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Title	Cancer incidence attributable to air pollution in Alberta, Canada in 2012
Authors	Abbey E. Poirier MSc, Anne Grundy PhD, Farah Khandwala MSc, Christine M. Friedenreich PhD, Darren R. Brenner PhD
Reviewer 1	Richard Burnett PhD
Institution	Health Canada
General comments (author response in bold)	Not sure why you are using a result from a single study (Pope et al 2002) when a much more extensive meta-analysis has been published (Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, Vineis P, Forastiere F, Saldiva P, Yorifuji T, Loomis D. 2014. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ Health Perspect 122:906–911; http://dx.doi.org/10.1289/ehp.1408092). You should at least cite this paper and indicate their summary risk estimate is not that different than Pope. ***To be consistent with the method used in the previous analysis by Norman, we used the β and standard error estimates from the Pope (2002) analysis. The Pope study included a population of 415,000 and used fixed site monitors to access air pollution exposure (consistent with our study). We thank the reviewer for this suggestion, and Hamra (2014) has been cited in the discussion to compare the risk estimate found in the meta-analysis with ours (lines 148-151).*** Should state the percentage of the Alberta population living in these 22 communities (you given numbers in Discussion only). There are complete spatial coverage estimates available for Alberta for PM2.5 that could have been used to cover all the population (van Donkelaar, A., R. V. Martin, R. J. D. Spurr and R. T. Burnett, High-resolution satellite-derived PM2.5 from optimal estimation and geographically weighted regression over North America (2015). Environ. Sci. and Tech., doi 10.1021/acs.est.5b02076, 2015). ***The percentage of the population living in the 22 communities is now included in the methods (lines 98-99).*** 3. The TMRED used in the GBD program is actually a uniform distribution from 5.8 to 8.8 ug/m3, not a fixed value. You should mention this and suggest a reason to select a value of 7.5 ug/m3 (near the midpoint and wanted to simplify the analysis?) ***An explanation for the use of 7.5 µg/m³ has been included in lines 117-122.*** 4. The TMREL is only based on a lack of observational evidence from cohort studies based on the distribution of PM2.5 used in those studies. It does not represent any actual analysis of the concentration-lung cancer association. Since the Alberta exposures are so low and near the TMREL I would suggest a sensitivity analysis using a counterfactual concentration at the minimum observed concentration. ***Thank you for this recommendation. A sensitivity analysis has been added using a counterfactual concentration of PM2.5 at the minimum observed concentration of 3.18 µg/m³ in place of the theoretical minimum risk of 7.5µg/m³.***
Reviewer 2	Mark Goldberg PhD
Institution	Department of Medicine, McGill University, Montréal, Que.
General comments (author response in bold)	I am afraid that this paper, while of some interest to Canadians, is not up to standard. The authors use a method developed by Norman et al. yet they did not describe the model nor the assumptions behind it. I did not look up this paper as the methods in the paper should be sufficiently described as well as all of the assumptions; they were not. ***We thank the reviewer for this suggestion. We have updated and expanded the methods to better explain the models used and their corresponding assumptions.*** 2. I can say, however, that the risk function that was used was based on US data, and in fact it is not described what the regression coefficients refer to (all cancer mortality, non-accidental mortality, cardiovascular deaths?). As well, why use US data when the largest most comprehensive long-term study in the world was conducted by my colleagues and I (Burnett, Crouse, et al.) here in Canada using the 1991 Census Cohort and air pollution data. ***Additional information has been added to the methods section (lines 117-124) to better convey how the relative risks were estimated. The Canadian cohort study has been cited in the discussion (lines 173-175). While we appreciate that the Burnett paper contains valuable data, these analyses were already completed at the time of the publication of the Burnett paper. In order to modify our analyses to employ the data from the Census Cohort, We would have to ask the authors for their beta estimate based on the slope of a linear concentration-response function to estimate a RR and then repeat our analyses. The next step in our work is to estimate the burden of cancer at the national level and to complete some projections of future burden as part of a nationally funded project. For this work we have expanded our team to include investigators on the Census Cohort and will update these analyses. For the current manuscript, however, we feel that this is beyond the scope of this particular manuscript.*** 3. I do understand the underlying assumptions behind these calculations: they are that the air pollution data today can be used as surrogates for etiologically-relevant exposures that occurred 10-30 years ago and that the various sub-populations populations were uniformly exposed at these levels for all etiologically relevant time periods . This of course is nonsense and relates to the assumption of assigning some prevalence of exposure (P), equation 2. ***We agree with the reviewer that the latency assumption for air pollution is particularly problematic. We have expanded the discussion of this limitation in the discussion section.*** The following sentence is patently incorrect, as there is no threshold for carcinogens: "The value 7.5 µg/m3 is the annual average theoretical minimum risk concentration of PM2.5 established in the global burden of disease study.[13] It represents the concentration below which there is no longer an an increased risk of disease." The value of 7.5 is simply a benchmark to compare risks by. ***These issues have been addressed and the text has been revised (lines 119-124).***

	5. One must also ask why 2012? Why not over some longer period of time? *Unfortunately, complete air pollution data were only available starting in 2011 for all of the 22 communities included in these analyses. The most recent cancer incidence data were available for 2012.* 6. Lastly, why not just use the Census Cohort to estimate the PARPs. One can use the Global Burden of Disease methodology to compute DALYs etc… Ask Rick Burnett and I'm sure he would help. *As stated in response number 2, while we appreciate that the Burnett paper contains valuable data, these analyses were already completed at the time of the publication of the Burnett paper. In order to modify our analyses to employ the data from the Census Cohort, We would have to ask the authors for their beta estimate based on the slope of a linear concentration-response function to estimate a RR and then repeat our analyses. The next step in our work is to estimate the burden of cancer at the national level and to complete some projections of future burden as part of a nationally funded project. For this work we have expanded our team to include investigators on the Census Cohort and will update these analyses.For the current manuscript, however, we feel that this is beyond the scope of this particular manuscript.*
Reviewer 3	Paul Hasselback MD MSc
Institution	Medical Health Officer, Vancouver Island Health Authority, Victoria BC
General comments (author response in bold)	There are many strengths and considerable value in this study. Using Population attributable risk estimations is a contribution to help prioritize cancer control efforts provincially and nationally. The study is well written, and the sense of interpretation is the authors are cognizant of the significant limitations to the ecologic monitoring – this is a strength of the study. This paper appears to be one of a series of investigations looking at population attributable risk for a number of cancers and number of exposures. It was challenging to review this paper in isolation of the series of while the exposure is prevalent, the PAR of the outcome was low, as is the proportion of fatal outcomes in the population due to air pollutants that are attributable to lung cancer specifically. There is reference to a 2000 study by the WHO. Noting that annual updates are available at http://www.who.int/phe/health_topics/outdoorair/databases/cities/en/ in particular the spread sheet information entitled ambient air pollution database by country and city and the link to burden of disease calculations. Current information would be preferable. The full methods for the 2000 study make for easier comparisons, however updated estimates using similar methodology are available through the above link. *Updated citations have been added to the manuscript (lines 74-76).* 2. The CASA data sets are a combination of data monitoring sites, including some specifically designed to monitor point source emission impacts in air sheds. Ministry of Environment or Environment Canada sites only might be preferable, or should be confirmed. *We did not use data from any monitoring sites specifically targeting air sheds.* 3. Certain communities have higher density of air monitoring devices. While information is provided on averaging across the province and point estimates are made for each community, insufficient information is provided on how populations were assigned to specific monitoring stations, or how multiple monitoring stations are blended for a population (eg Edmonton region). Table 1 does provide sufficient information to assess how estimated exposures were developed from multiple stations. *For communities with more than one monitoring stations, the average across stations was used. This information had been added to the manuscript (lines 106-107).* 4. The use of 7.5 ug/m3 annual mean as theoretical minimum risk needs justification or as noted below may be incorrect. Many communities achieve lower than this level routinely, and most science reviews would suggest there is no lowest observed effect level for PM2.5 and outcomes. Justification for the minimum is required for lung cancer for the purposes of this study. The cited article by Cohen was not locatable and seems to be missing key information. If the reference was intended to refer to Chapter 17 of the Global Burden of Disease document http://www.who.int/healthinfo/global_burden_disease/cra/en/ the 7.5 ug/m3 average per year was an assumption based on interpretation of the Pope article and was used for convenience in calculation and not as a theoretical minimum. *This section of the manuscript has been revised based on comments from other reviewers. Please see the manuscript lines 122-127).* 5. As currently written it is a significant issue of concern to the credibility of the article. It may be reasonable to consider changing wording to reflect the intent of using 7.5ug/m3 minimum as was done in Chapter 17 may suffice for the purposes of this article in that only 5.8% of the population were excluded as not exposed. It may however impact the confidence interval for the point estimate. Given the overall relatively low PM2.5 exposure averages within the province, the uncertainty of the point estimate of 36 cases is greater *Based on the reviewer's comments we have included a sensitivity analysis using 3.18µg/m3 (the lowest annual average concentration observed in the 22 communities included) has been to the analyses (lines 152-158).* 6. Given the PAR estimated as a 0.22-3.36% 95% CI based on the Monte Carlo simulations, the point estimate of 36 excess deaths should be presented with the same CIs (ie 4-64 deaths) *We thank the reviewer for point this out and this change has been made in the manuscript.*

7. One major fallacy that this article potentially propagates is that lung cancer is a significant outcome of air pollution. Even the WHO global studies would attribute only a small fraction (about 6%) of all deaths due to air pollution to lung cancer http://www.who.int/mediacentre/news/releases/2014/air-pollution/en/ . It would be important in this study to acknowledge this outcome is a significantly minor cause of air pollution mortality.
This has been addressed in the conclusion.

8. The analysis of limitations is appreciated and well done. These issues however are inherent to most studies associated with poor air quality exposures.

9. Latency for the development of lung cancer is a major issue and at least an attempt to address in Figure 3 of the second paper (appendix) is provided. Longer term estimates for PM exposure levels by community may have resulted in even greater uncertainty in the point estimate. Options to have considered would be to have run the models using past community specific monitoring information from the data warehouse.
We have addressed the issue of latency in our limitations section (lines 232-234).

10. As noted, population mobility is a challenge in undertaking this study and is addressed through explanation.