Author's response to reviews

Title: Cell-type specificity of lung cancer associated with low-dose soil heavy metal contamination in Taiwan: An ecological study

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Author's response to reviews: see over
Dear Prof. Mark Russi,

Once again, thank you very much for your assistance regarding our manuscript. We have carefully addressed the Associate Editor’s further comments, and have incorporated all the suggestions in the revised manuscript. The revised words or sentences were underlined and put on red. If you have any questions regarding the revisions, please contact me. The point-by-point responses to the editor's comments are as follows:

Q1: “… a Japan study used a disease mapping…” in line 60.
A1: It has been modified to “… a Japanese study used disease mapping…” Please see line 61 and 62.

Q2: “…indicators with the studied areas.” in line 62.
A2: It has been modified to “…indicators within the studied areas.” Please see line 63.

Q3: “Data of eight heavy metals…” in line 95
A3: It has been modified to “Data for eight heavy metals…” Please see line 97.

Q4: “The significant differences in standardized incidence rates are represented by seven colors….” in line 109 and 110.
A4: The significant differences in the sentence means statistically significant. We re-phrased it to “The statistically significant differences in standardized incidence rates are represented by the seven colors…” Please see line 111 and 112.

Q5: “…is a sporadically high…” in line 145.
A5: It has been modified to “… is sporadically high…” Please see line 139.
Q6: “However, according to a smoking prevalence in Taiwan [29], no smoking prevalence is clustered in western coastal townships for either men or women.” in line 208.
A6: We agree with the editor’s comment that the statement doesn’t seem to be true based on what is reported in Results section. The statement has been modified to “However, according to a smoking prevalence survey in Taiwan [29], smoking prevalence doesn’t cluster in accordance with lung cancer incidences for either men or women.” Please see line 202 and 203.

Q7: The statement “Because lung cancer incidence rates were spatially clustered in this study, and smoking behavior may not explain the clustering cluster, the potential for environmental risk factors may exist.” in line 210-212 following previous statement (Q6).
A7: Followed by the modification in previous statement, we slightly re-phrased the sentence next to it. The modification is “Since smoking behavior may not explain the clustering, the potential for environmental risk factors may exist.” Please see line 204 and 205.

Q8: “…lower level of…” in line 214 and 215.
A8: It has been modified to “…lower levels of…” Please see line 207 and 208.

Q9: “A study examining the heavy metal accumulation of lung tissue in lung cancer patients…” in line 245 and 246.
A9: It has been modified to “A study examining heavy metal accumulation in lung tissue of lung cancer patients…” Please see line 238 and 239.

Q10: “A proper amount of Zn is effective at preventing the incidence of cancer. However, ingesting excessive Zn is related to the incidence of specific cancers.” in line 271-273.
A10: It has been deleted according to the editor’s comment.

Q11: “…must be studied further.” in line 274.
A11: It has been modified to “…should be studied further.” Please see line 265.

Q12: The paragraph in line 275-284.
A12: The paragraph has been deleted since the links are weak according to the editor’s comment.
Q13: The sentence “First, it is ecological subjects to the ecological fallacy, since confounding factors of individuals cannot be adjusted for.” in line 285 and 286.
A13: It has been re-phrased to “First, it is ecological and subject to the ecological fallacy, since confounding factors of individuals cannot be adjusted for and regional metal concentrations may not reflect individual exposure levels.” Please see line 286-288.

Q14: “…, not address exposure pathways to human body…” in line 288 and 289.
A14: It has been modified to “…nor address the exposure pathways in the body…” Please see line 290 and 291.

Q15: “… In the Discussion, they need either to introduce the air pollutant logistic regression analysis earlier in the paper or eliminate it from this paper”. 
A15: We agree with the editor’s suggestion and had it relocated in the Discussion section as a single paragraph right before the limitation section. Please see line 266-285.

Q16: The forth limitation in line 302-305.
A16: It has been adjusted to the third limitation due to relocation in Q15. Please see line 291.

Q17: The sentence “Because of the time sequence incorporating smoking prevalence in the model for adjustment is inappropriate.” in line 304 and 305.
A17: It has been modified to “Because of this, we were not able to account adequately for the influence of any regional differences in smoking prevalence upon our results.” Please see line 293-295.

Q18: The statements “The current study suggests that a higher Cr concentration in soil is related to male and female lung SCC; a higher Cu concentration is related to male and female lung AC and lung SCC; a higher Ni concentration is related to male lung AC, and male and female lung SCC; a higher Zn concentration is related to female lung AC and male and female lung SCC.” in 307-311.
A18: They have been modified as “The current study suggests that a higher Cr concentration in soil is associated with male and female lung SCC; a higher soil Cu concentration is associated with male and female lung AC and lung SCC; a higher soil Ni concentration is
associated with male lung AC, and male and female lung SCC; and a higher soil Zn concentration is associated with female lung AC and male and female lung SCC.” Please see line 297-301.

Q19: The sentence “These findings can explain the spatial variations of lung SCC incidence rates that do not match the smoking prevalence for townships.” in line 311 and 312.
A19: The sentence has been deleted based on the editor’s comment.

Q20: “…a dose-response relationship exists…” in line 313.
A20: It has been modified as”…a dose-response relationship may exist…” Please see line 302.

Q21: “…according to cell-type specificity…” in line 314.
A21: It has been modified as “…according to specific cell type…” Please see line 303.