Association of Sauropus androgynus and Bronchiolitis Obliterans Syndrome: A Hospital-based Case-Control Study

Luo-Ping Ger,1,2 Ambrose A. Chiang,3 Ruay-Sheng Lai,3 Su-Mei Chen,3 and Ching-Jiunn Tseng1

In late April 1995, an outbreak of a poorly defined respiratory illness related to the ingestion of leaves of Sauropus androgynus was observed in southern Taiwan. To further evaluate the association between S. androgynus and bronchiolitis obliterans syndrome, a hospital-based case-control study was conducted with one case group and three different control groups at Veterans General Hospital-Kaohsiung between April and September 1995. A total of 54 cases (50 females, 4 males), 54 age- and sex-matched neighborhood controls, 54 matched routine physical check-up controls, and 54 matched self-referred patron controls (who had ingested S. androgynus yet without obstructive physiology) were interviewed for clinical symptoms, history of S. androgynus consumption, and potential confounding factors. All 54 cases (100%) ingested S. androgynus compared with only five (9%) neighborhood controls (matched odds ratio (OR) incalculable, \( p < 0.001 \)) and two (4%) physical check-up controls (matched OR incalculable, \( p < 0.001 \)). In the univariate analysis of 54 cases and 54 self-referred patron controls, factors associated with an increased risk of bronchiolitis obliterans syndrome were methods of food preparation (uncooked juice vs. stir fried or boiled dishes, matched OR 10.3 (95% confidence interval (CI) 1.3-64.4)); preparer of the S. androgynus-containing food (vendor only vs. patient only or patient plus vendor, matched OR 2.8 (95% CI 1.1-7.1)); total S. androgynus consumption quantity (>4,500 vs. 413-2,063 g, matched OR 10.0 (95% CI 1.9-53.0)); duration of consumption (>45 vs. 6-24 days, matched OR 2.1 (95% CI 1.2-3.8)); and midterm interruption (<2 vs. 2-5 days per week, matched OR 2.6 (95% CI 1.1-6.1)). Additionally, multiple conditional logistic regression analysis of cases and self-referred patron controls revealed that a larger total amount of S. androgynus consumption, preparation of S. androgynus food without cooking, and ingesting S. androgynus food prepared by a vendor were the significant risk factors associated with bronchiolitis obliterans syndrome. Am J Epidemiol 1997;145:842-9.

bronchiolitis obliterans; case-control studies; cookery; diet; food fads; vegetables

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Abbreviations: BO, bronchiolitis obliterans; CI, confidence interval; FEV1, forced expiratory volume in first second; FVC, forced vital capacity; OR, odds ratio; SD, standard deviation; VGH-K, Veterans General Hospital-Kaohsiung.

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nizing pneumonia (1, 2), who suffered from temporary insomnia and poor appetite followed by progressive difficulty breathing after ingestion of *S. androgynus*, were reported to the National Poison Center of Taiwan by physicians from the Taiwan area (1). Our previous clinical study (3) described the clinical, radiologic, and pathologic manifestations of *S. androgynus*-associated BO syndrome. That study definitely ruled out the possibility of collagen vascular diseases and postviral and mycoplasma infection (3).

The findings presented here are the results of a hospital-based case-control study that was conducted with one case group and three different control groups (neighborhood controls, routine physical check-up controls, and self-referred patron controls) at VGH-K. The purpose of our study was to evaluate the relation between *S. androgynus* and BO syndrome by comparing 54 cases, 54 neighborhood controls, and 54 routine physical check-up controls and to elucidate a possible association between BO syndrome and different methods of *S. androgynus* food preparation, different preparers of the *S. androgynus* food, distinct sources of *S. androgynus*, and various *S. androgynus* consumption quantity by comparing 54 cases and 54 self-referred patron controls.

**MATERIALS AND METHODS**

**Subjects**

A total of 56 eligible cases were identified between late April and mid-September 1995 at VGH-K, Taiwan. A case of BO syndrome was defined according to the following three criteria: 1) normal chest radiograph and diffuse central bronchiectasis and mosaic attenuation on high-resolution computerized tomography of the chest; 2) obstructive physiology (forced expiratory volume in the first second/forced vital capacity (FEV₁/FVC) < 70 percent) without bronchodilator response; and 3) progressive dyspnea and/or chest tightness. A total of 54 (96 percent) cases were interviewed, and the other two cases were lost to follow-up.

Three different control groups were recruited as follows: 1) Fifty-four neighborhood controls were one-to-one matched with each case on date of birth (±5 years), sex, and residence at the time of diagnosis. The neighborhood control was found by a door-to-door search, beginning at the home of the case and following a standard search pattern until a person was found matching the case on age and sex. 2) Fifty-four routine physical check-up controls who were selected from the VGH-K physical check-up ward and who had no obstructive physiology (FEV₁/FVC > 70 percent) were one-to-one matched on date of birth (±5 years), sex, date of admission (±3 days), and residence (same city). 3) Fifty-four self-referred patron controls who were selected from the VGH-K outpatient medicine department and who had ingested 37.5 g or more (equal to one “Liang” in traditional Taiwanese weight units) of *S. androgynus* per day for more than 6 days and yet were without obstructive physiology (i.e., FEV₁/FVC > 70 percent) were one-to-one matched on date of birth (±5 years), sex, and date of outpatient department visit (±7 days).

**Procedures for data collection**

Cases and hospital controls were interviewed in the ward or in the outpatient department, and neighborhood controls were interviewed at home. A structured questionnaire with closed-question format that was designed by an epidemiologist and two lung specialists was used to collect information on demographics, smoking, alcohol consumption, medical history, medication history, and occupational exposure (inhaled fiber such as asbestos and cotton; inhaled gas such as nitrogen dioxide, sulfur dioxide, ammonia, chlorine, and phosgene; and inhaled vapor such as herbicide and organic solvent). A detailed consumption history of *S. androgynus* was obtained, which included reasons for *S. androgynus* consumption, source of *S. androgynus* (imported, locally cultivated, or unknown), preparer of the *S. androgynus* food (patient or vendor), quantity of daily consumption, duration of consumption, midterm interruption (mean interruption in days per week), methods of food preparation (boiled, stir fried, or uncooked juice), as well as different supplements (such as mixing of *S. androgynus* uncooked juice with apple, pineapple, or guava). The interviewer was blinded to the case/self-referred patron control status because she had interviewed them before they had diagnostic tests (except for the first six cases); however, it was not possible for her to be blinded to neighborhood controls or physical check-up controls. Nonetheless, the interviewer and supervisor received intensive training in standardized interview techniques, and especially in the most impartial questioning methods. Photographs of *S. androgynus* were displayed to interviewees to validate their ingestion history, and each interview took about 40 minutes. If the questionnaire had not been completed, additional information was obtained either by personal interview or by telephone.

A random sample of 11 percent of the respondents were reinterviewed by the supervisor the next day. The kappa coefficient was used to assess the test-retest reliability for nominal variables. The items used for analysis showed acceptable reliability with kappa coefficients of 0.82 for source of *S. androgynus* and up to 1.00 for past medical history of organ transplanta-
tion. The correlation coefficient was calculated for continuous variables. The items used for analysis showed acceptable reliability with correlation coefficients of 0.96 for duration of *S. androgythus* consumption and up to 0.99 for total amount of *S. androgythus* consumption.

Smoking was defined as having smoked one cigarette or more per day for at least 1 year. Alcohol consumption was defined as having consumed alcohol-containing beverages once a week for at least 1 year. Chronic bronchitis was defined as having had a productive cough at least 3 months per year for 2 sequential years.

**Statistical methods**

Several statistical methods were used in data analysis. Matched odds ratios (ORs) of BO syndrome were estimated using the Mantel-Haenszel method. The Mantel-Haenszel summary $X^2$ test was used to test the statistical significance of the matched OR (4). Furthermore, when the matched OR was incalculable, the Fisher’s exact test was used to test the statistical significance of the incalculable matched OR. Various parameters characterizing the exposures were analyzed by a conditional logistic regression (5), taking into account the full matching of each case with each original control. Finally, the multiple conditional logistic regression method (5) was used to estimate the multivariate-adjusted odds ratio of BO syndrome for various characteristics of *S. androgythus* consumption history and to test their statistical significance.

