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Comments on the Measurement of Lung Cancer Tumor Markers in Workers of a Glass Wool Company

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Dear Editor,

We read with interest the article on the measurement of lung cancer tumor markers in a group of workers exposed to respirable synthetic vitreous fiber (SVF) and dust, recently published in the *IJOEM*.[1] The authors report on the relationship between exposure to respirable SVF and serum levels of two biomarkers implicated in lung cancer, suggesting that elevations in these biomarkers support a relationship between SVF exposure and lung cancer. However, several methodological and interpretational issues in their evaluation call the authors' conclusions into question. For example, the authors excluded smokers only from the study's control group, thus any effects of smoking would differentially influence any statistical comparisons made between the cases and controls. Moreover, the authors' basic two-sample statistical comparisons did not enable adjustment for the potential confounding factors including known risk factors for cancer such as age, alcohol use, and family history. In the Introduction of their paper, the authors also grossly misinterpreted the overwhelmingly negative scientific literature as providing evidence of a positive association between exposure to SVF and several lung diseases including lung cancer and pleural mesothelioma.

In addition to methodological flaws, the authors misrepresented the meaningfulness of the reported elevations in biomarker levels. The authors suggest that these biomarkers, carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA 21-1), are useful diagnostic and prognostic tools for lung cancer. Based on the literature cited, it is clear that neither CEA nor CYFRA 21-1 consistently displays diagnostic value.[2-3] Furthermore, these biomarkers are not specific to lung cancer. Nearly all of the observed associations reported in this study[1] attenuate after excluding smokers from the analysis and are no longer statistically significant. The main conclusion of the Abtahi, *et al*, study that remained statistically significant following the exclusion of smokers, is based on findings from a stratified analysis comparing workers by duration of employment (greater *vs* less than nine years). Age is a known prognostic factor for lung cancer and a possible source of heterogeneity in biomarker levels.[4-5] Therefore, the reported higher levels of CYFRA 21-1 among workers employed by the glass fiber manufacturing facility for greater than nine years may simply be due to the older ages among those with longer durations of employment. Lastly, for CEA and CYFRA 21-1 to have a prognostic value, both require concentrations in the blood higher than those reported in this cohort. Therefore, Abtahi, *et al*, relied on premises not supported by the scientific literature, that these biomarkers, at concentrations similar to those present in this cohort, have both diagnostic and prognostic values for prediction of lung cancer.

In conclusion, the recommendations set forth by Abtahi, *et al*, are not evidence-based. Neither the methodology nor the interpretation provided supports the authors' conclusions that their study suggests an increased risk of lung cancer in SVF-exposed workers. Therefore, their recommendation to move workers to areas with non-detectable concentrations of SVF is unwarranted based on their work.

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Authors' Reply

Dear Editor,

We would like to thank Marsh, *et al*, for their comments. In our study, we observed that long-term exposure to respirable SVF and dust is associated with higher serum levels of CYFRA 21-1, an indicator of any lung injury including [but not specific to] lung cancer.[1] Smokers were excluded from the control group; however, 13 out of 145 individuals in the case group were smoker. To eliminate this confounding variable, we excluded the smokers from our cases and re-ran the statistical analyses. However, the results had been much more reliable if we would have matched our cases and controls for smoking. The cases and controls we selected were age- and sex-matched. None of the cases and controls was alcohol users. Nor did they have history of lung cancer in their family members. In the Introduction section of our article, we clearly state that SVF is classified as a group 3 agent (not carcinogen to humans) by IARC.[1] Some sub-groups of SVF (including refractory ceramic fibers) are, however, considered carcinogen.[2] Nonetheless, there is inadequate evidence for human carcinogenicity of other subtypes.

Our study was cross-sectional and mostly observational rather than analytical. We have reported what was observed. The definite worthiness of the serum markers will be determined in long-term follow-up of participants. Regarding the cited articles and the values of CEA and CYFRA 21-1, the articles mostly discuss the prognostic value of these markers (as mentioned in our article), not their diagnostic value. As we have mentioned in our article, elevation of these markers has been observed in several disease conditions including chronic airway inflammatory diseases, chest trauma, and acute respiratory disease syndrome (ARDS);[3-4] they are not specific for lung cancer. In our study, we observed that smoking has a considerable association with serum CYFRA 21-1 level. After excluding smokers, the obtained p value still remained near significant (p=0.056). We believe that larger sample sizes could help to gain more powerful insights into these findings.

Regarding the comment on the age difference between workers with work experience greater *vs* less than nine years, we agree with Marsh, *et al*; the two groups were not age-matched (p=0.03). We would like to point out once again that our study was a cross-sectional (not a cohort) study and that there is no sure way to draw any cause-and-effect relationship solely based on our observations. There could be other possible explanations for our observations; these serum markers, referred to as lung cancer markers, may elevate in many conditions.

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