Category of paper: Original articles

Manuscript title: Increased risks of upper tract urothelial carcinoma in male and female Chinese herbalists

Short running title: Urothelial carcinoma in herbalists

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ABSTRACT

Background/Purpose: It has been shown that herbs containing aristolochic acid (AA) induce urological cancer. Chinese herbalists have easy access to herbs containing AA. Our previous mortality study showed a significantly increased risk of urological cancer in female but not male herbalists. To re-examine this risk in male herbalists, the incidences of urological cancers were analyzed.

Methods: All Chinese herbalists in Taiwan (6550 herbalists) registered during 1985–2000 were enrolled, and we retrospectively followed the development of cancers until 2001 by analysis of data collected from the Taiwan Cancer Registry. Standardized incidence ratios (SIRs) were calculated for urological cancers in herbalists and compared with those for urological cancers in the general population in Taiwan.

Results: There were 30 newly-diagnosed cases of urological cancers and most of them were transitional cell carcinoma (93.1%). The mean age at diagnosis for urothelial carcinoma was 51.6 years, and 51.9% were in the upper urinary tract. After adjustment for age and gender, the SIR for all urological cancers was 3.51 (95% CI 2.37- 5.01). When stratified by location, the SIRs for kidney and upper urinary tract cancers, and bladder cancer were 4.24 (95% CI 2.47- 6.80) and 2.86 (95% CI 1.52- 4.89), respectively. When analyzed by gender, the SIRs for all urological cancers, kidney and upper urinary tract cancers, and bladder cancer were also significantly increased in male herbalists.

Conclusion: The significantly increased risk of urological cancer in male herbalists raises the possibility that this disease is work-related.

Key words: Chinese herbal drugs, Chinese herbalist, aristolochic acid, urothelial carcinoma, urological cancer.

Introduction

Herbs have been used extensively throughout the world and all during human history.[1] Chinese herbal drugs are not only used in China but also in Taiwan, Korea, Japan and Hong Kong.[2-5] An important reason for such extensive usage is that people believe herbal drugs are mild and harmless.[6] In Taiwan, Chinese medicine is covered by National Health Insurance, which regularly reimburses the costs of Chinese herbal products.[7, 8] In 1993, Vanherweghem and his colleagues first reported that many young women who took Chinese herbs containing aristolochic acids (AA) developed renal failure and urothelial carcinoma.[9] AA has been found in many Chinese herbs.[10-13] Although nephropathy and urothelial carcinoma related to the use of herbs had been reported in Belgium, Hong Kong, China and Taiwan[9, 14-17], the occupational risks in Chinese herbalists have rarely been studied.[18] Herbalism is an ancient form of healing in Chinese society. Herbalists are not formally educated or trained in conventional medical or pharmacy schools. Instead, the knowledge of Chinese medicine passed down from generation to generation by the "master and apprentice" system. Herbalists as an occupational group have the greatest access to Chinese herbs.[19]

Our previous studies based on analysis of data from the Taiwan National Mortality Registry Database found that female herbalists had a higher mortality risk of both urological cancer and chronic kidney diseases. But in male herbalists, the increased risk was only significant for chronic kidney disease, not for urological cancer.[18] The mortality rate was

associated with the quality of the health care system, and patients with urological cancer had an 11-year life expectancy in Taiwan.[20] Since patients possibly die from another cause (not mentioned in the mortality registry which in addition does not contain pathology reports) than urological cancer, the use of these registers in our previous study might have led us to underestimate the risk of urothelial malignancy in male herbalists.

To examine whether the risk of urological cancer is increased in male Chinese herbalists, this study analyzed data from the National Cancer Registry.

Material and Methods

In Taiwan, the Labor Insurance Program began in 1960 and all workers aged 15 to 60 years are required to join. The Chinese Herbalist Union was established in 1985, and most herbalists in Taiwan who work in traditional Chinese herbal stores are members. In this study, we enrolled all Chinese Herbalist Union members who were insured under the Labor Insurance Program between 1985 and 2000. Date of birth, gender and employment history were obtained from the Bureau of Labor Insurance (BLI) database. Any case of missing data or coding error, such as the date of cancer diagnosis earlier than the date of first employment, was excluded from further analysis.

