Original Article

Increased Risks of Upper Tract Urothelial Carcinoma in Male and Female Chinese Herbalists

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Background/Purpose: It has been shown that herbs that contain aristolochic acid induce urological cancer. Chinese herbalists have easy access to such herbs. Our previous mortality study has shown a significantly increased risk of urological cancer in female but not male herbalists. To re-examine this risk in male herbalists, the incidence of urological cancer was analyzed.

Methods: We enrolled all 6550 Chinese herbalists in Taiwan registered during 1985–2000, and we retrospectively followed the development of cancer 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 the general population in Taiwan.

Results: There were 30 newly diagnosed cases of urological cancer 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 sex, the SIR for all urological cancers was 3.51 [(95% confidence interval (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 sex, the SIRs for all urological cancers, kidney and upper urinary tract cancers, and bladder cancer were also significantly increased in male herbalists.

Conclusion: The significant risk of urothelial carcinoma noted in male herbalists increases our suspicion that this is an occupational disease that renders regular health assessment of herbalists an urgent necessity.

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

Herbs have been used extensively throughout the world and 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...

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reimburses the costs of Chinese herbal products.\textsuperscript{7,8} In 1993, Vanherweghem and his colleagues first reported that many young women who took Chinese herbs that contained aristolochic acid (AA) developed renal failure and urothelial carcinoma.\textsuperscript{9} AA has been found in many Chinese herbs.\textsuperscript{10–13} Although nephropathy and urothelial carcinoma related to the use of herbs have been reported in Belgium, Hong Kong, China and Taiwan,\textsuperscript{9,14–17} the occupational risks in Chinese herbalists have rarely been studied.\textsuperscript{18} Herbal medicine 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 is passed down from generation to generation by the “master and apprentice” system. Herbalists as an occupational group have the greatest access to Chinese herbs.\textsuperscript{19}

Our previous studies based on analysis of data from the Taiwan National Mortality Registry Database have found that female herbalists have a higher mortality risk of urological cancer and chronic kidney diseases. However, in male herbalists, the increased risk is only significant for chronic kidney disease and not for urological cancer.\textsuperscript{18} The mortality rate is associated with the quality of the health care system, and patients with urological cancer have an 11-year life expectancy in Taiwan.\textsuperscript{20} Patients possibly die from causes other than urological cancer (not mentioned in the mortality registry, which, in addition, does not contain pathology reports), therefore, the use of these registers in our previous study might have led to underestimation of 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**

**Participants**

In Taiwan, the Labor Insurance Program began in 1960 and all workers aged 15–60 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, sex and employment history were obtained from the Bureau of Labor Insurance database. Any case of missing data or coding error, such as cancer diagnosis earlier than the date of first employment, was excluded from further analysis.

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; therefore, 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 the observation period.

The occurrence of cancer, date of diagnosis, histological pattern and cancer site coded in the International Classification of Diseases (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 neoplasms to the registry.\textsuperscript{21} For comparability, we converted all the ICD-9 diagnosis codes to ICD-10 codes.\textsuperscript{22} We followed the development of cancer 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 Life Table Analysis System for Personal Computers\textsuperscript{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 within every 5-year stratum. The expected number
was computed by multiplying the sex-, 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 and expected numbers of cancers were calculated by summing the numbers in all strata. The SIR was calculated by dividing the total observed cancers (in the numerator) by total expected cancers (in the denominator).

The 95% confidence interval (CI) and two-tailed $p$ values were calculated under the assumption that the observed cancers followed a Poisson distribution. We assumed that an exposure required a minimum induction period before it could cause cancer, and set lag periods to prevent recent exposure contributing to the cumulative level of exposure. By calculation of the incidence rate of cancer, exposure periods that occurred within the lag period were not accumulated into the person–years at risk, and cancers that occurred within the lag period were grouped into a non-occupational exposure to herbs group.\textsuperscript{22} The urological cancers progressed for 3–15 years depending on the cumulative dose of AA.\textsuperscript{23,24} Under the assumption that herbalists might have had chronic and low-dose exposure to herbs that contained AA, sensitivity analysis with 10- and 15-year lag periods was performed to calculate the SIR for urological cancers. In this study, urological cancer included malignant neoplasm of the bladder (ICD-9: 188), kidney and other unspecified urinary organs (ICD-9: 189). The SIR for malignant neoplasm of the prostate (ICD-9: 185) was calculated separately and was not included in urological cancer.

