November 3rd, 2021

Dear Prof. Lash,

On behalf of my coauthors, I am submitting the manuscript entitled “Towards a clearer causal question underlying the association between cancer and dementia?”, to be considered for publication within the category of Original Article, at the corresponding journal.

Over the last decades, several observational studies have studied the association between cancer and dementia incidence. Given that most results found an inverse association, several explanations have been proposed, from biological mechanisms to bias. However, no study has questioned why “cancer diagnosis” or “history of cancer” is an interesting exposure in the first place. To illustrate the complexities of inferring hypothetical or available cancer treatments’ effects on dementia from the observed cancer-dementia association, we focus on a specific question conceptualizing the Pin1 enzyme as the target of intervention. To explore how we might learn about this effect using real-world data on cancer and dementia, we progressively build a causal directed acyclic graph and outline the needed assumptions and potential sources of bias. We exemplify how these translate into the analytic decisions using data collected from the Rotterdam Study, a population-based cohort study.

This case study is just one example of how observed associations between two diseases or health states may be disentangled to more transparently unveil possible mechanisms (and sources of bias). We hope our work encourages researchers to be explicit about the causal question of interest to maximize what we can learn given available data.

All authors have reviewed and approved the content of the manuscript. This manuscript has not been published previously in any journal  and is not under revision at any other journal.

We look forward to your thoughts, and thank you very much for your consideration.

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