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Reply to "Non-cancer comparators in cancer survivorship studies"

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

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.[3,4] 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.[1] Cancer-free comparators would not be appropriate for this comparison, since 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 select the most appropriate comparator group for a range of questions in observational cancer survivorship research.[3,4] 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 hope

that this dialogue will be valuable for future investigators planning observational studies of cancer survivorship and aging.

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