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High incidence of brain and other nervous system cancer identified in two mining counties, 2001-2015: insufficient evidence to support association with heavy metal exposure

To the Editor,

In "High incidence of brain and other nervous system cancer identified in two mining counties, 2001–2015 Zhang et al. (2020) reported high incidence of brain and other nervous system cancers in two of eighteen age groups (0–4 and 30–34 years) in two Montana counties with historic mining (Deer Lodge and Silver Bow) compared to the rest of the state. Age-specific cancer rates had not been previously reported in these communities and these data could inform public health officials where to target interventions to decrease the burden of disease in the community. However, the article asserts that elevated brain cancer incidence in this population was due to community exposure to heavy metals. The authors came to this conclusion without adequately supporting the rationale behind their a priori hypothesis, or without providing sound toxicological information or a proper quantitative exposure assessment. Most importantly, the findings of Zhang et al. (2020) are overstated, and can cause undue anxiety and confusion regarding real, rather than perceived, health threats to the community. In this letter, we further explain what we view as problematic with these aspects of the Zhang et al. (2020) paper.

1. Zhang et al. (2020) does not provide an accurate summary of the literature to support the study rationale.

The authors state that residents in the two counties studied have historic and current exposure to eight metals: arsenic, cadmium, copper, iron, lead, manganese, molybdenum, and zinc. The stated rationale for their a priori hypothesis was based on incorrectly linking the neurotoxic impact of exposure to the metals in the community environment and the development of cancer in young children. First, there is no basis provided for making a leap from neurotoxic effects of some of the metals – most notably arsenic, copper, and manganese – to brain and other central nervous system (CNS) cancers in young children.

Second, of the metals classified as either carcinogenic to humans (arsenic and cadmium) or probably carcinogenic to humans (lead and molybdenum trioxide), only lead has been associated with brain cancer (International Agency for Research on Cancer [IARC], 2012a, 2012b, 2006, 2018; Agency for Toxic Substances and Disease Registry [ATSDR] 2020). Molybdenum sulfate, not molybdenum trioxide, is present in these counties. The association between lead and brain cancer is based on animal and occupational studies with high elevated blood lead levels (≥29.0 μg/dL) (IARC, 2006; ATSDR, 2020). IARC notes studies linking lead with brain and other cancers have yielded inconsistent cancer risk results, with interpretations being confounded by factors such as smoking, family history, and occupational exposures to other carcinogens (ATSDR, 2020; IARC, 2006).

Occupational studies demonstrated an increased risk of lung cancer in workers exposed to high levels of arsenic and cadmium (ATSDR, 2012; IARC, 2012a, 2012b). IARC also cited epidemiological studies conducted in populations where high levels of naturally occurring arsenic are found in drinking water. Evidence from these studies show an increased risk of developing lung, bladder, kidney, and skin cancers (IARC, 2012a). Neither IARC nor ATSDR discuss any association between arsenic or cadmium and brain or other CNS cancers. The other four metals (copper, iron, manganese, and zinc) have either not been evaluated or are not classifiable as to their carcinogenicity to humans, according to IARC.

We identified several examples where the papers the authors cited were not accurately summarized. The authors cited Jaishankar et al. (2014) to establish that cadmium is associated with the epigenetics of brain tumors and Mates et al. (2009) to show that data suggest lead, arsenic, cadmium, and other metals contribute to the formation of radicals in the brain. However, neither paper substantiate such statements. Jaishankar et al. (2014) is a review article that does not mention epigenetics, brain tumors, nor discuss cadmium's role in carcinogenic processes. Mates et al. (2009) is a review of the role of natural compounds in antioxidant functions; the role of metals, including lead, arsenic, or cadmium, are not mentioned once in the paper.

Similarly, Zhang et al. (2020) state that occupational studies document the association of cadmium, chromium, and lead exposure and brain and other CNS cancers. However, the citations provided do not support such associations. Schlehofer et al. (2005) and Wesseling et al. (2002), both cited by Zhang et al. (2020), indicate no statistically elevated incidences of brain and other CNS cancers among metal workers or workers exposed to high levels of chromium, lead, or cadmium. Another reference, Waisberg et al. (2003), is a review article about the cellular pathways and mechanisms by which cadmium may be carcinogenic but does not mention the role of cadmium in brain or other CNS cancers.

2. The study population's exposure potential is neither risk-based nor accurately characterized.

Zhang et al. (2020) crudely measured exposure to heavy metals by the presence of a mining Superfund site in each of the two counties studied. They asserted that ongoing exposure to heavy metals is widespread, uniform, and at levels known to cause adverse human health effects throughout Deer Lodge and Silver Bow counties. The authors also stated that risk to the communities in the counties was "substantial" and "extremely high." We observe no evidence to support these conclusions in the references Zhang et al. (2020) cited, nor did they present a quantitative exposure and risk assessment to substantiate their claims. Misclassification of heavy metals exposure in this way severely threatens the study's internal validity.

