Author's response to reviews

Title: Evaluation of different radon guideline values based on characterization of ecological risk and visualization of lung cancer mortality trends in British Columbia, Canada

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Author's response to reviews: see over
Response Document
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Please find below a detailed outline of the specific revisions taken to improve this manuscript. We appreciate the time and effort the reviewer took to provide feedback that has allowed us to improve the manuscript. Itemized responses are outlined below. In general, the main changes include:

- Changed the title to “Evaluation of different radon guideline values based on characterization of ecological risk and visualization of lung cancer mortality trends in British Columbia, Canada” to better clarify that this is not an epidemiologic study of the relationship between radon gas and lung cancer.
- The “Study Area” sub-section moved from the “Background” section to the “Methods” section.
- Changed term “geographic risk” to “ecological risk”
- Clarified the use of the term radon “vulnerability” as it relates to a specific definition of ecological radon risk derived from previous research.
- Added a sentence in the last paragraph of the background section and modified the first paragraph of the discussion section, in order to re-iterate the notion that our study was not an epidemiologic study of the association between radon exposure and lung cancer. Instead we emphasize that it is an ecologic study that sought to investigate the effect of using different radon concentration thresholds on ecologic radon risk characterization, and the subsequent changes in areas and populations characterised as “high risk” and the differences in crude lung cancer mortality trends between high and low radon risk areas.
- Addressed concerns regarding the need for a more thorough discussion of potential confounding variables by adding a more thorough discussion of bias and confounding due to misclassification of radon vulnerability as well as adding a description of the limitations of the mortality data in the discussion section.
- We tested our data for spatial dependence in order to justify the use of the balanced random forest algorithm for classifying indoor radon vulnerability.
- We re-phrase our conclusions in the Abstract and a section in the discussion that a 50 Bq m$^{-3}$ is justified for the province and instead make the argument the results contribute evidence towards the use of a lower concentration threshold than is currently employed by Health Canada.

REVIEWER 1

Major Compulsory Revisions
1. The authors have stated that the background for this study is that: ”There is no safe concentration of radon gas”, and “–there is no radon concentration at which
there is no risk of developing lung cancer”. Based on the background for the study, the result of the study should be obvious. Lowering exposure level reduces risk. I would have appreciated a more comprehensive discussion of the scientific basis for this background.

Addressed. There is general scientific consensus around a linear dose-response relationship for radon based on evidence from cohort studies involving uranium miners and summarized in the sixth committee of the Biological Effects of Ionizing Radiation [1]. Evidence for the application of this relationship at lower exposures typically found in a residential setting was further supported in European and North American studies which investigated the relationship between lung cancer risk and residential radon exposure directly using pooled data from 13 and 7 individual case-control studies respectively. Both studies found a similar linear dose-response relationships between residential radon exposure and risk of lung cancer with no evidence of a threshold [2–5]. The evidence of a non-threshold and linear dose-response relationship is summarized in some detail in the first chapter of the World Health Organizations “Handbook on Indoor Radon: A Public Health Perspective.”

Further references have been added to the introductory paragraph to better support the statement. It now reads as follows, with the references cited below:

“The dose-response relationship between radon exposure and lung cancer risk is understood to be linear, with no evidence of a threshold [2–5]. As such, there is no radon concentration at which there is no risk of developing lung cancer, and the probability of developing lung cancer increases with exposures to higher concentrations.”


2. Besides this the objective of the study was to “examine how different threshold were associated with geographic risk and lung cancer mortality trends”. Geographical risk seems to have been constructed by the authors, but not defined or explained further in detail. Within evidence based “hazard and risk assessment”, risk is normally calculated by different parameters and algorithms based on an exposure situation where understanding and description of hazard is an essential part. It seems that the authors use geographical as a surrogate for individual exposure to radon in buildings in different areas. The term geographical risk should have been better explained to ensure reliability and improve the outcome of the information Addressed. The term “geographic risk” was changed to “ecologic risk” to provide more clarity to the reader regarding its use as an ecological estimate of exposure. Furthermore, a sentence in the Background section was modified to clarify that ecologic radon risk refers to the characterization of a spatial area as more or less prone to having homes with higher indoor radon concentrations within their boundaries as another spatial area, as follows:.