Because some herbalists might have started to work in herbal stores before 1985 and many had begun to work after they completed their 9-year elementary school education or

were 15 years old, we defined the start of occupational exposure to herbs as age 15 years and the end of exposure as the date of departure from the union, occurrence of cancer, or the end of observation period.

The occurrence of cancer, date of diagnosis, histological pattern and cancer site coded in ICD-9 were obtained from the Taiwan Cancer Registry. The registry is a population-based cancer registry established in 1979 and funded by the Department of Health. Hospitals with more than 50-bed capacity that provide outpatient and hospitalized cancer care are expected to report all newly diagnosed malignant neoplasm to the registry.[21] For comparability, we converted all the ICD-9 diagnosis codes to ICD-10 codes.[22] We followed the development of cancers to the end of 2001. The study protocol was approved by the Ethics Committee of the National Taiwan University College of Public Health before commencement.

Statistical analysis

We used the PC Life Table Analysis System (LTAS)[22] Version 1.0d, developed by the National Institute for Occupational Safety and Health, to calculate (via indirect standardization methods) the standardized incidence ratio (SIR) for each cancer. The observed number of cancers was compared with the expected number of cancers within every five-year stratum. The expected number was computed by multiplying the gender-, age-, and calendar-time-specific reference rates of the general population in Taiwan by the observed person-years at risk in each stratum. The total observed number and total expected number of

cancers were calculated by summing the numbers in all strata. Then, the SIR was calculated by dividing total observed cancers (in the numerator) by total expected cancers (in the denominator).

The 95% confidence interval and two-tailed *P*-values were calculated under the assumption that the observed cancers followed a Poisson distribution. Assuming that an exposure requires a minimum induction period before it can cause cancer, we set lag periods to prevent the recent exposure contribute to the cumulative level of exposure. At calculating the incidence rate of cancer, exposure periods which occur within the lag period are not accumulated into the person years at risk and cancers occur within the lag period are grouped into a non-occupational exposure group to herbs.[22] The urological cancers progressed 3–15 years depending on the cumulative dose of AA.[23, 24] Under the assumption that herbalists might have chronic and low dose exposure to herbs containing AA, sensitivity analysis with ten- and fifteen-year lag periods was performed in calculating SIR for urological cancers. In this study, the urological cancer included malignant neoplasm of bladder (ICD-9: 188) and malignant neoplasm of kidney and other and unspecified urinary organs (ICD-9: 189). The SIR for malignant neoplasm of prostate (ICD-9: 185) was calculated separately and was not included in urological cancer.

Results

The cohort consisted of 6,555 Chinese herbalists. After excluding five herbalists with missing employment data, this study finally enrolled 6,550 herbalists (3,093 men and 3,457 women) for analysis. A total of 59,856 male person-years and 65,591 female person-years were accrued during the observation period. Among the 203 newly-diagnosed cases of cancer in the follow-up period, 30 cases were urological cancers. A positive association between exposure duration and the risk of urological cancer was illustrated by the trend of increased incidence rate of urological caner for longer exposure duration, as shown in Figure 1. After controlling the confounding effect of age by adjusted to the gender-, age-, and calendar-time-specific reference rates of general population, the SIR was still significantly higher for all urological cancers (SIR = 3.51, 95% CI 2.37- 5.01) in herbalists. When we further stratified urological cancers by location, the SIR for kidney and upper urinary tract cancers (SIR = 4.24, 95% CI 2.47 - 6.80) was higher than the SIR for bladder cancer (SIR = 2.86, 95% CI 1.52- 4.89). If we stratified by gender, the SIRs for all urological cancers, kidney and upper urinary tract cancer, or bladder cancer were all significantly increased in male herbalists with a 10-year lag period. With a 15-year lag period, male herbalists also had significantly elevated SIRs for all urological cancers, or kidney and upper urinary tract cancer. The SIRs for all urological cancers, kidney and upper urinary tract cancer, or bladder cancer in female herbalists with 10- and 15-year lag periods were all significantly increased and higher than those in male herbalists, as summarized in Table 2. Among cases of urological

cancers, most of them were, histologically, transitional cell carcinoma (93.1%). The mean age at diagnosis for urothelial carcinoma was 51.6 years, and approximately half of urothelial carcinomas (51.9%) were in the upper urinary tract (Table 3).