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For example, the authors cited Hailer et al. (2017) to support their assertion that “known” exposures are ongoing; however, we do not agree that the findings in this paper substantiate Zhang et al.’s claims. In fact, the mean and median air and soil concentrations of the metals reported by Hailer et al. (2017) were all below conservative health-based comparison values (CVs) (i.e., ATSDR minimum risk levels and EPA regional screening levels) or Montana background soil concentrations (for arsenic and manganese only). The CVs apply to long-term chronic exposures (i.e., $\geq$ 1 year) and are geared towards protecting public health, including the most sensitive populations (e.g., people with asthma, children, and the elderly).

Zhang et al. (2020) also cited the U.S. Environmental Protection Agency (USEPA) websites (USEPA, 2018, 2019) for data which document “known” exposures. These sites are the homepages for the two Superfund sites in each community and do not directly present data. We, respectfully, request the authors specify which EPA data indicate ongoing exposure to heavy metals at concentrations known to cause adverse health effects to humans.

Finally, determining whether an exposure potential even exists requires a comprehensive dataset and a site-specific analysis of potentially exposed populations, exposure pathways, how often and how long the populations may be exposed, routes of exposure, concurrent chemical/metal exposures, representative exposure points, and metal bioavailability. None of these data or the usual exposure assessment calculations are presented in the Zhang et al. (2020) paper.

3. The interpretation of findings were overstated given the data presented.

Zhang et al. (2020) was an ecological study of a relatively rare disease over a large geographic area (approximately 1460 miles^2) over a long time period (15 years). Evaluation of a small number of events subjects the analysis to great variability, the observation of extreme rates, and spatial and temporal autocorrelation problems resulting in the risk of a type I error (Morgenstern, 2008).

In this analysis, there were a total of 58 brain and other CNS cancer case subjects and the number of cases in each of the eighteen age groups ranged from zero to eight. The age-specific Incidence Rate Ratios (IRR) among the age groups reported in Figure 2 had very large confidence intervals (e.g., adjusted IRR 95% confidence interval for age group 0–4 years was 2.32 to 17.02). The age-specific IRR were adjusted using a modeling approach, presumably to correct for spatial and temporal autocorrelation issues. We question whether such a statistical approach was appropriate given the small number of events in each of the age groups evaluated. The Centers for Disease Control and Prevention recommends suppression of cancer rates based on fewer than 16 cases because they are deemed to be unstable (CDC, 2019).

Zhang et al. (2020) emphasized that their study’s main findings of elevated brain cancer among young children, 0–4 years, and adults, 30–34 years, were attributable to ongoing metal contamination in the two counties. However, interpretation of these findings in such a way does not make biologic sense. If there were a historic or current exposure pathway(s) that increased the risk of brain cancer, why were the elevated rates isolated to young children and young adults? Why do we not also observe elevated brain cancer among the age groups between 5 and 29 years? There were zero cases of brain cancer among those aged 10 to 24 years during the study period. If exposure to heavy metals played a causative role in these brain cancers, why did the study not observe elevated brain cancers among older adults?

There may have been exposure to a higher concentration of heavy metals among community members in these counties before Superfund cleanup activities were initiated in 1987 and among historic mine workers. However, the data do not show elevated rates of brain and other CNS cancers among county residents aged 35 years and older compared to the rest of Montana. Given that the medical community does not have a firm understanding of the cause or causes of brain cancer, even if the curious findings in two of eighteen age groups were valid, it would be prudent to examine a variety of hypotheses to explain the observations of this study.

The authors did acknowledge that further research is needed including “residential history, exposure to radiation, family history of conditions associated with brain and nervous system cancer and other known risk factors.” The authors correctly stated that their data source, the Montana Central Tumor Registry, does not collect information about residential history or individual exposures. Yet the authors go on to state “…nonetheless, the risk for higher incidence of diseases associated with metal exposure to the residents of the two past and present mining counties is substantial…” This study provided no data regarding metal exposure among the study population, rather the authors assumed it was happening. They concluded by generalizing the study’s findings to “the millions of Americans who live near a Superfund designated area or active mining site…,” which is wholly inappropriate given the data presented.

In summary, we believe that the authors’ conclusions are not supported by the data presented. This ecological study provided insufficient evidence to support the study rationale and hypothesis, inaccurately characterized the study population’s exposure risk, and inappropriately overstated the findings of this study.

As public health officials at the Montana Department of Public Health and Human Services, we are deeply concerned that these overstated conclusions will have immediate and long-term negative consequences for these two communities. The immediate consequence was sensationalistic local media coverage of this article’s content that implicated metal exposure is ongoing and brain cancer is the result of this exposure (DeLeon, 2020). This inaccurate presentation of risks stimulated anxiety and confusion regarding real, in contrast to perceived, health threats to the community. Legitimate risk communication to the public and decision makers is greatly challenged when misinformation is published in authoritative sources, such as peer-reviewed journals. The bottom line is that the cause or causes of brain cancer are unknown; and we do not know why elevated brain cancer was observed among only two of eighteen age groups in Deer Lodge and Silver Bow counties during this 15-year study period.

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