Response

Su et al. express concern about the sample representativeness and the comparability of age and sex distributions between the case and control groups in our study (1). We included all newly diagnosed patients with urinary tract cancer in Taiwan for the case patients, and the control subjects (n = 174 701) were selected from a simple random sampling of the general population; thus, the study sample was representative of the general population of Taiwan. Because we adjusted for age and sex in the logistic regression model, the comparability within individual strata was assured. Because matching in case–control studies may produce selection bias and must be combined with a stratified analysis to

improve efficiency, we chose to construct a multivariable logistic regression model (2). In fact, both age and sex were previously found to be associated with the frequency of having been prescribed Chinese herbal products (3). We reanalyzed the data by limiting both case patients and control subjects to those who were older than 50 years and obtained similar results (Table 1).

Su et al. suggested that we include the use of acetaminophen and nonsteroidal anti-inflammatory drugs in the analysis. We have conducted such an analysis and obtained results that were similar to those of our original analysis (Mu Tong: at 61–100 g, odds ratio = 1.4, 95% confidence interval = 1.1 to 1.9; at >200 g, odds ratio = 1.7, 95% confidence interval = 1.1 to 2.7). In fact, the association between analgesic consumption and increased risk of urinary tract or bladder cancer might be controversial (4,5). To avoid misinterpretation of potential interactions among different risk factors, we deliberately excluded participants who were prescribed more than 500 pills of analgesics.

In our study, more than 100 g of Fangchi was statistically significantly associated with an increased crude odds ratio for urinary tract cancer; however, the association did not reach statistical significance after adjustment for other risk factors, probably because of the small number of case subjects. In the estimation of total dose, we accumulated the prescribed doses for case subjects up to 1 year before diagnosis, whereas the prescribed doses for control subjects were accumulated to the end of 2002, which might have increased misclassification and underestimated the effect.

Finally, Su et al. comment that we should have controlled for comorbid conditions and the medications used to treat them. Because a confounder must be a risk predictor of the outcome (2), only medications that are reported to be associated with urinary tract cancer [eg, cyclophosphamide (6)] can be a potential confounder, whereas indications for being prescribed Mu Tong that have never been reported to potentially cause urinary tract cancer (eg, chronic hepatitis, rhinitis, dysmenorrhea, or eczema) cannot produce confounding in this study. Even though no case subject in our study was ever prescribed cyclophosphamide before the development of the cancer and even though we controlled for arsenic exposure and chronic urinary tract infection and partially controlled for smoking (through the surrogate indicator of sex), we still found an association between having been prescribed Chinese herbal products containing aristolochic acid and the risk of urinary tract cancer. Given the potential underestimation of the effect as mentioned above, we concluded that such an association exists.

Table 1. Frequency distributions of various risk factors and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for new occurrence of urinary tract cancer in patients older than 50 years from multivariable logistic regression model*

Risk factor	Case subjects (N = 3954)	Control subjects (N = 31081)	Adjusted OR (95% CI)†	*P*
Sex				
Female	1371	14150	1.0 (referent)	
Male	2583	16931	1.6 (1.5 to 1.7)	<.001
Age, y				
50–59	753	14429	1.0 (referent)	<.001
60–74	1932	11308	3.2 (3.0 to 3.5)	<.001
75–99	1269	5344	4.6 (4.2 to 5.0)	<.001
Residence in township where black foot disease was endemic				
No	3871	30948	1.0 (referent)	
Yes	83	133	4.6 (3.5 to 6.2)	<.001
Chronic UTI				
No	3873	30708	1.0 (referent)	
Yes	81	373	1.7 (1.3 to 2.1)	<.001
Mu Tong, total amount prescribed, g				
0	3440	27069	1.0 (referent)	
1–60	416	3512	1.1 (0.9 to 1.2)	.191
61–100	42	243	1.7 (1.2 to 2.5)	.003
101–200	38	178	2.1 (1.4 to 3.1)	<.001
>200	18	79	2.2 (1.2 to 3.8)	.007
Each 30-g increase‡	NA	NA	1.1 (1.07 to 1.2)	<.001
Fangchi, total amount prescribed, g				
0	3377	25851	1.0 (referent)	
1–60	535	4934	0.9 (0.8 to 1.0)	.232
61–100	15	148	0.7 (0.4 to 1.3)	.282
>100	27	148	1.3 (0.9 to 2.1)	.212
Xi-Xin, total amount prescribed, g				
0	3166	24741	1.0 (referent)	
1–100	723	5823	1.1 (1.01 to 1.2)	.029
101–300	48	420	0.8 (0.6 to 1.2)	.294
>300	17	97	1.0 (0.6 to 1.8)	.955

* NA = not applicable; UTI = urinary tract infection.

† Adjusted for age, sex, residence in a township where black foot disease was endemic, and history of chronic UTI with logistic regression model for different dosages of Chinese herbs.

‡ Estimation of odds ratio based on continuous variable for every 30-g increment of Mu Tong.

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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. Rothman KJ, Greenland S, Lash TL. Design strategies to improve study accuracy. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology.* 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2008: 171–182.
3. Hsieh SC, Lai JN, Lee CF, Hu FC, Tseng WL, Wang JD. The prescribing of Chinese herbal products in Taiwan: a cross-sectional analysis of the national health insurance reimbursement database. *Pharmacoepidemiol Drug Saf.* 2008;17(6):609–619.
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 J-M, Gago-Dominguez M, et al. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. *Br J Cancer*. 2000;82(7):1364–1369.
6. Travis LB, Curtis RE, Glimelius B, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst*. 1995;87(7):524–530.

Notes

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