**RESULTS**

The mean ages and standard deviations (SDs) in years were: for cases, 43.0 (SD 8.7, range 21–66); for neighborhood controls, 42.2 (SD 8.5, $p = 0.63$ by $t$ test); for routine physical check-up controls, 42.7 (SD 8.6, $p = 0.83$ by $t$ test); and for self-referred patron controls, 44.4 (SD 9.4, $p = 0.43$ by $t$ test). Ninety-three percent of the cases (50 of 54) were female, as were 93 percent of the neighborhood, routine physical check-up, and self-referred patron controls. There were no significant differences in educational levels among cases and neighborhood controls ($X^2 = 1.08$, df = 2, $p = 0.58$), routine physical check-up controls ($X^2 = 3.73$, df = 2, $p = 0.16$), and self-referred patron controls ($X^2 = 1.85$, df = 2, $p = 0.40$). The body weights in kilograms were for cases, 50–105 (mean 65.6, SD 11.2), and for self-referred patron controls, 47–105 kg (mean 65.3, SD 11.6, $p = 0.89$ by $t$ test). The mean FEV$_1$/FVC and SDs in percentages were: for cases, 47 (SD 9, range 30–66); for routine physical check-up controls, 83 (SD 5, range 73–95, $p < 0.01$ by the Mann-Whitney $U$ test); and for self-referred patron controls, 84 (SD 6, range 71–95, $p < 0.01$ by the Mann-Whitney $U$ test).

**Occupational exposure and past medical history**

We did not identify any significant differences in any occupational exposures, self-reported past medical histories, or medication histories between cases and three different controls (table 1). In addition, none of the cases or controls had previously undergone any type of transplantation surgery or had taken penicilamine or lomustine.

**S. androgythus consumption history**

Reasons for ingesting *S. androgythus* given by the 54 cases included their attempts to control the following: body weight in 38 (70 percent), hypertension in six (11 percent), hyperlipidemia in five (9 percent), and constipation in 13 (24 percent). Reasons for consuming *S. androgythus* given by the 54 self-referred patron controls were to control body weight in 46 (85 percent), hypertension in six (11 percent), hyperlipidemia in two (4 percent), and constipation in 14 (26 percent). Additionally, reasons given by the five neighborhood controls who ingested *S. androgythus* were body weight control for four (80 percent) and constipation control for one (20 percent). Reasons given by the two routine physical check-up controls who ingested *S. androgythus* were body weight control for one (50 percent) and constipation control for one (50 percent).

**Comparison between 54 cases, 54 neighborhood controls, and 54 routine physical check-up controls.** All 54 cases had ingested *S. androgythus* food (including uncooked juice and stir fried or boiled dishes) compared with only five of 54 neighborhood controls (incalculable matched OR, $p < 0.001$ by the Fisher’s exact test), and only two in 54 routine physical check-up controls (incalculable matched OR, $p < 0.001$ by the Fisher’s exact test). The median total amount of *S. androgythus* consumption was 4,935 g for the 54 cases (range 788–56,063 g) and 330 g for the five neighborhood controls (range 75–1,725 g); the total amounts were 75 and 150 g for the two routine physical check-up controls.

**Comparison between 54 cases and 54 self-referred patron controls.** Methods of *S. androgythus* food preparation (stir fried or boiled dishes, stir fried dishes or uncooked juice, uncooked juice), preparer of the *S. androgythus* dish or juice (patient only, patient or vendor, vendor only), total consumption amount, duration of consumption, and midterm interruption (days per week) were associated with the BO syndrome. Furthermore, trends in risk were observed in methods of...
TABLE 1. Occupational exposure and past medical and drug history reported by cases and specific controls in Veterans General Hospital-Kaohsiung, Taiwan, April 21 to September 15, 1995