Discussion

The role of Chinese herbal drugs in the pathogenesis of kidney disease and urological cancer has attracted much interest in recent years, and virtually nothing is known about the health risks for workers chronically exposed to them. Consistent with our observation that male herbalists have a high exposure to herbs containing AA at work, this study provides evidence that male herbalists have increased risk of upper urinary tract urothelial carcinoma and shows that changing the lag period did not change the risk estimates (Table 1 and 2).

Yet we must rule out other alternative explanations before proposing any new hypothesis. Cigarette smoking is a major risk factor for urothelial carcinoma.[25] However, the prevalence of cigarette smoking was much smaller in herbalists (17.1%) than in other Taiwanese workers (26.7%).[26, 27] Thus, we believe that smoking is not the responsible agent. Long term use of analgesics is also another important risk factor.[28] Based on deeply rooted beliefs in the efficacy of Chinese medicine, herbalists do not typically prescribe Western medicines except in cases of severe illness. Indeed, only 2.9% of herbalists reported chronic use of analgesics[26] in comparison with 7.28% among the general population of Taiwan that had been prescribed

with more than 501 pills of NSAID (non-steroidal anti-inflammatory drugs) during 1997–2002 based on the re-imbursement database of National Health Insurance.[29] Use of analgesics cannot therefore account for the increased risk in herbalists. Arsenic is a carcinogen associated with urological cancer, and its concentration is known to be high in artesian-well water from some areas where black-foot disease is endemic.[30, 31] We checked the addresses of individuals with urological cancer, and none of them lived in the regions with contaminated artesian-well water. Thus drinking arsenic-contaminated water is probably not related to the increased risk.

As summarized in Tables 3, urological cancers among herbalists (compared to the general population of Taiwan) are mainly transitional cell carcinoma and more likely to occur in the upper urinary tract. The histological pattern and location are similar to AA-related urological cancers reported in Belgium, and are different from the urological cancers (in general) reported in Taiwan.[9, 24, 32] AA is derived from extracts of *Aristolochia*, *Bragantia*, and *Asarum* species, and is a common ingredient in many Chinese herbs, such as Madouling (*Aristolochia debilis*), Tianxianteng (*Aristolochia contorta*), Qingmuxiang (*Aristolochia cucurbitifolia*), Guangfangji (*Aristolochia fangji*), Guanmutong (*Aristolochia manshuriensis*), and Xixin (*Radix et Rhizoma Asari*).[10-13] As the histological pattern and location of the urological cancers in our sample are similar to those of AA-related urological cancers, we postulate that the increased risk among herbalists might be related to their chronic exposure

to Chinese herbs, which sometimes contain AA.

Based on our survey of herbalists in many traditional Chinese herbal stores, we suspect two possible exposure routes: (1) Ingestion of herbal powders or powder-contaminated food. Traditional Chinese herbal stores are usually small enterprises. In the past, workers usually participate in all procedures (cutting, drying, grinding, processing and packing), all of which generate lots of dust. Herbal powders may be inhaled, deposited in the oral pharynx, and then swallowed. Moreover, herbalists usually work and live in herbal stores. Many of their activities are performed in the backyard and there is no distinction between the dining room and workplace, so food may be contaminated by herbal powders. (2) Habitual use of herbal drugs. Herbalists generally prefer to use herbal drugs for treating all illnesses, because they are considered natural, mild and harmless. To promote the Yin-Yang balance according to the theory of Chinese medicine,[33-35] many herbalists also take daily herbal tonics to improve their state of well-being. Therefore, the use of herbal drugs is more prevalent in herbalists than in the general population.[19] In 2003, the Committee on Chinese Medicine and Pharmacy of the Department of Health issued a regulation prohibiting the use of herbal drugs containing Madouling, Tianxianteng, Qingmuxiang, Guangfangji and Guanmutong. But earlier exposure to herbal drugs containing AA may account for the increased risk of urological cancer observed in herbalists.

