Letters to the Editor

**RE: “ELEVATED LUNG CANCER IN YOUNGER ADULTS AND LOW CONCENTRATIONS OF ARSENIC IN WATER”**

We read with interest the study by Steinmaus et al. (1), in which they found an association between lung cancer and arsenic concentrations less than 100 µg/L in drinking water. The authors used a matched case-control design to study drinking water in 2 regions in Chile. However, we are concerned about the methodology and the conclusions drawn. Our first concern is with selection bias; cases were ascertained from all pathologists, hospitals, and radiologists in the area, but it was unclear whether the cases constituted all lung cancer cases. Our second concern is with the study base and the possibility that cases and controls were chosen from dissimilar sampling frames. Cases had been diagnosed with lung cancer, but controls were free from lung, bladder, and kidney cancers. Moreover, proxy interviews were conducted with 54% of cases and only 7% of controls, which increased the likelihood of information bias due to differences in data quality (2, 3). Our third concern is with the statistical analysis itself. Because the only statistically significant association between arsenic and lung cancer was for the 40-year lag time, a better description of the analysis is required to understand that all persons who contributed to this analysis were at least 40 years of age. It would also be helpful to present a clear statement of the study design (the study was not a matched case-control study) that would explain the choice to use unconditional logistic regression modeling (4). Lastly, we are concerned that the title of the article has the potential to raise the alarm of a new health risk from local drinking water. Exposure histories were developed using arsenic levels in public drinking water from 1930–1994, residential history (all subjects), and reported water intake currently and 20 years prior (live subjects). Two exposure measures were used—arsenic level (µg/L) (all subjects) and arsenic intake (µg/day) (live subjects). Analyses were conducted in approximate exposure tertiles and with a 5-, 20-, or 40-year lag.

Steinmaus et al. (1) found no significant association with 5-, 20-, or 40-year lags in analysis by arsenic level (Web Table 4 of their article) or analysis by intake (Web Table 3 of their article). A significant association was found only in the combined analysis in which live subjects were categorized by tertiles of arsenic intake and deceased subjects were categorized by tertiles of arsenic level and in the analysis in which exposures were lagged by 40 years (Table 2 vs. Web Table 2 of Steinmaus et al. (1)) and either unadjusted or partially adjusted but not fully adjusted (Web Figure 2 of Steinmaus et al. (1)).

The study group in the combined analysis comprised 2 groups—the 42 cases and 269 controls who were alive at time of interview and were categorized by tertile of arsenic intake and the remaining 50 cases and 19 controls who were deceased and categorized by tertile of arsenic level. Tertiles ceased and categorized by tertile of arsenic level. Tertiles

**ACKNOWLEDGMENTS**

Conflict of interest: none declared.

**REFERENCES**


Zeinab F. N. Slim and Maida J. Sewitch
(e-mail: maida.sewitch@mcgill.ca)
1 Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
2 Department of Medicine, McGill University, Montreal, Quebec, Canada

of intake were not equivalent to tertiles of exposure level. Tertiles were expected to each contain one-third of the controls. However, the tertiles of controls for live cases in the analyses that were lagged 40 years were biased downward (the first intake tertile included 38% and the third intake tertile included 28%; Web Table 3 of Steinmaus et al. (1) and Web Table 1, available at http://aje.oxfordjournals.org/), whereas the tertiles of controls for deceased subjects in the analyses that were lagged 40 years were biased upward (the first exposure level tertile included 29% and the third exposure level tertile included 37%; Web Table 4 of Steinmaus et al. (1) and Web Table 1). Further, because the preinterview mortality rate was markedly higher for the lung cancer cases (50 of 92; 54.3%) than for the controls (19 of 288; 6.6%), there were few deceased controls. Most of the cases (n = 50) but few of the controls (n = 19) had entered the combined analysis after the upward biased controls, whereas the great majority of the controls (269 of 288; 93.4%) followed the downward biased controls. In the combined analysis, the deceased cases were essentially compared with the distribution of the live controls.

One method (Web Appendix) for taking this imbalance into account would be to have the controls enter the combined analyses in the same proportion as do the cases. Because 42 of the 92 cases (45.7%) entered the combined analysis by intake tertile, 45.7% of the 288 controls (n = 131) should have entered the combined analysis by intake tertiles. Similarly, because 50 of 92 cases (54.3%) entered by arsenic level tertile, so should have 54.3% of the 288 controls (n = 157). The intertertile distributions of each set of the controls should be the same as the group from which they came. In our analyses, the unadjusted odds ratio (third tertile vs. first tertile) for the 40-year lag was 1.63 (95% confidence interval: 0.90, 2.94) (Web Table 1) rather than 1.90 (90% confidence interval: 1.13, 3.13) (Table 2 of Steinmaus et al. (1)); for the 5-year lag, it was 0.95 (95% confidence interval: 0.55, 1.65) (Web Table 2) rather than 1.23 (90% confidence interval: 0.77, 1.97) (Web Table 3 of Steinmaus et al. (1)). Thus, when using appropriately balanced controls, there was no significant association (P = 0.14) between lung cancer and arsenic levels below 100 µg/L in drinking water. The rationale for a 40-year lag was clear in the earlier paper by Steinmaus et al. (2) which included very high (860 µg/L) exposures that had ended 40 years earlier. However, in their more recent paper (1), it is not clear for the low-level (1–60 µg/L) exposures, which remained constant from 1930 through 1994.

Further, the analysis with a 40-year lag excluded the more recent 40 years of arsenic intake, which appears to have been twice as great (third tertile cutpoint >106.4 µg/day) (Web Table 3 of Steinmaus et al. (1)) as that of the 40-year lagged intakes (third tertile cutpoint >63.6 µg/L) (Web Table 3 of Steinmaus et al. (1)). In conclusion, the reported significant association seems to be the consequence of having used unbalanced controls in the analysis.

Acknowledgments

Conflict of interest: none declared.

References


Steven H. Lamm1,2,3, Nana Ama Afari-Dwamena1, Hamid Ferdosi1,4, and Lu Qian1,5 (e-mail: Steve@ceoh.com)
1 Center for Epidemiology and Environmental Health, Consultants in Epidemiology and Occupational Health, Washington, DC
2 Department of Health Policy and Management, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD
3 Department of Pediatrics, Georgetown University School of Medicine, Washington, DC
4 Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, Washington, DC
5 Department of Mathematics and Statistics, American University, Washington, DC

DOI: 10.1093/aje/kvw118; Advance Access publication: May 29, 2015

© The Author 2015. Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

Three Authors Reply

We agree with the overall concept that we believe Slim and Sewitch (1) are trying to express: Important novel findings like ours should be critically reviewed and, at least initially, interpreted cautiously. Notably, our study was the first with individual-based data on lifetime exposures to identify an association between arsenic concentrations below 100 µg/L in drinking water and increased risks of lung cancer (2). Given this novelty, we believe it is also important to note that our findings met several of the criteria commonly used to evaluate causality (3). For example, we found evidence of dose-response relationships in several of our analyses. We also found very low P values, which suggests that several of our findings are unlikely to be due to chance. We also reported evidence that confounding by smoking, diet, occupation, or other major determinants of lung cancer risk did not cause our results. With regard to the causal criteria of consistency and biologic plausibility, we cited data showing that arsenic reaches our target organ site (the lung) and that it causes...