<table>
<thead>
<tr>
<th>Past history</th>
<th>Cases (n = 54)</th>
<th>Controls</th>
<th>Cases vs. neighborhood controls</th>
<th>Cases vs. hospital controls</th>
<th>Cases vs. patron controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
<td></td>
<td>OR§ 95% CI</td>
<td>OR§ 95% CI</td>
<td>OR§ 95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiber-related jobs</td>
<td>4 5 3 2</td>
<td>0.8 0.2-3.4</td>
<td>1.5 0.3-9.0</td>
<td>2.0 0.4-10.9</td>
<td></td>
</tr>
<tr>
<td>Asbestos-related</td>
<td>1 1 0 1</td>
<td>1.0 0.1-16.0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>1.0 0.1-16.0</td>
</tr>
<tr>
<td>Textile-related</td>
<td>3 4 3 1</td>
<td>1.0 0.1-4.0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>1.0 0.1-7.1</td>
</tr>
<tr>
<td>Gas-related jobs</td>
<td>2 4 2 0</td>
<td>0.5 0.1-2.7</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>3.0 0-28.8</td>
</tr>
<tr>
<td>Ammonia-related</td>
<td>0 0 1 0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>Chlorine-related</td>
<td>1 4 1 0</td>
<td>0.3 0.03-2.2</td>
<td>2.5 0.9-7.1</td>
<td>1.0 0-16.0</td>
<td></td>
</tr>
<tr>
<td>Nitrogen dioxide-related</td>
<td>1 0 0 0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>Vapor-related jobs</td>
<td>1 4 0 4</td>
<td>0.3 0.03-2.2</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>0.3 0-2.2</td>
</tr>
<tr>
<td>Herbicide-related</td>
<td>0 1 0 2</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>Organic solvent-related</td>
<td>1 3 0 2</td>
<td>0.3 0.03-3.2</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>0.5 0.1-5.5</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>0 0 2 1</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>3 1 3 2</td>
<td>3.0 0.3-28.8</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>0.5 0.1-16.0</td>
</tr>
<tr>
<td>Allergies</td>
<td>4 7 5 5</td>
<td>0.4 0.1-2.1</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>0.6 0.2-3.4</td>
</tr>
<tr>
<td>ENT disorders</td>
<td>1 2 6 2</td>
<td>0.5 0.1-5.5</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>0.5 0.1-5.5</td>
</tr>
<tr>
<td>Benign tumors</td>
<td>3 5 1 2</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>2.0 0.2-22.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 1 2 4</td>
<td>1.0 0.1-16.0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>1.0 0.1-7.1</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>9 4 13 12</td>
<td>2.7 0.7-10.1</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>0.3 0-22</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>3 7 10 2</td>
<td>0.4 0.1-1.7</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>1.5 0.3-9.0</td>
</tr>
<tr>
<td>Genitourinary disorders</td>
<td>2 1 1 4</td>
<td>2.0 0.2-22.1</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>0.5 0.1-27</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>2 0 6 2</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>0 0 0 0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>Smoking</td>
<td>0 3 6 4</td>
<td>0.3 0.03-2.2</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>0.7 0.1-4.0</td>
</tr>
<tr>
<td>Drinking</td>
<td>0 3 2 2</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>Medication history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herb drugs</td>
<td>0 3 1 1</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>Weight reduction medicine</td>
<td>1 2 0 0</td>
<td>0.5 0.1-5.5</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
<tr>
<td>NSAIDS*</td>
<td>1 1 1 1</td>
<td>1.0 0.1-16.0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>1.0 0.1-16.0</td>
</tr>
<tr>
<td>Cardiac disease medicine</td>
<td>1 1 7 1</td>
<td>1.0 0.1-16.0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>1.0 0.1-16.0</td>
</tr>
<tr>
<td>Contralcoreceptors</td>
<td>0 0 0 0</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
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<tr>
<td>Penicillamine</td>
<td>0 0 0 0</td>
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<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
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<tr>
<td>Lomustine</td>
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<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
<td>Incalculable</td>
</tr>
</tbody>
</table>

*All hospital controls received routine physical examinations.
† OR, odds ratio; CI, confidence interval; ENT, ears, nose, and throat; NSAIDS, nonsteroidal antiinflammatory drugs.
§ Matched. (If matched odds ratio was incalculable, the p value was obtained by the Fisher's exact test.)