Some people might query that herbalists might had started their work with herbs before

1985 when the Chinese Herbalist Union was not established, and traditional herbal stores are usually family owned businesses so that many herbalists may contact herbs as a child. Thus, the actual person-years at risk might be greater than the number reported. But if we had obtained earlier employment data and extended the observation period, the number of cases reported and person-years at risk would simultaneously become larger. Since the risk of exposure to herbs probably containing AA did not change substantially before 2003, the estimates of SIR would not differ significantly before and after the year of 1985. Another potential confounder is the possibility that cases of urological cancer existed at the time when the herbalists joined the union and were insured. However, the estimates were not affected by setting lag period (10 and 15 years; Table 2) and suggested that the factor was not a confounder. Even though some family members of herbalists may insure the Labour Insurance through the Chinese Herbalist Union, and they have another or no job. But they live in herbal stores and consequently may also had been exposed to herbal dusts. We think that this potential limitation in classification had no effect on our results. As Chinese herbal drugs have been widely used in Taiwan with more than 39.3% of general population having been prescribed AA-containing Chinese herbal products from a national survey,[36] many Taiwanese people (categorized as non-exposed) could have been exposed to AA. This potential misclassification might have resulted in an underestimate of the SIRs for urological cancers in this study. Thus, the actual risk in Chinese herbalists may be greater than our

estimate.

This study showed that the risk of urological cancers was higher in female herbalists than male herbalists. In the Belgian cohort, all patients with AA-related urothelial carcinoma were women who took slimming regimens. [23, 24] Our another national survey using the data of the National Health Insurance from 1997 to 2003 found that most patients taking AA-containing Chinese herbal products were female.[36] Similar findings in a medical center of China showed that the majority of renal transplant recipients with urothelial carcinoma and had history of taking Chinese herbs containing AA were female.[17] These findings all indicate more frequent use of herbs in women might be the cause of higher risk. But in the endemic of the Balkan Peninsula, residents ate bread contaminated by AA and then developed upper tract urothelial carcinoma; female had higher risk than male.[37-39] Our another retrospective study in Taiwan also found that young women were more likely to develop chronic kidney disease if taking more than the threshold cumulative dose of herbs containing AA.[29] Therefore, we could not rule out the possibility that female gender is more susceptible to AA-related renal damage, and the alternative explanation could explain why female herbalists had higher risk of urological cancers than male herbalists that theoretically had higher exposure to herbs containing AA at work. We recommend future study to clarify them.

Some potential limitations of this study are inherent in retrospective cohort studies. In Taiwan, raw Chinese herbs are mainly imported from mainland China, and many Chinese

herbs from China are reported to be contaminated by heavy metals, including arsenic.[19, 40-44] We can't rule out the possibility that arsenic contamination might play a role in the increased risk of urological cancer among herbalists. Moreover, this study used the length of employment as a surrogate for the degree of exposure to herbs. Thus more epidemiological data on the occupational exposure, environmental exposure, lifestyle and medical history are needed to clarify causality.

Since 2003, the Committee on Chinese Medicine and Pharmacy has prohibited the use of Madouling, Tianxianteng, Qingmuxiang, Guangfangji and Guanmutong, and herbalists are becoming aware of the hazards of aristolochic acids. Moreover, the procedures of manufacturing and processing herbs have been shifted to mainland China in this decade. By our interview survey, most herbal stores do not process herbs but only sell herbal products now. We suspect the incidence of urological cancer among herbalists would decrease gradually in the next decade because the occurrence of cancer may develop years after discontinuation of exposure. Although there was still an increased trend of upper tract urothelial carcinoma in general population of Taiwan from the National Cancer Registry in these years, a higher risk in the herbalists was proved after standardization of their gender, age and period. Our another study using the data from the National Health Insurance in Taiwan between 1997 and 2003 showed that one-third of people in Taiwan had been prescribed with Chinese herbs that were potentially adulterated by AA.[36] A more strict

prohibition including all herbs contaminated with AA is warranted to cease the trend.

In conclusion, the significant risk of urothelial carcinoma noted in male herbalists increases our suspicion that urothelial carcinoma is an occupational disease that renders regular health assessment of herbalists an urgent necessity.

