Drs Kao and Liang Reply

To the Editor: We appreciate the comments of Selaman and colleagues.

Our population-based retrospective cohort study unexpectedly found a significant increase in overall cancer risk, as well as some individual cancers. Our findings contradict the previous thinking and lack of theoretical rationale. We know that evidence derived from our cohort study is generally not as strong as that from randomized controlled trials (RCTs) because the cohort study design is subject to many biases related to the presence of many confounding factors. Therefore, as suggested by the comments of Selaman et al, before any firm conclusions can be drawn, our findings would require confirmation by further large population-based, unbiased studies and the direction of investigational resources toward prospective, highly powered polysomnographic RCTs to scrutinize causality.

In addition, as noted in our article, the study had some limitations: (1) detailed information such as smoking habits, alcohol consumption, body mass index, socioeconomic status, and family history of cancer were not available from our database; all of these variables are major risk factors for multiple cancers and could plausibly be associated with benzodiazepine use; (2) the organ-specific pattern of cancer occurrence does not appear

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to correspond to any theoretical rationale of benzodiazepine action, and we think it is likely that our findings in part reflect a healthy nonuser effect; (3) despite our meticulous study design with adequate control of confounding factors, a key limitation is that bias could still remain if there are unmeasured or unknown confounders; and (4) the diagnoses in National Health Insurance claims primarily serve the purpose of administrative billing and do not undergo verification for scientific purposes. We were unable to contact the patients directly about their benzodiazepine use because of anonymity of their identification number. Finally, prescriptions for these drugs before 1996 would not have been captured in our analysis; this could have resulted in underestimation of the cumulative dosage and may weaken the observed association.

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