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food preparation, preparer of the S. androgynus food, total consumption amount, and duration of consumption. However, the source of S. androgynus and the average consumption amount per day were not associated with the risk of BO syndrome (table 2).

A multiple conditional logistic regression was used to examine the joint effects of methods of food preparation, preparer of the S. androgynus food, total consumption quantity, duration of consumption, and midterm interruption. The multiple conditional logistic regression model was constructed with a step-up procedure in which significant variables were added one at a time to assess their effect on the fit of the model. Finally, only the statistically significant risk factors, including methods of food preparation, preparer of the S. androgynus food, and total consumption amount, were included in the model (table 3). The adjusted ORs (and 95 percent CIs) of BO syndrome were 4.9 (0.5–48.2) for those with food preparation of stir fried dishes or uncooked juice and 8.2 (1.0–69.7) for uncooked juice only compared with stir fried or boiled dishes. The adjusted OR (and 95 percent CI) of BO syndrome was 2.5 (0.9–6.8) for the preparer of the S. androgynus food of vendor only compared with patient only or patient plus vendor. The adjusted ORs (and 95 percent CIs) of BO syndrome were 3.2 (0.6–17.8) for those with moderate S. androgynus consumption (2,064–4,500 g) and 8.1 (1.5–43.6) for excessive
**TABLE 2. Various characteristics of Sauropus androgynus (SA) consumption history reported by cases and self-referred patron controls in Veterans General Hospital-Kaohsiung, Taiwan, April 21 to September 15, 1995**

<table>
<thead>
<tr>
<th>SA consumption history</th>
<th>Cases (n = 54)</th>
<th>Controls (n = 54)</th>
<th>OR*, †</th>
<th>95% CI*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods of food preparation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stir-fried or boiled dishes‡</td>
<td>1</td>
<td>9</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stir-fried dish or uncooked juice</td>
<td>13</td>
<td>14</td>
<td>6.9</td>
<td>0.8–69.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Uncooked juice only</td>
<td>40</td>
<td>31</td>
<td>10.3</td>
<td>1.3–64.4</td>
<td>0.03</td>
</tr>
<tr>
<td>p for trend§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.021</td>
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<tr>
<td><strong>Preparer of SA dish or juice</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient only</td>
<td>23</td>
<td>34</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient or vendor</td>
<td>6</td>
<td>7</td>
<td>1.6</td>
<td>0.4–6.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Vendor only</td>
<td>25</td>
<td>13</td>
<td>2.8</td>
<td>1.1–7.1</td>
<td>0.02</td>
</tr>
<tr>
<td>p for trend§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Source of SA</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Locally cultivated</td>
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<td>15</td>
<td>1.0</td>
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<td></td>
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<tr>
<td>Imported</td>
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<td>29</td>
<td>1.7</td>
<td>0.7–4.2</td>
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<td>Unknown</td>
<td>12</td>
<td>10</td>
<td>1.9</td>
<td>0.6–5.7</td>
<td>0.28</td>
</tr>
<tr>
<td>p for trend§</td>
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<td><strong>Total amount (g)</strong></td>
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</tr>
<tr>
<td>413–2,063</td>
<td>7</td>
<td>17</td>
<td>1.0</td>
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<tr>
<td>2,064–4,500</td>
<td>17</td>
<td>19</td>
<td>4.1</td>
<td>0.9–19.5</td>
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<tr>
<td>4,501–56,063</td>
<td>30</td>
<td>18</td>
<td>10.0</td>
<td>1.9–53.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>p for trend§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Average amount (g/day)</strong></td>
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</tr>
<tr>
<td>6–75</td>
<td>15</td>
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<td>76–149</td>
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<td>15</td>
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<td>0.6–3.7</td>
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<tr>
<td>150–303</td>
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<td>19</td>
<td>1.7</td>
<td>0.6–4.7</td>
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<td>p for trend§</td>
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<td></td>
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<tr>
<td><strong>Duration of consumption (days)</strong></td>
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<td></td>
</tr>
<tr>
<td>6–24</td>
<td>7</td>
<td>18</td>
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<tr>
<td>22–45</td>
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<td>18</td>
<td>3.0</td>
<td>0.9–9.9</td>
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<tr>
<td>46–320</td>
<td>29</td>
<td>18</td>
<td>2.1</td>
<td>1.2–3.8</td>
<td>0.01</td>
</tr>
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<td>p for trend§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.014</td>
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<tr>
<td><strong>Midterm interruption (days/week)</strong></td>
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<td>2–5</td>
<td>19</td>
<td>30</td>
<td>1.0</td>
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<tr>
<td>&lt;2</td>
<td>35</td>
<td>24</td>
<td>2.6</td>
<td>1.1–6.1</td>
<td>0.03</td>
</tr>
<tr>
<td>p for trend§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.426</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Matched.
‡ One case and one control always ingested stir-fried dishes; one control always ingested boiled dishes; two controls sometimes ingested stir-fried dishes and sometimes ingested boiled dishes; five controls sometimes ingested boiled dishes and sometimes ingested uncooked juice.
§ Determined by model $\chi^2$ with 1 df from conditional logistic regression.