Acknowledgements

The study was carried out independently without any sponsorship. All authors declare that they have no potential conflict of interest or any financial and personal relationships that might bias their work.

References

1. Tyler VE. Herbal medicine: from the past to the future. *Public Health Nutr* 2000;3:447-52.

2. Chen FP, Chen TJ, Kung YY, et al. Use frequency of traditional Chinese medicine in Taiwan. *BMC Health Serv Res* 2007;7:26.

3. Hong CD. Complementary and alternative medicine in Korea: current status and future prospects. *J Altern Complement Med* 2001;7 Suppl 1:S33-40.

4. Yamashita H, Tsukayama H, Sugishita C. Popularity of complementary and alternative medicine in Japan: a telephone survey. *Complement Ther Med* 2002;10:84-93.

5. Chung V, Wong E, Woo J, et al. Use of traditional Chinese medicine in the Hong Kong special administrative region of China. *J Altern Complement Med* 2007;13:361-7.

6. Lee CH, Chen JJ, Liang WM. Attitudes and intentions of patients toward integrated Chinese and Western medicine in Taiwan. *J Altern Complement Med* 2006;12:233-6.

7. Liu CT. Health care systems in transition. II. Taiwan, Part I. A general overview of the health care system in Taiwan. *J Public Health Med* 1998;20:5-10.

8. Chi C, Lee JL, Lai JS, et al. The practice of Chinese medicine in Taiwan. *Soc Sci Med* 1996;43:1329-48.

9. Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi*). N Engl J Med* 2000;342:1686-92.

10. Zhang C, Wang X, Shang M, et al. Simultaneous determination of five aristolochic acids

and two aristololactams in Aristolochia plants by high-performance liquid chromatography. *Biomed Chromatogr* 2006;20:309-18.

11. Wu KM, Farrelly JG, Upton R, et al. Complexities of the herbal nomenclature system in traditional Chinese medicine (TCM): lessons learned from the misuse of Aristolochia-related species and the importance of the pharmaceutical name during botanical drug product development. *Phytomedicine* 2007;14:273-9.

12. Jong TT, Lee MR, Hsiao SS, et al. Analysis of aristolochic acid in nine sources of Xixin, a traditional Chinese medicine, by liquid chromatography/atmospheric pressure chemical ionization/tandem mass spectrometry. *J Pharm Biomed Anal* 2003;33:831-7.

13. Drew AK, Whyte IM, Bensoussan A, et al. Chinese herbal medicine toxicology database: monograph on Herba Asari, "xi xin". *J Toxicol Clin Toxicol* 2002;40:169-72.

14. Lai MN, Wang SM, Chen PC, et al. Population-based case-control study of Chinese herbal products containing aristolochic acid and urinary tract cancer risk. *J Natl Cancer Inst* 2009;102:1-8.

15. Yang CS, Lin CH, Chang SH, et al. Rapidly progressive fibrosing interstitial nephritis associated with Chinese herbal drugs. *Am J Kidney Dis* 2000;35:313-8.

16. Chang CH, Wang YM, Yang AH, et al. Rapidly progressive interstitial renal fibrosis associated with Chinese herbal medications. Am J Nephrol 2001;21:441-8.

17. Li XB, Xing NZ, Wang Y, et al. Transitional cell carcinoma in renal transplant recipients:

a single center experience. *Int J Urol* 2008;15:53-7.

18. Yang HY, Wang JD, Lo TC, et al. Increased mortality risk for cancers of the kidney and other urinary organs among Chinese herbalists. *J Epidemiol* 2009;19:17-23.

19. Chang HC, Tsai KH. Characteristics of Chinese herbalists in Taiwan. *Disquisitions on the Past and Present* 2004;11:96-114. [in Chinese]

20. Chu PC, Wang JD, Hwang JS, et al. Estimation of life expectancy and the expected years of life lost in patients with major cancers: extrapolation of survival curves under high-censored rates. *Value Health* 2008;11:1102-9.

21. Department of Health of the executive branch of the central government. Taiwan Cancer Registry. Available http:// crs.cph.ntu.edu.tw/main.php?Page=N1 Accessed September 4, 2009.