“Radon concentration thresholds are used to inform policy and to enable risk communication. For example, radon risk maps characterize the ecologic radon risk associated with indoor radon by identifying spatial areas more prone to high radon concentrations”

3. The authors have constructed the term “radon vulnerability” as a part of the hazard situation. This construction is nor explained or argued for. As vulnerability usually is used for increased risk based on personal predisposing susceptibility, radon vulnerability is rather confusing for this reviewer and should be further explained. Addressed. The sentence below was added to the methods section and explains that the term radon vulnerability refers to assigning a spatial area an ordinal classification of radon risk in which a greater probability for a given home within a classified area is high or low. For example, in an area classified as low vulnerability we would expect that the 95th percentile observed radon concentrations of homes within that region would be less than the specified concentration threshold, whereas in a high vulnerability area we would expect the 95th percentile concentration would exceed that threshold. Using this classification, we would expect areas classified as high to have more homes above a certain concentration threshold than areas classified as low, as such would be more prone to higher rates of radon induced lung cancer. Because there is scientific consensus surrounding a no threshold linear dose-response relationship there is no scientifically valid way to select a specific threshold, hence why the authors chose to model multiple scenarios of risk.
“Indoor radon concentration values were used to construct the response variable for the purposes of statistical classification. We used the same classification of indoor radon risk, termed indoor radon vulnerability, developed in previous work [12]. Indoor radon vulnerability refers to a way of characterizing ecologic risk, where classes of risk are assigned based on whether the observed 95th percentile concentration was above or below a specified threshold. In this way indoor radon vulnerability classification describes the relative potential for homes to have a concentration higher than the threshold value.”

4. To assess exposure, 13 independent variables are constructed. It is not sufficiently scientifically argued why the 13 constructed “independent variables” should be a significant assessment of individual exposure to radon.

Independent variables refer to the environmental conditions within an individual spatial unit that could individually or jointly affect concentrations of indoor radon. The relationship between the 13 independent variables, each of which consisted of either environmental or aggregate housing measures, and a rating of ecological indoor radon vulnerability was quantified through a balanced random forest algorithm. Detailed rationale for the inclusion of each independent variable in the model is included in a previous publication which we have included below for
5. A binary classification of smoking based on information from local health areas was constructed. The confounding from the poor exposure assessment and the binary smoking classification might add more to bias than findings in the study. However, confounding and bias in the assessments are hardly discussed at all. Also, in variants of ecological studies - like this one - references to, and discussions about, ecological fallacies should be obligatory. There is hardly any
information or discussion of ecological fallacies in the paper.

Addressed. The authors acknowledge that a discussion of confounding and bias is warranted. As a result we added two paragraphs to the discussion section address this concern, where we first discuss the limitations of the study design and data, and then discuss how bias and confounding can potentially affect visualizations of the crude lung cancer mortality trends. Discussion of ecological fallacy was limited because we are not intending that these results be interpreted at the individual level. The objective of the study was to evaluate different radon thresholds at the population scale.

“Although this approach was designed to evaluate policy options with respect to radon guideline values, and it has important limitations from an epidemiologic perspective. First, both radon and smoking categories were assigned ecologically based on the geographic area of residence, meaning that most individuals were misclassified. For example, 100% of decedents who lived in an area with 5% of homes over the threshold value were classified as having high radon exposure. Although this approach is crude, experts argue that it can be useful in studies where geographic differences drive population variability in exposure [39]. Second, we did not consider the life course exposure to radon and other environmental or occupational lung carcinogens [40] in these analysis, which were conducted with secondary administrative data. The residential and occupational histories of all decedents were unknown, thereby excluding the possibility of accounting for migration of populations during the latency period of lung cancer formation.

Given these limitations, it is important to consider how the visualisations of lung cancer mortality in the province stratified by radon may be biased or confounded. Bias would result in the ratio of lung cancer mortality to all natural mortality appearing to be higher or lower than in reality. For example, consider a situation in which we observe 7% lung cancer mortality in the low radon group and 10% in the high radon group. First, let us assume that there is no misclassification in the low radon group, but that many decedents in the high radon group actually had low radon exposure. Second, let us assume that a smaller proportion of the lung cancer cases has been misclassified compared with the deaths from all natural causes given that radon is known risk factor for lung cancer. If 90% of all lung cancer cases were misclassified and 95% of all other natural deaths were misclassified (because we used the 95th percentile values to establish the categories), the mortality ratio in the low group would actually be 8% compared with 22% in the high group. On the other hand, confounding would occur if the differences that appeared to be the result of exposure to radon were actually due to another factor associated with both lung cancer and ecologic radon exposure. For example, both radon exposures and smoking prevalence are higher in the rural areas of BC than in urban centres. When we stratified analyses by geographic smoking prevalence to evaluate whether the relationship between radon and lung cancer mortality could be observed in both higher and lower smoking areas, we found that it could not be observed in areas of higher smoking prevalence. This result is consistent with previous work demonstrating the confounding between ecologic measures of radon exposure and smoking[41].”

6. The authors should address if the exposure assessment is truly blinded towards outcome data. Any indirect influence on social factors or occupation could potentially affect the results.
Addressed within the response to Major Compulsory Revision #5. These analyses were conducted with administrative mortality data that did not include any information about social factors or occupational exposures. The limitations of the data are now further described in the discussion section as a part of our response to the previous question (Major Comment #5).

7. The number total numbers of lung cancer deaths have not been reported. The authors should have given an estimate of the potential for reducing disease burden (lung cancer) when reducing threshold concentration.

We agree with the reviewer that the number of deaths reported in the study is pertinent information and as a result have added this information into the results section of the manuscript.

We acknowledge the importance and utility of a study that estimates the number of lung cancer deaths in a region due to a specific disease in terms of formulating policy as well as communicating risk, however, the estimation of the disease burden due to radon in Canada is the subject of several studies that have taken place in the last decade. References for these studies are given below. These studies make use of a specific risk model and calculate the population attributable risk for specific age rates and lung cancer mortality as well as smoking prevalence. While such an analysis is certainly a worthwhile endeavour, and one that has not taken place in the province of British Columbia, the authors feel it is beyond the scope of this paper.

The following sentence and table was added to the results section in order to provide more information on the mortality data used in these analyses:

“The total number of natural and lung cancer deaths occurring in high radon vulnerability areas increased with decreasing radon thresholds, but the ratio of the proportions between the groups remained stable (Table 2).”

Table 2. The number of deaths during the study period (1998-2013) due to lung cancer and all natural causes stratified by the ecologic exposure variables assigned to each mortality by geographic location including smoking prevalence (high) and radon vulnerability (high).

<table>
<thead>
<tr>
<th>Threshold in Bq m⁻³</th>
<th>All Natural Deaths ( % of Total)</th>
<th>Lung Cancer Deaths ( % of Total)</th>
<th>Ratio of the percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N)</td>
<td>457.242</td>
<td>34.443</td>
<td></td>
</tr>
<tr>
<td>Higher Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High radon</td>
<td>600</td>
<td>3.3%</td>
<td>3.7%</td>
</tr>
<tr>
<td>High radon</td>
<td>500</td>
<td>3.2%</td>
<td>3.7%</td>
</tr>
<tr>
<td>High radon</td>
<td>400</td>
<td>4.2%</td>
<td>4.8%</td>
</tr>
<tr>
<td>High radon</td>
<td>300</td>
<td>6.5%</td>
<td>7.0%</td>
</tr>
<tr>
<td>High radon</td>
<td>200</td>
<td>8.6%</td>
<td>9.5%</td>
</tr>
<tr>
<td>High radon</td>
<td>150</td>
<td>11.1%</td>
<td>12.4%</td>
</tr>
<tr>
<td>High radon</td>
<td>100</td>
<td>16.5%</td>
<td>18.0%</td>
</tr>
</tbody>
</table>


Chen J, Tracy B: Canadian Population Risks of radon induced lung cancer. *Can J Respir Ther* 2005

8. Given p.7, the authors should have discussed the lack of change between in the distance between high and low vulnerability liners with decreasing radon thresholds. In my opinion, this could be an indication on confounded results.

