Author’s response to reviews

Title: The Unveiling of a New Risk Factor Associated with Bladder Cancer in Lebanon

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Reviewer #1: The manuscript by Temraz et al., titled: "The Unveiling of a New Risk Factor Associated with Bladder Cancer in Lebanon" strives to calculate the contribution of smoking and water pollution on bladder cancer risk. The manuscript seems to be a reconstructing of a previous published work with new insights about Trihalomethanes (THM) contamination.

Cancer is a multifactorial disease, and smoking is a well-known risk factor. The authors pointed that the aim was to "examine the significance of smoking and water pollution on the incidence of bladder cancer in Lebanon". However, in abstract, the conclusion was only about THM.

Response: We thank the reviewer for this comment and have changed the conclusion of the abstract to include also smoking in addition to THM.

In Methods section authors must correct the sentence: "Data was stratified by age and gender, data were stratified as: smokers, ex-smokers and non-smokers for all age and gender categories."

Response: Thank you, the sentence in section 2.2 was corrected by deleting the following “Data was stratified by age and gender”. 
Although the manuscript highlights the significance of THM in bladder cancer risk it is important to separate smokers from non-smokers. Authors must better justify why they did not analyzed separately.

Response: This is a very important note by the reviewer, which we have added as a limitation in the last paragraph of the discussion and elaborated further on the matter. We did not further stratify the risk from THM among smokers and non-smokers because our data is limited. As we mentioned, unlike smoking risk, no national study on THMs exposure in Lebanon exists.

(Reviewer 2): Authors have assessed the impact of smoking and water disinfection by product i.e. Trihalomethanes on bladder cancer risk in Lebanese population. I have following suggestions for the authors to modify the manuscript

1. Introduction: Authors' needs to deliberate on the potential role of THM in causation of bladder cancer, as the matter is still far from settled.

Response: Thank you for your comment. We have modified the wording in the introduction that directly implies a causation of THMs with bladder cancer and provided several studies which support the potential risk posed by THMs on bladder cancer.

2. Authors' used data from previously done work to determine the impact of these factors and this needs to reflect in the abstract.

Response: We thank the reviewer for this comment. We have mentioned in the methods section of the abstract the previous works from which we obtained the population at risk.

3. At places authors' extrapolated for example RR of smoking and ex smokers from Korean data, they have not provided actual figures from either population to show the basis except for Korean study reference [14].

Response: Thank you, we have provided actual figures from Korean study for both smokers and ex-smokers. These are included in table 1 (reference 14 is now reference 22).

4. The description provided by Authors' in using various studies data to extrapolate is incomplete and either authors can provide further details and actual data from the studies used to determine the impact and risk or provide a supplementary file detailing these calculations.
Response: As per your request, we have added a section detailing the formula and modified Levin formula used to calculate each risk factor in the methods section and also a detailed explanation for the calculations done for each risk factor in the results section.

5. Authors need to deliberate further on the role of THMs in bladder cancer. In a recent population based work Beane Freeman et al (Environ Health Perspect. 2017 Jun 21;125(6):067010.) observed a modest association between ingestion of water with higher THMs (>95th percentile vs.<25th percentile) and bladder cancer. In addition there are score so other studies which noted a unclear role of THMs in bladder cancer.

Response: Thank you, we have elaborated more on the issue that you raise. For sure, THMs are not a strong causative factor for bladder cancer like smoking; however, there seems to be an association even though modest. We added several studies in the introduction section (first paragraph) and in the discussion section which support the association between THMs and bladder cancer as well as the study by Beane Freeman which shows a modest association between bladder cancer and THMs.

6. Authors’ need to rephrase conclusions as they don't reflect the data presented.

Response: We thank the author for this comment and have modified the conclusion to reflect the data presented.