

## Association of Benzodiazepine Use With Increased Cancer Risk Is Misleading Due to Lack of Theoretical Rationale and Presence of Many Confounding Factors

**To the Editor:** In the April 2012 issue of the *Journal*, Kao et al<sup>1</sup> examined the possible relationship between benzodiazepine use and cancer risk. While increased mortality with benzodiazepine use has been demonstrated in several studies, studies examining the association between cancer and benzodiazepine use have yielded conflicting results.<sup>2-6</sup> Kao et al have attempted to demonstrate a possible relationship between benzodiazepine use and increased cancer risk; however, important limitations call into question the conclusions of their study.

A significant concern is the lack of theoretical rationale and biological pathway that might explain any potential link between benzodiazepines and cancer. General comments about immune dysfunction are not specific to benzodiazepine exposure. The absence of rationale can lead to the discovery of misleading relationships within the data that often produce spurious results with dangerous clinical and public health implications. In this regard, careful control of a broad range of confounding factors is vital to the integrity of the study. The authors offer a mechanism whereby anxiety leads to benzodiazepine use and benzodiazepine use leads to cancer. However, they do not provide convincing support for this explanation. The authors are concerned with whether the increase in cancer risk is from benzodiazepine use or from underlying psychological problems. We too are concerned, but also about several other more plausible, and unaddressed, potential etiologic factors.

Of greater concern is the study's lack of control for these potential confounding variables. While subjects with a history of malignant cancer and those with missing information about age or sex were excluded from the study, there was no information about or control for comorbid conditions, specifically current or past medical or psychiatric illness, smoking, alcohol use, or use of other substances and medications. This is a fundamental omission that directly challenges the causal inferences of the article, given the strong and consistent relationships between these factors and both benzodiazepine use and cancer.<sup>7-9</sup> While we acknowledge that this omission is due to limitations in the National Health Insurance Research database, this lack of information raises the possibility of significant confounding effects. The specific finding of increased liver cancer among benzodiazepine-exposed individuals, for example, underscores the necessity of adjustment for alcohol and drug use. Importantly, a study by Rosenberg et al,<sup>2</sup> which controlled for factors such as medical history, lifetime medication use, and smoking and factors specific to some cancers, found no significant associations between cancer risk and benzodiazepine use.

We believe that key limitations render the reported association between benzodiazepine use and increased cancer risk inaccurate. We suggest that future studies use databases that include more information on lifestyle and risks associated with cancer so as to better control for these factors and that the authors might attempt propensity score matching to control for these variables.

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