22. National Institute for Occupational Safety and Health. Life Table Analysis System. Available: http://www.cdc.gov/niosh/LTAS/default.html Accessed September 4, 2009.

23. Cosyns JP, Jadoul M, Squifflet JP, et al. Urothelial lesions in Chinese-herb nephropathy. *Am J Kidney Dis* 1999;33:1011-7.

24. Lemy A, Wissing KM, Rorive S, et al. Late onset of bladder urothelial carcinoma after kidney transplantation for end-stage aristolochic acid nephropathy: a case series with 15-year follow-up. *Am J Kidney Dis* 2008;51:471-7.

25. Zeegers MP, Tan FE, Dorant E, et al. The impact of characteristics of cigarette smoking

on urinary tract cancer risk: a meta-analysis of epidemiologic studies. *Cancer* 2000;89:630-9.

26. Lo TC. A case-control study of chronic renal disease on herbalists in Taiwan [Dissertation]. Taipei, Taiwan: Taiwan University 2003.

27. Liang WM, Kuo HW, Wang CB. Prevalence of tobacco smoking, drinking and betel nut chewing among Taiwanese workers in 1999. *Mid-Taiwan J Med* 2002;7:146-54.

28. Gago-Dominguez M, Yuan JM, Castelao JE, et al. Regular use of analgesics is a risk factor for renal cell carcinoma. *Br J Cancer* 1999;81:542-8.

29. Lai MN, Lai JN, Chen PC, et al. Increased risks of chronic kidney disease associated with prescribed Chinese herbal products suspected to contain aristolochic acid. *Nephrology* (Carlton) 2008;14:227-34.

30. Chiou HY, Chiou ST, Hsu YH, et al. Incidence of transitional cell carcinoma and arsenic in drinking water: a follow-up study of 8,102 residents in an arseniasis-endemic area in northeastern Taiwan. *Am J Epidemiol* 2001;153:411-8.

31. Chen CJ, Hsu LI, Wang CH, et al. Biomarkers of exposure, effect, and susceptibility of arsenic-induced health hazards in Taiwan. *Toxicol Appl Pharmacol* 2005;206:198-206.

32. Department of Health of the executive branch of the central government. Annual report of Taiwan Cancer Registry in 2004. Available: crs.cph.ntu.edu.tw/main.php?Page=A5. Accessed September 4, 2009.

33. Chan K. Progress in traditional Chinese medicine. *Trends Pharmacol Sci* 1995;16:182-7.

34. Cheng JT. Review: drug therapy in Chinese traditional medicine. *J Clin Pharmacol* 2000;40:445-50.

35. Unschuld PU. Huang Di Nei Jing Su Wen: Nature, Knowledge and Imagery in an Ancient Chinese Medical Text. London: University of California Press. Ltd, 2003.

36. Hsieh SC, Lin IH, Tseng WL, et al. Prescription profile of potentially aristolochic acid containing Chinese herbal products: an analysis of National Health Insurance data in Taiwan between 1997 and 2003. *Chin Med* 2008;23:13.

37. Arlt VM, Ferluga D, Stiborova M, et al. Is aristolochic acid a risk factor for Balkan endemic nephropathy-associated urothelial cancer*? Int J Cancer* 2002;101:500-2.

38. Hranjec T, Kovac A, Kos J, et al. Endemic nephropathy: the case for chronic poisoning by aristolochia. *Croat Med J* 2005;46:116-25.

39. Grollman AP, Jelaković B. Role of environmental toxins in endemic (Balkan) nephropathy. *J Am Soc Nephrol* 2007;18:2817-23.

40. Koh HL, Woo SO. Chinese proprietary medicine in Singapore: regulatory control of toxic heavy metals and undeclared drugs. *Drug Saf* 2000;23:351-62.

41. Wu TN, Yang KC, Wang CM, et al. Lead poisoning caused by contaminated Cordyceps, a Chinese herbal medicine: two case reports. *Sci Total Environ* 1996;182:193-5.

42. Au AM, Ko R, Boo FO, et al. Screening methods for drugs and heavy metals in Chinese

patent medicines. *Bull Environ Contam Toxicol* 2000;65:112-9.