**S. androgynus** consumption (>4,500 g) compared with those who consumed less (<2,064 g). Additionally, clear and significant increasing trends in risk with increasing degrees of **S. androgynus** food rawness and total consumption amount were observed.

**DISCUSSION**

**S. androgynus** (also known as *Sauropus albicans*) of the family Euphorbiaceae, a small perennial shrub of 0.7–1.3 m in height, is often found growing wild in many parts of southeast Asia. The dark green leaves, 2–6 cm long and 1.5–3 cm wide, have various nutritive value and are commonly used for human consumption after cooking in Malaysia (6). In a survey of 12 Malaysian villages, the amount consumed, usually once a week, averaged 156 g (range 116–200 g) (7). However, in an examination of **S. androgynus** nutritional potential, it was found to contain a considerable amount of alkaloid "papaverine" (580 mg of papaverine per 100 g of fresh leaf) (6). Another study found that the leaf of **S. androgynus** contains large amounts of all nutrients, and the different food preparations were well accepted by a selected panel of eight judges in India. Nevertheless, they concluded that **S. androgy-
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**Sauropus androgynus** cannot be recommended for wide and frequent consumption until the safety issue has been studied carefully due to the presence of papaverine (8).  

*S. androgynus* was first introduced in Taiwan about 9 years ago and was prepared in some restaurants only as a fried dish (9). It was not until 1 1/2 years ago that *S. androgynus* was cultivated locally on a commercial scale, and uncooked *S. androgynus* juice was widely advertised as a “natural diet vegetable containing large amounts of nutrients and good for rapid weight reduction.” Additionally, it was promoted as being effective in controlling hypertension, gynecologic problems, hyperlipidemia, hyperuricemia, urolithiasis, gall stones, and constipation. Analysis of the reasons for ingesting *S. androgynus* among our cases and self-referral patron controls supported the phenomenon of consumption of *S. androgynus* for medical purposes.

The association between the consumption of *S. androgynus* and BO syndrome was firmly established in our study. However, it should be noted that no *S. androgynus*-associated BO syndrome case has ever been reported in other southeastern Asian countries. The fact that our cases ingested *S. androgynus* more frequently (more than twice a week, as presented in table 2) and in large amounts (average amount per week = 814 ± 417 g) could possibly explain this discrepancy. Furthermore, our data support the idea that the method of *S. androgynus* food preparation was another important risk factor. To our knowledge, Malaysians traditionally ingest boiled *S. androgynus* salad, boiled *S. androgynus* soup, or stir fried dishes. In contrast, our patients commonly consumed uncooked juice.

BO (also known as obliterative bronchiolitis) is an uncommon pulmonary disease characterized by inflammatory changes of the membranous and respiratory bronchioles. Histopathologic features varied from subtle cellular infiltrates surrounding the small airways to extensive infiltrates with fibrosis and smooth muscle hyperplasia, and to complete obliteration of bronchiolar lumens (10-13). Its incidence is probably higher than generally believed and is continuously rising (13). Diverse clinical conditions have been associated with the development of BO syndrome such as in certain allograft recipients (bone marrow, heart, or lung transplant recipients) (13-18) or in patients with collagen vascular diseases such as rheumatoid arthritis, eosinophilic fasciitis, systemic lupus erythematosus (13, 15, 19), ulcerative colitis (13, 15), postviral infection (respiratory syncytial virus, adenovirus, influenza, parainfluenza) or mycoplasma infection (13, 15, 20), toxic fume exposure (nitrogen dioxide, sulfur dioxide, ammonia, chlorine, and phosgene), and drug reactions (penicillamine and lomustine) (13, 15).

