Author's response to reviews

Title: Pancreatic Cancer Clusters and Arsenic-Contaminated Drinking Water Wells in Florida

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Author's response to reviews: see over
May 14, 2012

Christna Chap, PhD
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RE: MS 1032211416636929 - Pancreatic Cancer Clusters and Arsenic-Contaminated Drinking Water Wells in Florida

Dear Dr. Chap,

Thank you for sending us the reviewers’ comments which were very helpful. We have substantially revised the manuscript to reflect these comments. We have addressed specific reviewers’ comments below in Response to Reviewers. With the inclusion of the reviewers’ helpful comments, we believe we have assembled a stronger manuscript.

Your consideration is deeply appreciated and we look forward to hearing from you soon.

Sincerely,

Wen Liu, MD, PhD
Response to Reviewers
Reviewer's report 1
Title: Pancreatic Cancer Clusters and Arsenic-Contaminated Drinking Water Wells in Florida
Version: 1 Date: 11 February 2012
Reviewer: Victor Martinez
Reviewer's report: REVISION
Authors present a manuscript titled "Pancreatic Cancer Clusters and Arsenic-Contaminated Drinking Water Wells in Florida". Main focus is to establish if clusters of persons diagnosed with pancreatic cancer were more likely to be located near arsenic-contaminated drinking water wells. Strength of this work is that authors provide novel information about the relationship between arsenic and pancreatic cancer. Title "Pancreatic Cancer Clusters and Arsenic-Contaminated Drinking Water Wells in Florida" does not completely represent main findings of this works (the relationship between clusters and distance to arsenic-contaminated water).
Background is very good written and provides relevant information for the theme; however some references and details are missed, please, refers to "minor essential reviews" for description. Methodology is well described and relevant for the main question of this work. Results are well explained on Tables and Figures (with minor exception on Table 1 (please, see revisions) Discussion needs to be completely revised, please check Major Compulsory Revisions.

Minor Essential Revisions
1. [page 2] Please, provide references for the following phrase "Late diagnosis, lack of therapeutic options, and the aggressive biological nature of pancreatic cancer cells play major roles in the traditionally poor prognosis of pancreatic cancer"

In response to reviewer comments, we have added the reference.

2. [page 3, last paragraph] Authors mentioned that “Arsenic is linked to bladder, skin, and lung cancer occurrence in populations highly exposed to arsenic occupationally, medicinally, or through contaminated drinking water (Agency for Toxic Substances and Disease Registry, 1999; IARC, 1987)“. However, some studies have demonstrated correlation between some of these cancer types and low to moderate concentration of arsenic (PMID: 20049123). This is especially relevant in North America. Please, adapt the text and provide appropriate references.

In response to reviewer comments, we have added a citation (Heck et al, 2009) and revised the introduction.

3. [page 3, last paragraph] Please, provide references (other than Taiwan) in order to support arsenic-lung cancer relationship). There are other countries affected by this problem.

In response to reviewer comments, we have added appropriate references and revised the introduction.

4. [Page 4, first paragraph]. Please, check missed reference about Florida Cancer Registry in the following phrase "... few invasive malignancies that had been slightly
rising in Florida (The National Program of Cancer Registries 2002-2006), and the mortality rate of this fatal cancer has not changed"

In response to reviewer comments, we have added the reference (http://www.cdc.gov/cancer/npcr/).

5. [Table 2] Please, adjust the text. Each component of column 1 should have a correspondent with number in column 2 (if not, Results on the Multi-variable Logistic Regression analyses" becomes confusing

In response to reviewer comments, we have modified the table 2.

Major Compulsory Revisions
1. [DISCUSSION -"Screening" SECTION]. As presented, this section is not relevant for Discussion, since no results from the research are analyzed. Basically, this is background about screening on pancreatic cancer. Please, link this subsection with obtained results (e.g. is proximity to arsenic a good parameter for screening people at risk of pancreatic cancer?

In response to reviewer comments, this section has been removed.

2. [DISCUSSION -"Smoking" SECTION]. Same issue as mentioned above. Please, circumscribe Discussion to obtained result

In response to reviewer comments, this section has been removed

3. [DISCUSSION -page 11, 2nd paragraph]. Authors mentioned “While these studies have identified important adverse health effects associated with relatively high-dose arsenic exposure, results cannot be extrapolated to US populations which are typically exposed to lower levels of arsenic exposure". First, is no clear if authors are discussing about "pancreatic" or any type of cancer associated with arsenic. Then, some studies (even among those cited by authors), specifically highlight that arsenic is linked with cancer at low/moderate levels in US population (PMID: 20049123, 19371619, 19834714) (Heck et al, 2009, Chen et al, 2009, Kwong et al, 2010)

Most of these studies focused on other types of cancers. As mentioned earlier in this section, “There was one study in the literature that reported a non-significant association between arsenic and pancreatic carcinogenicity”. In response to reviewer comments, the above sentence has been modified.