**Results**

The cohort consisted of 6555 Chinese herbalists. After excluding five herbalists with missing employment data, we finally enrolled 6550 herbalists (3093 men and 3457 women) for analysis. A total of 59,856 male 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 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 cancer for longer exposure duration, as shown in the Figure. After controlling for the confounding effect of age by adjustment to the sex-, age- and calendar-time-specific reference rates of the general population, the SIR was still significantly higher for all urological cancers (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 (4.24, 95% CI: 2.47–6.80) was higher than that for bladder cancer (2.86, 95% CI: 1.52–4.89). If we stratified by sex, the SIRs for all urological cancers, kidney and upper urinary tract cancers, 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 cancers. The SIRs for all urological cancers, kidney and upper urinary tract cancers, 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 who are chronically exposed to them. Consistent with our observation that male herbalists have a high occupational exposure to herbs that contain AA, this study provided evidence that male herbalists had an increased risk of upper urinary tract urothelial carcinoma, and showed that changing the lag period did not change the risk estimates (Tables 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 lower 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 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 have reported chronic use of analgesics,26 in comparison with 7.28% among the general population in Taiwan who have been prescribed with more than 501 tablets of non-steroidal anti-inflammatory drugs during 1997–2002, based on the reimbursement database of National Health Insurance.29 Use of analgesics cannot therefore account for the increased risk in herbalists. Arsenic is a carcinogen that is 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

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**Table 1. Standardized incidence ratio for different types of cancer in Chinese herbalists**

<table>
<thead>
<tr>
<th>Cancer site (ICD-10)</th>
<th>Observed, n</th>
<th>Expected, n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>203</td>
<td>236.06</td>
<td>0.86&lt;sup&gt;b&lt;/sup&gt; (0.75–0.99)</td>
</tr>
<tr>
<td>Nasopharynx (C11)</td>
<td>15</td>
<td>12.29</td>
<td>1.22 (0.68–2.01)</td>
</tr>
<tr>
<td>Esophagus (C15)</td>
<td>3</td>
<td>3.95</td>
<td>0.76 (0.16–2.22)</td>
</tr>
<tr>
<td>Stomach (C16)</td>
<td>9</td>
<td>13.26</td>
<td>0.68 (0.31–1.29)</td>
</tr>
<tr>
<td>Colon and rectum (C18–21)</td>
<td>13</td>
<td>22.76</td>
<td>0.57&lt;sup&gt;b&lt;/sup&gt; (0.30–0.98)</td>
</tr>
<tr>
<td>Liver and intrahepatic bile ducts (C22)</td>
<td>21</td>
<td>31.04</td>
<td>0.68 (0.42–1.03)</td>
</tr>
<tr>
<td>Pancreas (C25)</td>
<td>6</td>
<td>2.63</td>
<td>2.28 (0.83–4.97)</td>
</tr>
<tr>
<td>Larynx (C32)</td>
<td>2</td>
<td>1.72</td>
<td>1.16 (0.14–4.19)</td>
</tr>
<tr>
<td>Trachea, bronchus, and lung (C33–34)</td>
<td>13</td>
<td>18.63</td>
<td>0.70 (0.37–1.19)</td>
</tr>
<tr>
<td>Breast (C50)</td>
<td>24</td>
<td>25.92</td>
<td>0.93 (0.59–1.38)</td>
</tr>
<tr>
<td>Urinary organs (C64–68)</td>
<td>30</td>
<td>8.55</td>
<td>3.51&lt;sup&gt;c&lt;/sup&gt; (2.37–5.01)</td>
</tr>
<tr>
<td>Kidney and upper urinary tract (C64–66, C68)</td>
<td>17</td>
<td>4.00</td>
<td>4.24&lt;sup&gt;c&lt;/sup&gt; (2.47–6.80)</td>
</tr>
<tr>
<td>Bladder (C67)</td>
<td>13</td>
<td>4.55</td>
<td>2.86&lt;sup&gt;c&lt;/sup&gt; (1.52–4.89)</td>
</tr>
<tr>
<td>Eye (C69)</td>
<td>2</td>
<td>0.23</td>
<td>8.53&lt;sup&gt;c&lt;/sup&gt; (1.03–30.79)</td>
</tr>
<tr>
<td>Brain (C71)</td>
<td>1</td>
<td>2.67</td>
<td>0.37 (0.01–2.08)</td>
</tr>
<tr>
<td>Other parts of nervous system (C70, C72)</td>
<td>1</td>
<td>0.27</td>
<td>3.37 (0.09–20.73)</td>
</tr>
<tr>
<td>Thyroid gland (C73)</td>
<td>4</td>
<td>5.52</td>
<td>0.73 (0.20–1.85)</td>
</tr>
<tr>
<td>Connective tissue (C46.1, C49)</td>
<td>1</td>
<td>1.43</td>
<td>0.70 (0.02–3.88)</td>
</tr>
<tr>
<td>Leukemia and aleukemia (C91.0–91.3, C91.5–91.9, C92–95)</td>
<td>4</td>
<td>5.05</td>
<td>0.79 (0.22–2.02)</td>
</tr>
</tbody>
</table>

