Correspondence

# Reply to "Noncancer comparators in cancer survivorship studies"

We thank Chubak and Lund for their thoughtful response to our review article,[1] which builds on our discussion of noncancer comparators in cancer survivorship research to include situations in which noncancer comparators are not necessary or appropriate. We agree wholeheartedly with their points, especially the idea that the selection and identification of the relevant comparator group should be driven by the research question. Our review article is focused on etiologic research questions about how the experience of cancer may alter functional outcomes over and above chronological aging alone, for which Chubak and Lund agree that noncancer comparators are usually appropriate. Chubak and Lund describe 2 additional situations in which noncancer comparators are appropriate in cancer survivorship research, namely studies of the effects of cancer treatments on aging-relevant outcomes and whether health promotion or clinical recommendations should differ for older adults on the basis of their cancer history.

A strategy to allow the research question to drive the selection of the most appropriate comparator group is consideration of the counterfactual outcomes for cancer survivors considered to be "treated" or "exposed" had they not experienced such treatment or exposure.[2,3] Chubak and Lund are correct that for studies aiming to investigate the effects of a specific cancer treatment regimen on subsequent aging outcomes, the appropriate comparator group would be patients who receive an alternative treatment regimen. Cancer-free comparators would not be appropriate for this comparison because they are not eligible to receive cancer treatments, and thus their outcomes do not represent the counterfactual outcomes that the treated patients would have experienced had they not been treated. This logic is formalized in the epidemiological counterfactual framework, which can be used to help investigators to select the most appropriate comparator group for a range of questions in observational cancer survivorship research.[2,3] Counterfactual thinking helps us as investigators to improve the validity of causal inference in observational research by helping us to plan studies with treatment or exposure and comparator groups that are as exchangeable as possible in all respects except for the treatment or exposure of interest. This framework also helps us to identify confounding variables to be adjusted for in statistical modeling when this exchangeability is not possible through comparator group selection alone, as is almost always the case in observational research. We thank Chubak and Lund again for their insightful response to our article, and we hope that this dialogue will be valuable for future investigators planning observational studies of cancer survivorship and aging.

## CONFLICT OF INTEREST DISCLOSURES

Katrina R. Ellis reports honoraria from the University of Michigan School of Social Work (the Winkleman Lecture), a collaborator contract with the American Cancer Society for analysis of American Cancer Society data (nonpaid), and service on the professional advisory board of the Cancer Support Community of Ann Arbor (nonpaid) outside the submitted work. Lauren P. Wallner reports a supplement off a National Cancer Institute Cancer Center Core Grant (P30AG012846) as well as an American Cancer Society Research Scholar Grant (RSG-19-015), service on the data safety and monitoring board as chair for the Engaging Primary Care in Cancer Survivorship study (R01CA249419 from the National Cancer Institute), and travel support for a plenary session at the American Community Cancer Centers Annual Meeting outside the submitted work. The other authors made no disclosures.

## REFERENCES

1. Kobayashi LC, Westrick AC, Doshi A, et al. New directions in cancer and aging: state of the science and recommendations to improve the quality of evidence on the intersection of aging with cancer control. *Cancer*. 2022;128:1730-1737. doi:10.1002/cncr.34143
2. Höfler M. Causal inference based on counterfactuals. *BMC Med Res Methodol*. 2005;5:28. doi:10.1186/1471-2288-5-28
3. Bours MJL. A nontechnical explanation of the counterfactual definition of confounding. *J Clin Epidemiol*. 2020;121:91-100. doi:10.1016/j.jclinepi.2020.01.021

Lindsay C. Kobayashi, PhD [iD]
*Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan*
*Cancer Control and Population Sciences Program, Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan*

Ashly C. Westrick, PhD
*Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan*

Aalap Doshi, MS
*Michigan Institute for Clinical and Health Research, University of Michigan, Ann Arbor, Michigan*

Katrina R. Ellis, PhD

*Cancer Control and Population Sciences Program, Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan*
*University of Michigan School of Social Work, Ann Arbor, Michigan*

Carly R. Jones, BSc

*University of Michigan School of Social Work, Ann Arbor, Michigan*

Elizabeth LaPensee, PhD

*Michigan Institute for Clinical and Health Research, University of Michigan, Ann Arbor, Michigan*

Alison M. Mondul, PhD iD

*Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan*
*Cancer Control and Population Sciences Program, Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan*

Megan A. Mullins, PhD iD

*Cancer Control and Population Sciences Program, Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan*
*Center for Improving Patient and Population Health, University of Michigan, Ann Arbor, Michigan*

Lauren P. Wallner, PhD iD

*Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan*
*Cancer Control and Population Sciences Program, Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan*
*Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan*