Reviewer's report

Title: Analgesic and anti-inflammatory drug use and risk of bladder cancer: A population-based case control study.

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Reviewer: Antonio González-Pérez

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General

This interesting study attempts to elucidate the still uncertain relation between NSAIDs and bladder cancer. The authors perform a case-control study including 376 incident cases and 463 controls. The authors do a great job in characterizing bladder cancer cases including examination of tumor specimens by study pathologist in order to validate original diagnosis. Unfortunately the method used by the authors for drug exposure ascertainment reveals some serious problems that need to be addressed in more depth.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Retrospective interview-based ascertainment of drug exposure has been widely criticized in pharmacoepidemiology due to potential for recall bias. This bias is due to differential recall between cases and controls. In this study, bladder cancer patients had on average two years to learn about bladder cancer risk factors and to scrutiny their memory searching for past exposures that could explain the appearance of the disease. Even though authors state that NSAID exposure has not been traditionally perceived as bladder cancer risk factors, it is quite probable that at the time of the interview cases were aware of the withdrawal of the once broadly used drug phenacetin due to increased kidney and urinary tract cancer risk. In this context, cases’ recall of prior phenacetin use could be much more precise than that of controls, more so if we bear in mind that they had to remember an exposure that occurred more than ten years before the study was conducted. This is likely to result in underestimation of phenacetin use in controls. This bias could explain part if not all of the increased risk observed in this study for phenacetin potentially invalidating the study results.

Recall bias might have also affected estimates for NSAIDs and acetaminophen although to a much lesser extent. In fact, the study was able to detect a decreased risk associated with these drugs.

As previously mentioned there are some issues with the exposure ascertainment. In the case of phenacetin is difficult to rule out recall bias and in the case of aspirin and other NSAIDs the amount of misclassification and how it could affect the results is unclear. It would be certainly reassuring if authors could somehow estimate the magnitude of misclassification in cases and in controls. Have the authors considered obtaining prescriptions from medical records of a sample of patients in order to compare this information with patient’s response to the interview?

The association observed for aspirin, which in the authors' opinion is driving the result seen in NSAIDs as a whole, is somewhat puzzling. According to table 4, aspirin use was in fact slightly more common among cases than among controls. However the reported fully adjusted estimate is well below one and statically significant (0.6, 0.4-0.9). It would help in understanding this result if authors could discuss what factor or factors are driving down this estimate in the multivariate model and why could this be happening. Could this be related to the existence of commonly used products that contained a combination of both phenacetin and aspirin? In any case this should be discussed.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests