COMMENT & RESPONSE

In Reply We appreciate the thoughtful comments on our cohort study published in JAMA Oncology1 and thank the authors for their suggestions.

In reply to Kao et al, our study1 showed that among fully vaccinated patients, those with cancer were at increased risk for SARS-CoV-2 breakthrough infections compared with matched patients without cancer. The study population comprised patients who had medical encounters with health care organizations within the TriNetX Network during the period of December 2020 to November 2021. We agree with Kao et al that patients with cancer may have had more frequent COVID-19 testing or medical visits. Nonetheless, our findings show that patients with different cancer types had different risks for breakthrough infections, suggesting that reasons other than COVID-19 testing or medical visits may also play important roles. Clearly, future research is needed to better understand the underlying mechanisms, and findings from our study certainly need to be examined in other countries. Regarding severity, we showed that breakthrough infections in patients with cancer indeed resulted in substantial severe outcomes, including both hospitalizations and mortality.

In reply to Zhao et al, we agree that vaccines differ in their effectiveness in protecting against SARS-CoV-2 infections and outcomes.2 When comparing risks for breakthrough infections and outcomes, cohorts were propensity matched for vaccine types and COVID-19 therapeutics.1 During the study period, at least 2 virus variants, Alpha and Delta, predominated in the US. However, we did not explicitly control for variants. Instead, the outcome of breakthrough SARS-CoV-2 infection was followed up starting from the index event of vaccination in both the cancer cohort and noncancer cohort for the same length of time. We agree that future studies are needed to further examine how risks for breakthrough infections and associated outcomes in patients with cancer differ based on different virus variants. There was indeed a significant age difference between the cancer cohort and noncancer cohort before propensity matching. However, after extensive matching for age and other variables, the 2 cohorts were balanced.

In reply to Chang et al regarding potential collider bias introduced by vaccination, potential confounders such as immune dysfunctions, detection bias introduced by loss of follow-up and frequency of visits, and treatment differences between patients with and without active cancer, we note that vaccination was not a collider in this study1 because there was no causal relationship from the outcome (breakthrough infection) to the vaccination. For Kaplan-Meier survival analysis, breakthrough infections were followed up after the index event (vaccination). Instead of excluding patients with other immunocompromised conditions, cohorts were propensity matched for these conditions and other variables. Kaplan-Meier survival analysis had taken loss of follow-up into account. The concern of Chang et al regarding the frequency of medical visits among patients with cancer compared with those without was addressed previously in response to Kao et al.

Overall, these responses to our study1 emphasize the need for additional research to better understand the mechanisms of breakthrough infections and severity of the outcomes with different variants, vaccines, and in different countries, especially because infections with SARS-CoV-2 appear again to be on the rise.

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