We have added the study of Heck et al in the Background section. The study of Chen et al (2009) found that low-to-moderate (0.1 to 864 microg/L, mean 99 microg/L) arsenic exposure from drinking water was associated with an increased risk of pre-malignant skin lesions (Chen et al, 2009) instead of skin cancer. The study of Kwong et al (2010) showed that among bladder cancer cases, the toenail arsenic exposure was related to bladder cancer survival (toenail arsenic > or =75 percent versus <25th percentile). Since they studied either cancer survival or skin lesions (instead of cancer), these two studies were not cited since they were not directly related to this study.

4. [General comment] Discussion need to be redesigned. There is basically more background and recommendation related to different aspects of pancreatic cancer;
however, little is discussed about actual results obtained. Questions remains no discussed, for example:
a. Are smoking rates on the clusters similar to those found in other parts of the country?

In response to reviewer comments, we have discussed smoking data in the Limitations section.

b. There are others co-carcinogens described on this area that can affect results?

It is not known if there were other co-carcinogens. These data were not collected at the individual or geographic level.

c. There are differences when gender is considered (this is not a parameter considered on analyses)

In the section discussing Logistic Regression Modeling, we described that: “Gender and age were not part of the multivariate logistic regression models because they were already incorporated as covariates on SaTScan analysis to identify areas of higher than expected incidence”. Therefore, we cannot examine the possible separate role of gender in the logistic regression analyses.

Reviewer's report 2
Title: Pancreatic Cancer Clusters and Arsenic-Contaminated Drinking Water Wells in Florida
Version: 1 Date: 25 February 2012
Reviewer: How-Ran Guo
Reviewer's report:
This study evaluated if there were any pancreatic cancer clusters in Florida and tried to identify socio-demographic and behavioral correlates associated with these clusters. In particular, the authors aimed to determine that, after controlling for these factors, if the cancer cluster membership was associated with proximity to identified arsenic-contaminated drinking well water. As the result, the authors found that cases living within 1 mile of known arsenic-contaminated wells were significantly more likely to be diagnosed within a cluster of pancreatic cancers relative to cases living more than 3 miles from known sites and concluded that exposure to arsenic-contaminated drinking water wells may be associated with an increased risk of pancreatic cancer. The topic is a relevant public health issue, and the finding is interesting.

Major Compulsory Revisions
1. The research question is well defined, but the authors should provide more information to support the hypothesis of an association between arsenic and pancreatic cancer. Reference 23 was cited to support the argument “there is some suggestion of a possible connection of arsenic-contaminated drinking water and pancreatic cancer” in the Background and the statement “There was one study in the literature that reported a non-significant association between arsenic and pancreatic carcinogenicity (23).” in the Discussion. However, the meta-risk ratio in that study was in fact 1.0 (95% confidence interval 0.6 to 1.5), which is equal to the null value, indicating no (neither a positive nor a negative) association at all. Are there any other epidemiological evidences besides a previous finding of an association between bladder cancer and proximity to known arsenic-contaminated drinking water wells using the similar study design (Reference 22)?
As the reviewer indicated, few previous studies have investigated the relationship between arsenic exposures and pancreatic cancer risk. There was one published meta-analysis which indicated no associations between occupational arsenic exposures and pancreatic carcinogenicity (1.0; 0.6 to 1.5) (Ojajärvi et al 2000). As discussed earlier, we have now added other epidemiological evidence to the Background section.

2. A brief description of the cancer registry should be provided, so that the readers can learn about the strengths and limitations of the data.

In response to reviewer comments, we have added a brief description of the cancer registry to the Methods section.

3. The logistic regression model used to generate the major results (Table 2) should be given in mathematical formula. The dependent variable was described as “a patient with pancreatic cancer living in a cluster versus being diagnosed outside of a cluster,” which is confusing because logistic regressions generally model the probability of an event occurring versus that of an event not occurring. Since the authors used residence at the time of diagnosis as the indicator, they seemed to model the probability of a patient living in a cluster versus living outside of a cluster. A more direct approach is to model the probability of a disease occurring in a participant versus not occurring, such as in a case-control study. There is a gap between a patient occurring and a patient being diagnosed in a cluster. The authors should discuss briefly the issues involved in extrapolating the model used in this study to the model corresponding to the research question directly.

