

Re: Population-Based Case-Control Study of Chinese Herbal Products Containing Aristolochic Acid and Urinary Tract Cancer Risk

Lai et al. (1) assessed the association between having been prescribed aristolochic acid-containing Chinese herbs and the risk of urinary tract cancer. However, it is inappropriate to conclude from their data that consumption is associated with risk in a dose-dependent fashion. Because this was a population-based case-control study, the sample demographic and clinical characteristics should have been comparable between the case and control groups—except for exposure to aristolochic acid—so that meaningful comparisons could be made. We raise some concerns regarding their selected variables of analysis, sampling strategy, and study design and also offer some potential solutions.

Age is widely accepted as the greatest single risk factor for developing bladder cancer, a neoplasm that occurs predominantly in patients older than 50 years and in men (2,3). However, in the study by Lai et al., 69.7% of the case subjects were 60 years or older, whereas 66.3% of the control subjects were younger than 40 years. In addition, the sex ratios in the case and control groups were not identical. Together, the differences in age and sex distribution raise concerns about the sample representativeness and the comparability of the two groups. Because all of the sampled subjects were drawn from Taiwan's National Health Insurance reimbursement database, age- and sex-matched subjects should have been easily selected to avoid these confounding effects.

Lai et al. concluded that the effects of acetaminophen and nonsteroidal anti-inflammatory drugs on urinary tract cancer were inconclusive based on previous articles (4,5) and thus did not consider the use of acetaminophen and nonsteroidal anti-inflammatory drugs by excluding subjects who used more than 500 pills, which we believe is not reasonable. Because the histopathology reports of the study subjects were unavailable, it is impossible to determine whether nephropathy was associated

with aristolochic acid or with analgesics. The use of acetaminophen and nonsteroidal anti-inflammatory drugs should have been included in the multivariable logistic regression model to examine the effect on the risk of the urinary tract cancer and to adjust for the confounding effect of analgesic use with other factors in a dose-stratified manner. Adopting a hierarchical regression model to analyze the relationships between these factors (eg, use of analgesics and the prescribed dosage of Chinese herbs) seems advisable. Furthermore, the exclusion of subjects who were ever prescribed more than a total of 500 pills of acetaminophen and the inclusion of subjects with less than 500 pills require strong justification.

Finally, the estimated average doses of aristolochic acid per gram of Guan Mu Tong and Guang Fangchi were quite close at 2.59 and 2.04 mg, respectively. However, the adjusted odds ratios for different amounts of prescribed Mu Tong and Fangchi did not reveal the same results in their logistic regression model 1. These incompatible results indicate that some other factors, which may or may not interact with aristolochic acid, may influence the association with the risk of urinary tract cancer. Nephropathy is not caused solely by aristolochic acid and analgesics; it can be induced by other drugs, such as antidepressants, antimicrobials, and diuretics (6). It is likely that the study subjects had also taken other drugs for their comorbid conditions during time period that they were prescribed aristolochic acid-containing herbal products. Therefore, these comorbid conditions and the medications used to treat them should have been controlled for in the analysis. In summary, the conclusions of Lai et al. about the relationship between the Chinese herbal products containing aristolochic acid and the risk of urinary tract cancer are not without controversy.

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References

1. Lai MN, Wang SM, Chen PC, Chen YY, Wang JD. Population-based case-control

study of Chinese herbal products containing aristolochic acid and urinary tract cancer risk. *J Natl Cancer Inst.* 2010;102(3):179–186.

2. Shariat SF, Milowsky M, Droller MJ. Bladder cancer in the elderly. *Urol Oncol.* 2009;27(6):653–667.
3. Cohen SM, Shirai T, Steineck G. Epidemiology and etiology of premalignant and malignant urothelial changes. *Scand J Urol Nephrol Suppl.* 2000;34(205):105–115.
4. Kaye JA, Myers MW, Jick H. Acetaminophen and the risk of renal and bladder cancer in the general practice research database. *Epidemiology.* 2001;12(6):690–694.
5. Castelao JE, Yuan JM, Gago-Dominguez M, Yu MC, Ross RK. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. *Br J Cancer.* 2000;82(7):1364–1369.
6. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician.* 2008;78(6):743–750.

Notes

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DOI: 10.1093/jnci/djq180

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Advance Access publication on May 17, 2010.