43. Ernst E, Thompson Coon J. Heavy metals in traditional Chinese medicines: a systematic review. *Clin Pharmacol Ther* 2001;70:497-504.

44. Cheung TP, Xue C, Leung K, et al. Aristolochic acids detected in some raw Chinese medicinal herbs and manufactured herbal products--a consequence of inappropriate nomenclature and imprecise labeling? *Clin Toxicol* 2006;44:371-8.

Figure legends

Figure 1. The incidence rate of urological cancer stratified by exposure duration. Figure shows positive association between exposure duration and the risk of urological cancers.

Tables

Table 1. Standardized incidence ratio (SIR) for different types of cancer in Chinese herbalists

Table 2. Standardized incidence ratio (SIR) for urological cancers, stratified by gender and different lag periods

Table 3. Comparison with urological cancers classified by location and histological patterns

Supplementary Material

Table S1**.** Urological cancers among Chinese herbalists. Table lists the cancer types, gender, age, cancer site and histological types of the patients of urological cancers among Chinese herbalists.

Table S2. Standardized incidence ratios (SIRs) for cancers in Chinese herbalists, data are stratified by gender.

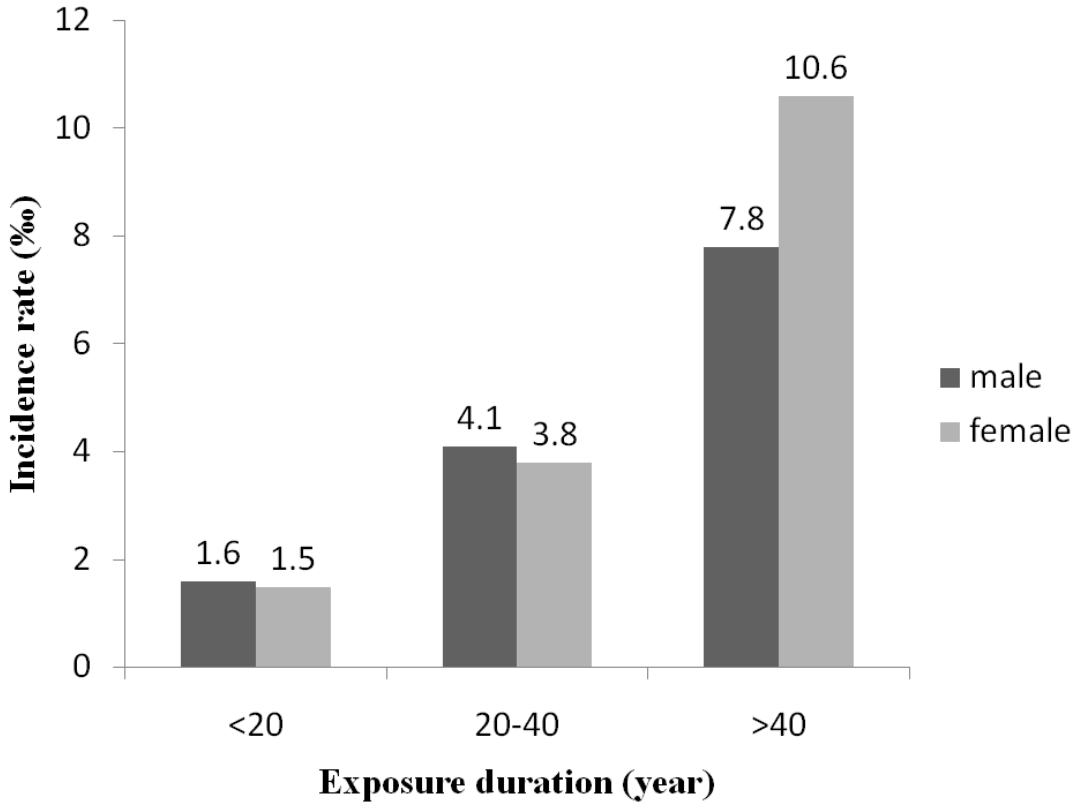

Figure 1. The incidence rate of urological cancer stratified by exposure duration. Figure shows positive association between exposure duration and the risk of urological cancers.

