RE: PARENTAL AGE AT BIRTH AND RISK OF HEMATOLOGICAL MALIGNANCIES IN OLDER ADULTS

We read with interest the study by Teras et al. (1) in which they found a positive association between advanced paternal age and the risk of hematological malignancies at 40 years of age or older among offspring with no siblings but no overall association. The mechanism proposed to explain the subgroup-specific association (1), namely the joint effects of paternal age (through genetic and epigenetic changes) and dysregulated immune function caused by the early-childhood environment, has some support in the literature (1, 2). We would like to ask for clarification about certain details of the study design and analysis that might have biased the association that they found, specifically, the late start of follow-up, exclusion of prevalent cancer cases, and the subgroup analysis of participants with no siblings.

First, selection bias potentially affected the association of paternal age with hematological malignancies in older age because paternal age could be related to cancer-free survival to middle age. The evidence that suggests a high risk of adverse health effects associated with old parental age (1) could create selective loss of offspring by paternal age. A sensitivity analysis using external data to examine the association of paternal age with cancer-free survival rates until older age could help in assessing the extent of such selection bias. It would also be worthwhile to report the paternal age gradient among the 12% of participants in the Cancer Prevention Study-II Nutrition Cohort who were excluded because of a history of cancer and in particular because of a history of hematological malignancies, as well as among the subgroup with no siblings (3).

Second, restricting the analysis to participants with no siblings might have caused further selection bias by inducing a biased association between paternal age and socioeconomic status in childhood. Using directed acyclic graph terminology, it resulted in collider stratification bias (4), in which conditioning on no siblings induces stratum-specific associations of paternal age and childhood socioeconomic position (Figure 1). Many participants were born during the Great Depression (1929–1939), given the average age of 63 years in 1992–1993. Widespread economic hardship reduced the fertility rate (5) and increased the number of families with only 1 child (6). Therefore, among individuals with no siblings, those who had older fathers were more likely to have been only children because of low parental fertility (7), whereas those with younger fathers were more likely to have faced economic hardship. A cross-tabulation of participant educational level by paternal age among those who were only children would clarify the plausibility of this mechanism operating in the study. If true, the participants who were only children and had younger fathers might have had a greater chance of developing cancer before 1992–1993 because greater economic hardship in childhood might have had persistent effects on cancer risk and all-cause mortality in childhood and young adulthood (8). Because follow-up started when participants were at an older age and because subjects with prior deaths or cancers were excluded, the baseline susceptibility to cancer could be particularly lowered in the only children of younger fathers. This “survivor bias” might contribute substantially to the observed risk by paternal age. Additionally, the potentially greater risk of cancer due to older parental age, which was discussed in the previous paragraph, might have counteracted this survivor bias. We would appreciate it if the authors would provide the additional data to clarify the potential presence of selection bias in their study.

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REFERENCES
We appreciate the interest of Drs. Radin, Sallmén, and Kristensen (1) in our study (2). In their letter, they requested additional data to help clarify potential selection bias, and we provide that information below. From our understanding, the first concern is about the age of Cancer Prevention Study-II Nutrition Cohort participants at the time of the study (40 years of age or older). Although we agree that an assessment of the association between parental age and hematologic cancer at any age would be interesting, our research in the Cancer Prevention Study-II Nutrition Cohort (like in all other cohorts in which baseline begins in adulthood) is only intended to be valid within the context of having lived to adulthood. Although selection bias due to “late start of follow-up” is theoretically possible, we do not think it played a major role in our study. For this to be the case, there would need to be a strong association between parental age and survival to middle age, as well as an unmeasured covariate that is strongly associated with both death before middle age and risk of hematologic cancer. As requested, Table 1 shows the frequency of paternal age among the Cancer Prevention Study-II Nutrition Cohort participants who were excluded because of a history of cancer, those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excluded specifically because of hematologic cancer, and those excludes...