Addressed. We agree with the reviewer that the lack of change in the distance between high and low vulnerability lines in the overall trends could be evidence of confounded results. We attempt to account for some confounding by further stratifying mortalities by a smoking prevalence indicator (high or low). The distance is observed to decrease with decreasing thresholds in areas of low smoking prevalence indicating confounding has been mitigated to an extent (see Figure 5). In order to address the reviewers concerns we added a sentence to the discussion to acknowledge the potential for confounding by smoking. We added a further sentence to explain the confounding may have been mitigated by smoking in areas of lower smoking prevalence.

“The crude lung cancer mortality ratio within areas classified as high vulnerability was higher than within areas classified as low vulnerability for every concentration threshold through time. However, the distance between high and low vulnerability lines was consistent across thresholds, possibility indicating the presence of a confounding variable.”

“In areas with higher smoking prevalence, we observed no differences in lung cancer mortality trends between high and low vulnerability areas. In areas with lower smoking prevalence, however, differences between radon vulnerability areas were clear across all threshold values. The distance between trend lines decreased with lower thresholds, possibly indicating some ecological control of confounding effects of smoking rates.”

Minor Essential Revisions

1. “Susceptibility to high radon concentrations“ is in my opinion incorrectly used to describe exposure level – not susceptibility.

Addressed. Use of term susceptibility removed and change is shown in sentence below:
“Each mapping unit was labelled as a “Bedrock Dissemination Area” (BDA) and was assumed to represent a homogenous spatial area with respect to the environmental and housing conditions that would affect its potential for high indoor radon concentrations”

2. It is rather unclear what kind of study this is. It is a mixture of dichotomous comparison in some aspect and crude estimate of dose response based on poor exposure assessment in other aspect. There are measurements - one or more - of radon concentration from 1054 of the 36051 BDA – 3% of the BDA. There is no information or discussion of how representative the measurements are as assessment of individual exposure, and no information or discussion of how representative measurement in the 1054 BDA are for individual exposure in the other BDAs.

It is important to consider that is not an epidemiologic study of the association between radon exposure and lung cancer. This is an evaluation of different radon thresholds using multiple sources of data. First, we used indoor radon measurements and environmental variables in 1054 BDAs to estimate the radon vulnerability in 26,719 unmeasured BDAs using different threshold values. Then we used those estimates to classify all deaths as occurring in high or low radon areas for each threshold value to examine changes in crude lung cancer mortality trends. In order to clarify the objectives of the study we have added and modified the following sentences to the end of the “Background” section and beginning of the “Discussion” section respectively:

“This is not intended nor designed to be an epidemiologic study of the association between radon exposure and lung cancer, but we use ecologic information about both to assess the implications of different radon thresholds from an environmental health policy perspective.”

“Many epidemiologic studies have examined the association between radon exposure and lung cancer, but there has been little systematic evaluation of how decisions about guideline values affect important policy considerations. These include the accuracy with which risk can be classified, the extent of geographic areas classified as high risk, the size of the populations classified as high risk, and the observed relationships between risk areas and lung cancer mortality trends.”

3. Could migration within the populations during latency for the development of lung cancer affect the outcome?

Addressed within the response to Major Compulsory Revision #5

4. The authors should have explained the measured time trends (figure 5 and 6) in more detail.

Addressed. The sub-section explaining the temporal trends in crude lung cancer mortality ratios was modified for clarification and reads now as follows:

“Visual Comparison with Lung Cancer Mortality Trends”
The visual relationship between radon thresholds and temporal lung cancer mortality trends was assessed by comparing the annual ratio of lung cancer mortality to all natural mortality in high and low vulnerability regions. Each death was spatially assigned to a radon vulnerability class for each of the eight predictive maps. Additionally, each death was assigned to higher or lower smoking prevalence based on the LHA in which it occurred. By attributing each death with both radon and smoking classifications we were able to compare trends across high and low radon vulnerability while crudely accounting for the confounding factor of smoking prevalence. For each radon concentration threshold, the annual sum of lung cancer deaths was divided by annual sum of all natural deaths in the high and low vulnerability areas. The values for 1998 through 2013 were plotted, and a temporal trend line was fitted using a locally weighted LOESS smoother. The same was done to explore potential differences between males and females, as was previously observed in BC [11]."
REVIEWER 2

The present paper is an interesting and well written paper on different radon levels in British Columbia in Canada and lung cancer mortality.

Major comments

The title and background of the study does not give the reader an idea of the study design and the population that is studied. Number of inhabitants, confounders such as possible occupational exposure (mining, asbestos) are lacking here.

Addressed. The title of the paper was changed to “Evaluation of different radon guideline values based on characterization of ecological risk and visualization of lung cancer mortality trends in British Columbia, Canada”

The recommendations of radon thresholds, risk maps, radon areas are thoroughly discussed in the background part of the paper and the reader is left wondering if there are studies in of occupational groups or from the general population that have dealt with cancer mortality among radon exposed individuals.

There are many on individual radon exposure and lung cancer risk in occupational and residential contexts. Further reference has been made to these studies in the Background section, as per the suggestion of Reviewer #1.

Also details on technical matters e.g. concentrations of measurements of radon takes much place (3 ½ page) in the methods part, whereas only little space is left for the outcome of interest namely cancer mortality. Here, number of participants and a characterization of them should be more detailed and they should be characterized according to potential confounders. Are there any missing data?

We acknowledge the reviewers concern for a lack of discussion surrounding potential confounders and as a result have added much more detail regarding discussion of confounding factors and bias as a part of a response to Reviewer #1, Major Compulsory Revision #5.

In addition, to better characterize the data used to generate mortality visualizations for the reader, we have also added a table to the results which shows the total number of deaths due to cancer or all natural causes. The table shows the total number of lung cancer and all natural mortality deaths during the study period, as well as the number of lung cancer and all natural mortality deaths which occurred in areas defined as high smoking, and high radon.

The discussion part starts with recommendations on radon concentration etc but should maybe start with the main results of the study.

It is important to consider that our study is not an epidemiologic study of the association between...
radon exposure and lung cancer. This is an evaluation of different radon thresholds using multiple sources of data. We have added a statement about this to the end of the Background section to ensure that readers are clear on the objectives. As such, we believe the beginning of the discussion is appropriate as it stands, though we modify it slightly for greater clarity. The last paragraph as the end of the Background section now reads as follows:

“Our objective is to evaluate how different radon concentration thresholds are associated with the accuracy of ecological radon risk classification, geographic areas classified as higher or lower radon risk, populations classified as higher or lower risk, and visual temporal trends in lung cancer mortality. Understanding these relationships has important implications for informing policy on appropriate guideline values. Following Branion-Calles et al. (2015) we map the radon vulnerability of geologic units using eight thresholds ranging from 50 to 600 Bq m$^{-3}$. Radon vulnerability refers to the potential for a geographic area to exceed a specified concentration threshold. Maps of indoor radon vulnerability are then used to visually explore the association between radon concentration thresholds and lung cancer mortality trends stratified by sex and smoking prevalence. This is not intended nor designed to be an epidemiologic study of the association between radon exposure and lung cancer, but we use ecologic information about both to assess the implications of different radon thresholds from an environmental health policy perspective.”

