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LETTER TO THE EDITOR OF

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Continued evidence for harm, comment on "Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case-control study"

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We were pleased to see our previous report of cancer associated with hypnotics[1] confirmed by Pottegard et al.[2] Pointing out that even a moderate risk would have "major public health implications," they found a significant cancer risk ratio of 1.09 (95% CI 1.04, 1.14), with risk ratios particularly elevated for esophagus and lung. The mechanism for that may involve hypnotics producing gastric regurgitation which irritates the esophagus and airway, areas also irritated by smoking. Adjusted odds ratios by defined daily doses (DDD) were 1.03 (1.01,1.05) for 1-99 DDD, 1.04 (1.00,1.08) for 100-199 DDD, 1.08 (1.04,1.13) for 200-499 DDD, and1.09 (1.03,1.15) for 500-999 DDD. Their dose-response results in Table 3 offer internal validation.

Imagine our dismay when the authors argued there might be no association of benzodiazepines and related drugs to cancer, as they claimed that only tobacco-related cancers were elevated. They suggested that their significant result merely represented confounding with tobacco effects which they failed to control. They tried to compensate using control for chronic obstructive pulmonary disease as a proxy. Had this proxy control worked, the cancers could not have been due to tobacco. Were the cancers due to tobacco, the OR would increase without control for obstructive pulmonary disease, but a sub-analysis testing this association was not reported. The paper also lacked information on the overall rate of smoking, and quantitative evidence of an association of tobacco use and use of benzodiazepine-related drugs. To our reading, the site-specific cancer risks of Pottegard et al. correlated better with risk ratios in other studies of hypnotics risks[1,3] than with studies of risks of smoking.[4,5,6]

In challenging our findings, in a previous note (their reference 35), these authors argued that a time-dependent regression model should be used in analyses of this kind, yet they failed to use this method themselves. They argued that our method of selecting non-user controls introduced a bias against cancer-prone controls, resulting in false positive results. We believe that they misread our paper, and that their assertion of methodological bias is incorrect. We did not report (as they wrote repeatedly) that there was "a 35% excess cancer risk among users of hypnotics." The 35% elevation was found only in our high-dose group. Had we created a bias against cancer-prone controls, our low-dose-hypnotic group would have had cancer risk ratios elevated over controls. But that was not the case. Their theory of bias also failed to explain the significant dose-response relationships in our results and mirrored in their own. Their theory of bias regarding cancer outcomes notwithstanding, they make no argument against our finding of a more than 3-fold excess mortality among users of benzodiazepine-related drugs.[1] Indeed, as terrible as the possible cancer outcomes may be, the excess risks of death, particularly in younger users, represent a major concern for public health.

The difference in overall risk ratios between the Pottegard et al. paper and ours may be explained by their conservative exclusion of hypnotic use data for the crucial year before final cancer ascertainment, by differences in drugs included, and by their use of inappropriate controls (as demonstrated by the agreement of their results with ours when they applied our design). Our report has since been supported by several new studies.[3,7,8]

Unrecognized or uncontrollable confounders that methodologies cannot resolve may be

present in any case-control study. Thus, we would hope that these authors would use the ties they disclosed to makers of these drugs to champion randomized controlled trials large enough to resolve whether benzodiazepine-related drugs are safe, whether they cause cancer, and whether they cause a more than 3-fold excess in mortality.

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