<sup>a</sup>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 a 10-year lag period; <sup>b</sup>two-tailed p < 0.05; <sup>c</sup>two-tailed p < 0.01. ICD-10 = International Classification of Diseases, 10<sup>th</sup> Revision; SIR = standardized incidence ratio; CI = confidence interval.
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 Table 3, urological cancers among herbalists (compared with 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 The histological pattern and location of the urological cancers in our sample were similar to those of AA-related urological cancers; therefore, 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; therefore, food might 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, 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. In 2003, the Committee on Chinese Medicine and Pharmacy of the Department of Health issued a regulation prohibiting the use of herbal drugs that contained Madouling, Tianxianteng, Qingmuxiang, Guangfangji and Guanmutong. However, earlier exposure to herbal drugs that contain AA might account for the increased risk of urological cancer observed in herbalists.

Some people suggest that herbalists might have started their work with herbs before 1985, when the Chinese Herbalist Union was not established, and traditional herbal stores are usually family owned businesses, thus many herbalists might come into contact with herbs as children. Thus, the actual person–years at risk might be greater than the number reported. However, if we had obtained earlier employment data and extended the observation period, the number of cases reported and person–years at risk would simultaneously have become larger. The risk of exposure to herbs that probably contained AA did not change substantially before 2003; therefore, the estimates of SIR would not have differed significantly before and after 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 a lag period (10 and 15 years; Table 2), and suggested that the factor was not a confounder, even though some subjects in this cohort might be the family members and did not actually worked in herbal stores and have another or no job. However, they live in herbal stores and consequently might also have been exposed to herbal dusts. We think that this potential limitation in classification had no effect on our results. Chinese herbal drugs have been widely used in Taiwan, with 39.3% of the general population having been prescribed AA-containing Chinese herbal products; therefore, 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 our study. Thus, the actual risk in Chinese herbalists might be greater than our estimate.

This study showed that the risk of urological cancers was higher in female than male herbalists. In the Belgian cohort, all patients with AA-related urothelial carcinoma were women who followed herbal slimming regimens. Our other national survey that used National Health Insurance data from 1997 to 2003 found that most patients that took AA-containing Chinese herbal products were female. Similar findings in a medical center in China have shown that the majority of renal transplant recipients with urothelial carcinoma, who had a history of taking AA-containing Chinese herbs, were female. These findings all indicate that the more frequent use of herbs in women might be the cause of higher risk. However, in the endemic of the Balkan Peninsula, residents ate bread contaminated by AA and then developed upper tract urothelial carcinoma, and women had a higher risk than men. Our other retrospective study in Taiwan also has found that young women are more likely to develop chronic kidney disease if they consume more than the threshold cumulative dose of herbs that contain AA. Therefore, we cannot rule out the possibility that
women are more susceptible to AA-related renal damage, and the alternative explanation could explain why female herbalists have a higher risk of urological cancers than their male counterparts, who theoretically have higher occupational exposure to herbs that contain AA. We recommend a future study to clarify this.

Some potential limitations of this study are inherent in retrospective cohort studies. In Taiwan, raw Chinese herbs are mostly imported from mainland China, and many Chinese herbs from China are reported to be contaminated by heavy metals, including arsenic.\textsuperscript{19,40–44} We cannot rule out the possibility that arsenic contamination plays a role in the increased risk of urological cancer among herbalists. Moreover, our study used the length of employment as a surrogate for the degree of exposure to herbs. Thus, more epidemiological data on 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 AA. Moreover, the procedures for manufacturing and processing herbs have been shifted to mainland China during the present decade. According to our interview survey, most herbal stores do not now process herbs, but only sell herbal products. We suspect the incidence of urological cancer among herbalists will decrease gradually in the next decade because cancer might develop for several years after discontinuation of exposure. Though the incidence of upper tract urothelial carcinoma in Taiwan between 1998 and 2002 is higher than the incidence in five continents after adjusted to age.\textsuperscript{21} This study used the general population in Taiwan as reference population and the standardized incidence ratio suggested an increased risk in Chinese herbalists. Stricter prohibition, including all herbs contaminated with AA, is warranted to cease this 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.

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