Table 1. Standardized incidence ratio (SIR) for different types of cancer in Chinese herbalists

Cancer site (ICD-10)	Observed no.	Expected no.§	SIR (95% CI)
All cancers	203	236.06	0.86* (0.75-0.99)
Nasopharynx (C11)	15	12.29	1.22 (0.68-2.01)
Esophagus (C15)	3	3.95	0.76 (0.16-2.22)
Stomach (C16)	9	13.26	0.68 (0.31-1.29)
Colon and rectum (C18-21)	13	22.76	0.57* (0.30-0.98)
Liver and intrahepatic bile ducts(C22)	21	31.04	0.68 (0.42-1.03)
Pancreas (C25)	6	2.63	2.28 (0.83-4.97)
Larynx (C32)	2	1.72	1.16 (0.14-4.19)
Trachea, bronchus, and lung (C33-34)	13	18.63	0.70 (0.37-1.19)
Breast (C50)	24	25.92	0.93 (0.59-1.38)
Urinary organs (C64-68)	30	8.55	3.51**(2.37-5.01)
Kidney and upper urinary tract (C64-66,C68)	17	4.00	4.24** (2.47-6.80)
Bladder (C67)	13	4.55	2.86** (1.52-4.89)
Eye (C69)	2	0.23	8.53* (1.03-30.79)
Brain (C71)	1	2.67	0.37 (0.01-2.08)

Other parts of nervous system (C70,C72)	1	0.27	3.37 (0.09-20.73)
Thyroid gland (C73)	4	5.52	0.73 (0.20-1.85)
Connective tissue (C46.1, C49)	1	1.43	0.70 (0.02-3.88)
Leukemia and aleukemia (C91.0-91.3, C91.5-91.9,C92-95)	4	5.05	0.79 (0.22-2.02)

Note: ICD-10 = International Classification of Diseases, 10th Revision.

CI = confidence interval.

§The expected number of cancer patients was calculated based upon the age and calendar year-specific incidence rates of the general population of Taiwan with 10-year lag period.

* two tailed $P < 0.05$

** two tailed $P < 0.01$

Table 2. Standardized incidence ratio (SIR) for urological cancers, stratified by gender and different lag periods

Cancer site (ICD-10)	10-year lag		15-year lag	
	No.	SIR (95% CI)	No.	SIR (95% CI)
Male				
All urinary organs (C64-68)	14	2.45**(1.34-4.10)	14	2.47**(1.35-4.14)
Kidney & upper urinary tract (C64-66,C68)	7	2.96**(1.19-6.11)	7	2.99**(1.20-6.17)
Bladder (C67)	7	2.08(0.83-4.29)	7	2.10(0.84-4.33)
Female				
All urinary organs (C64-68)	16	5.66**(3.23-9.19)	15	5.39**(3.01-8.89)
Kidney & upper urinary tract (C64-66,C68)	10	6.09**(2.91-11.19)	9	5.58**(2.55-10.59)
Bladder (C67)	6	5.06**(1.85-11.02)	6	5.13**(1.87-11.16)

Note: No. = observed numbers of cancer patient, ICD-10 = International Classification of Diseases, 10th Revision.

CI = confidence interval.

** two tailed $P < 0.01$

Table 3. Comparison with urological cancers classified by location and histological patterns

	Urological cancers in herbalists (n=30)§	Urological cancers in Belgian cohort† (n=38)	Urological cancers in Taiwan reported in 2004¶ (n=3,541)
Location			
Kidney parenchyma (%)	3 (10.0)	0	628 (17.7)
Pelvis and ureter (%)	14 (46.7)	17 (44.7)	1055 (29.8)
Bladder (%)	13 (43.3)	15 (39.5)	1858 (52.5)
Histological group			
Renal cell carcinoma (%)	2 (6.9)	0	502 (14.8)
Transitional cell carcinoma (%)	27 (93.1)	32 (100)	2654 (78.4)
Adenocarcinoma (%)	-	0	70 (2.1)
Squamous cell carcinoma (%)	-	0	46 (1.4)
Others (%)	-	0	113 (3.3)

§ One case of urological cancer had no microscopic confirmation and was excluded from analysis.

† Reference 24

¶ Reference 32