The modified paragraph at the beginning of the discussion reads as follows:

“Different regions, countries, and organizations recommend different radon concentration thresholds that essentially classify the associated risk of lung cancer as being acceptable or unacceptable. In reality, however, radon is a non-threshold carcinogen and any level of exposure carries some risk [2]. Established guideline concentration values reflect a balance between the health evidence, what is practically achievable, and other political and public health priorities. Many epidemiologic studies have examined the association between radon exposure and lung cancer, but there has been little systematic evaluation of how decisions about guideline values affect important policy considerations. These include the accuracy with which risk can be classified, the extent of geographic areas classified as high risk, the size of the populations classified as high risk, and the observed relationships between risk areas and lung cancer mortality trends. Here we have addressed this gap by exploring the impacts of thresholds ranging from 50 – 600 Bq m$^{-3}$ in one Canadian province with previously demonstrated spatial variability in radon risk [11, 12, 33].”

In my opinion the most interesting results are summarized from line 332 until 340 and again from 346 to 350.

In the discussion part other studies of similar populations exposed to radon or even literature from occupational settings are missing.

We make further reference to studies of individual radon exposure and lung cancer risk, in residential and occupational settings in the Background section as per the suggestion of Reviewer #1.
Minor comments

The objective of the study should be at the end of “Background” part – before “Methods” addressed. The “Study Area” sub-section was moved from the end of the Background section to the beginning of the Methods section so that the objectives were at the end of the Background section.

END REVIEWER 2
I found this to be a well-written manuscript based on a well-designed study. I was especially pleased by the extensive discussion of the results and limitations of the study. That being said, I feel that there are a couple points that require further justification or discussion before this manuscript is ready to be published.

Major Compulsory Revisions:

1. The authors use a balanced random forest to classify radon vulnerability. This method assumes independent and identically distributed observations. I feel it is important to justify the assumption that the observations are spatially independent given the independent variables if this method is to be used for classification.

   Addressed. We thank the reviewer for their thorough evaluation of our model selection. We understand the reviewer's concern regarding spatial independence of our response values. We tested both the 4352 independent radon concentration values for spatial independence and our 95th percentile aggregated (bedrock dissemination area units) data using a 10 k-nearest neighbour weight matrix and Geary's C analysis to account for non-contiguous polygons and log-normal distribution of our data. Both exhibited no significant spatial auto correlation (Geary's C statistic (0.86,p=0.2) & (0.89,p=0.186)). We have not added this information to the manuscript, but will do so if the editors prefer.

2. In the section “Lung Cancer Mortality Trends”, it is not surprising to me that lowering the radon vulnerability resulted in decreased separation between the lung cancer trends between the high and low vulnerability locations, and this is telling of the issue at hand. If radon exposure presents a health risk at any concentration, then mitigating as much radon exposure as possible is ideal. However, this is, of course, not plausible. Therefore, I think it is important to explicitly frame the problem as a population-based classification problem and less as a problem of determining a guideline for acceptable radon exposure. I felt that lines 360-365 were worded a bit strongly given the results of the classification. I think the language should be one of providing additional information to the guidelines discussion, and not one of suggesting new guidelines.

   Addressed. We acknowledge the reviewers concern and rephrased the identified section to reflect the idea the study adds pertinent information for the discussion surrounding implementing lower radon concentration guidelines as follows:

   “Based on the results of our study and the principle that no radon concentration is safe, we contribute evidence surrounding the discussion of implementing a lower concentration threshold than the 200 Bq m\(^{-3}\) value currently employed by Health Canada.”

   We also rephrased the abstract as follows to reflect the same change:
“Conclusions: Radon contributes to lung cancer in British Columbia. The results of the study contribute evidence to support the use of a reference level lower than the current guideline of 200 Bq m\(^{-3}\) for the province.”

Minor Essential Revisions:

1. Line 22 lists the radon concentration units as Bq/m\(^3\), whereas the rest of the paper uses the convention BQ m\(^{-3}\). This should be made consistent.

    Addressed. Notation in line 22 was changed to be consistent with the rest of the manuscript.