In response to reviewer comments, we have changed the phrase “a patient with pancreatic cancer living in a cluster versus being diagnosed outside of a cluster,” to “a patient with pancreatic cancer living in a cluster versus being diagnosed not in a cluster.”

The unit of analysis for this study was the block group. The patient level data from Florida's statewide, population-based registry were aggregated by race and age group at the block group level. The aggregated patient data served as the numerators, and the aggregated census population (also stratified by race and age group) as the denominators for the spatial analysis. The results of the spatial analysis identified block groups of higher-than-expected pancreatic cancer incidence. Logistic regression analysis, which can be used to model binary outcomes, was used to document the probability of a block group having a higher-than-expected incidence of pancreatic cancer. Of note, the words “neighborhoods” and “area” used throughout this paper are intended to be synonymous with the term “block group(s).”

4. Given that most studies which evaluated the associations between arsenic ingestion and the whole spectrum of cancers did not observe such an association on pancreatic cancer, the authors should discuss other potential explanations for the association observed in this study.

We have revised the Discussion section to address this important suggestion. The etiology of pancreatic cancer is largely unknown after many decades of research. Smoking is one of the few factors found to be consistently associated with pancreatic cancer. Smoking could be one of the potential factors that explains some of the pancreatic cancer clusters. It was estimated that smoking accounts for 20-25% of all pancreatic tumors. Previously studies demonstrated that smokers have 1.5-3 times increased risk of developing pancreatic cancer. In animal models, it was reported that low concentration of arsenic exposures alone did not cause skin cancers.
Synergistic effects of arsenic and other carcinogens (such as smoking and ultraviolet irradiation) are suggested to enhance the tumorigenicity (Klein et al, 2007).

Drinking water arsenic exposure has been associated with increased bladder cancer susceptibility. The findings of an increased bladder cancer risk among smokers but not among nonsmokers by Steinmaus et al (2006), Karagas et al (2004), suggest that the ingestion of low to moderate arsenic levels may affect bladder cancer incidence, and that cigarette smoking may act as a co-carcinogen as a DNA damaging agent.

5. The biological plausibility of an association between arsenic and pancreatic cancer should be discussed further.

Arsenic is an established human carcinogen. However, the mechanism(s) of arsenic carcinogenesis are still unclear because there are few satisfactory animal models for arsenic-induced carcinogenesis. The biological plausibility has been included in the Discussion section.

6. In comparison with people who never smoke, current smokers had a higher risk (OR=1.1) whereas former smokers had a lower risk (OR=0.9), both with marginal statistical significance (95% CI with 1.0 as the upper or lower bound). Please discuss it.

As indicated above, smoking is one of the few factors found to be consistently associated with pancreatic cancer. Therefore, smoking cessation would reduce the risk. Our data indicated such trends. However, over one fourth of patients (26.9%) did not report their smoking status. The misclassification on this important risk factor is likely present; this is noted as a study limitation.

Minor Essential Revisions
1. Report the percentages in Table 1 to the same number of digits below the decimal point.

In response to reviewer comments, Table 1 has been revised.

2. Report the odds ratios in Table 2 to the same number of digits below the decimal point.

In response to reviewer comments, Table 2 has been revised.

3. Please indicate in the legend the meaning of green spots in Figure 1.

In response to reviewer comments, the following title has been added:

Figure 1. Pancreas Cancer Clusters overlaid with Arsenic Contaminated Wells in Florida 1998-2002 (green circles represent arsenic contaminated wells, and red areas represent higher than expected pancreatic cancer clusters)

Reviewer's report 3
Title: Pancreatic Cancer Clusters and Arsenic-Contaminated Drinking Water Wells in Florida
Version: 1 Date: 26 February 2012
Reviewer: Melissa Slotnick
Reviewer's report:
Major Revisions
This manuscript is fairly well-written and reads easily, and the methods are well documented. However, I am hesitant to recommend this paper for publication based on many weaknesses in the methodology; the fact that a fairly substantial odds ratio is reported seems unusual and I suspect it’s artificial. It would be unusual to see such strong results for an ecological study when the exposure level is relatively low (10 ppb, but not exactly specified) and the exposure-disease relationship has not been previously demonstrated. Specifically, because this is an ecologic study, no individual-level data on exposure were collected, resulting in a high degree of exposure misclassification (especially over the lifetime). Because an individual lives near a contaminated well does not mean that they are exposed to that drinking water. In fact, if many of the contaminated wells were in urban areas it might be likely that the patients were drinking city water as opposed to private well water. The results may have been more convincing if a stratification of exposure supported the association. I would be surprised to see a true association for 10ppb, but might be more convinced if the exposures were much higher. Furthermore, lifetime exposure was in no way addressed or calculated. In a state like FL where a high percentage of the population may have migrated there later in life, residential stability must at least be considered. There is the potential for geographic bias, which the authors touch upon, but which seems significant. If the wells sampled were only sampled based on complaints or industrial contamination, it seems as though there would be a disproportionate number of wells sampled in urban areas. If this is the case, you may see false clustering in high population areas. This potential bias deserves further analyses and exploration. Lastly, there is little support throughout the document for the suspected relationship between pancreatic cancer and arsenic exposure. The discussion of this association is very general and unconvincing.

More of an argument needs to be developed throughout the manuscript, and the reader is left feeling as though this is a very exploratory analysis. If the authors wish to examine the association further, I would suggest fully assessing the geographic bias, working towards individual-level exposure estimates through geographic modeling and model validation using random well water sampling. Most importantly, the source of drinking water needs to be incorporated into the analyses, even if an attempt is made based by municipality boundaries.

With regards to the limitations to our study noted by the Reviewer above:

a) The exposure level is relatively low (10 ppb) and the exposure-disease relationship has not been previously demonstrated. In this ecologic study, the arsenic exposure collected was not individual-level data resulting in potential exposure misclassification. A few of previous studies have indicated a low-moderate arsenic exposure associated with cancer risk, but for other types of cancers than pancreatic cancer such as bladder cancer. However, pancreatic cancer is a relatively rare cancer and prior studies have not focused on its possible association with arsenic exposure. We believe that our ecological study is hypothesis generating with respect to a possible link between the proximity to arsenic contaminated drinking water wells and pancreatic cancer clusters which warrants further investigation. Our enhanced discussion section now puts the results of this ecologic analysis in this context (including the limitations of such analyses).

b) Little is known for the relationship between pancreatic cancer and arsenic exposure. There was only one study available in the literature that showed a non-significant finding. Per reviewers’ suggestion, we added the possible biological plausibility of an association between arsenic and pancreatic cancer in the revised Discussion section.
c) We agree that full assessment of individual-level exposure using random well water sampling would be needed as the next step in pursuing this possible link. And importantly, the source of drinking water needs to be incorporated into the analyses. Future case-control studies are required to investigate the effect of arsenic exposure on pancreatic cancer risk, and its interactions with other co-carcinogens such as smoking in the development of pancreatic cancer.

**Minor Revisions**

**Abstract**
- concentration of arsenic should be defined

In response to reviewer comments, the abstract has been modified accordingly.

**Background**
- original articles should be cited when discussing association between pancreatic cancer and arsenic
- the significant findings seem like an afterthought give the way the last paragraph is written

In response to reviewer comments, we have modified the manuscript so that the original articles are cited.

**Methods**
- Should mention population calculation methods here as were reported in limitations. Why was the population multiplied by 5? Is this a standard way of extrapolating population data?

Block group level population was downloaded from the U.S. 2000 Census Bureau Web site. The population data were stratified at the block group level by gender, race, and age group. There are 9,112 block groups in Florida. The individual block group annual 2000 population estimates were multiplied by five to provide 5-year sex/race/age–specific denominators for the 1998 to 2002 study period.

- Why was the 3-mile distance selected? What happens if you change the distance slightly? Do the results hold?

We used the cut points: >3 miles, 1-3 miles and <=1 mile for the analyses. We performed the analyses using another cut point, (i.e. 4 miles) with similar results (data not presented). Cases living within 1 mile of known arsenic-contaminated wells were significantly more likely to be diagnosed within a cluster of pancreatic cancers relative to cases living more than 4 miles from known sites (Odds Ratio= 2.0; 95% CI=1.59-2.52).

**Discussion**
- see major revisions
- I’m not sure the statement “… well water may serve as a proxy for environmental arsenic contamination in the soil and air” is true. Citations should be added.

If arsenic is in the soil and air, then arsenic could be dissolved from the arsenic-bearing soil and air into the ground water (particularly given the heavy rainfall experienced in Florida). Therefore, well water may serve as a proxy for environmental arsenic contamination in the soil and even possibly air.
Figures and Tables
- Because of the geographic nature of analysis, I would like to see more figures.

The figure in this manuscript presents information of arsenic contaminated wells and the pancreatic clusters needed for this manuscript.

The Figure is lacking and needs more description. Is this showing all of the wells?

In response to reviewer comments, the title of the figure has been changed in the revised manuscript. The data show all the known arsenic contaminated wells based on non systematic testing at the levels described in the manuscript.