype (11). Currently there is no consensus on this finding, since some earlier studies also observed the strongest associations with adenocarcinoma (12–14), while others observed stronger associations for other subtypes (15–17).

One final issue mentioned 61 years ago (1) was the importance of examining the joint effects of air pollution and smoking. Because of the study design, Villeneuve et al. were unable to examine the impacts of air pollution among persons with different smoking histories, although they mention that results restricted to never smokers were attenuated (4). To date, in the studies that have examined associations by smoking status, results have been mixed as to the group with the highest risk, and almost no study has observed statistically significant effect modification. For example, in the ESCAPE meta-analysis of European cohorts (11), the associations were strongest among never and former smokers; in the Canadian case-control study (10), the group with the highest risk differed by pollutant; in the American Cancer Society study, results restricted to never smokers (19) were elevated in comparison with those for the full cohort (18); and in a reanalysis of the Six Cities Study (20), risks were similar among never and current smokers but highest for former smokers. Given the small numbers of cases among never smokers, it may only be possible to truly disentangle the effects of smoking and air pollution through a meta-analysis.

In conclusion, Villeneuve et al. (4) have made a valuable contribution to the literature on the adverse effects of air pollution on lung cancer risk, especially in terms of the unique

aspects of exposure assessment. Future studies should build on the strengths of this work, while also attempting to address the lingering questions.

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