In early July, before the outbreak was reported by the mass media, two samples of uncooked *S. androgynus* juice were analyzed by gas chromatography and mass spectrometers. One sample produced by a vendor was provided by a case who had ingested 2,250 g of *S.

### TABLE 3. Multiple conditional logistic regression of *Sauropus androgynus* (SA) consumption associated with bronchiolitis obliterans syndrome among cases and self-referred patron controls in Veterans General Hospital-Kaohsiung, Taiwan, April 21 to September 15, 1995

<table>
<thead>
<tr>
<th>SA consumption history</th>
<th>Cases (n = 54)</th>
<th>Controls (n = 54)</th>
<th>OR*, †</th>
<th>95% CI*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods of food preparation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stir-fried or boiled dishes†</td>
<td>1</td>
<td>9</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stir-fried dish or uncooked juice</td>
<td>13</td>
<td>14</td>
<td>4.9</td>
<td>0.5–48.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Uncooked juice only</td>
<td>40</td>
<td>31</td>
<td>8.2</td>
<td>1.0–69.7</td>
<td>0.05</td>
</tr>
<tr>
<td>p for trend‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.022</td>
</tr>
<tr>
<td>Preparer of SA dish or juice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient only or patient + vendor</td>
<td>29</td>
<td>41</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vendor only</td>
<td>25</td>
<td>13</td>
<td>2.5</td>
<td>0.9–6.8</td>
<td>0.08</td>
</tr>
<tr>
<td>p for trend‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.415</td>
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<td>Total amount (g)</td>
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<td>413–2,063</td>
<td>7</td>
<td>17</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,064–4,500</td>
<td>17</td>
<td>19</td>
<td>3.2</td>
<td>0.6–17.8</td>
<td>0.19</td>
</tr>
<tr>
<td>4,501–56,063</td>
<td>30</td>
<td>18</td>
<td>8.1</td>
<td>1.5–43.6</td>
<td>0.01</td>
</tr>
<tr>
<td>p for trend‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Each odds ratio was simultaneously adjusted by multiple logistic regression for all other characteristics of SA consumption history in this model.
‡ One case and one control always ingested stir-fried dishes; one control always ingested boiled dishes; two controls sometimes ingested stir-fried dishes and sometimes ingested boiled dishes; five controls sometimes ingested boiled dishes and sometimes ingested uncooked juice.
§ Determined by model $\chi^2$ with 3 df from conditional logistic regression.
*androgynus* during the past 15 days; the other sample was produced by another case who had ingested 3,000 g of *S. androgynus* during the past 20 days. No suspicious chemical agent was found in these two samples except for caffeine and indomethacin in the sample that was produced by the vendor. In late July, after the outbreak had been covered by the mass media, the Bureau of Food Sanitation also examined five samples of *S. androgynus* vegetable and two samples of *S. androgynus* uncooked juice produced by vendors (which were obtained from northern, central, and southern Taiwan). Laboratory testing revealed no papaverine or any other suspicious chemical except for the presence of unknown alkaloids (Dr. D. H. Hsieh, Bureau of Food Sanitation, personal communication, 1996).

Our finding suggested that patients who consumed *S. androgynus* dishes or juice made by vendors have a greater chance of developing BO syndrome than those who consumed homemade *S. androgynus* dishes or juice (adjusted OR = 2.5, *p* = 0.08). However, this might be the result of selection bias of self-referred patron controls since this group of controls probably pay more attention to their health and possibly are more inclined to make *S. androgynus* food themselves. Additionally, we cannot rule out the possibility that some of the unethical vendors might have added supplements to the *S. androgynus* juice, which could have produced a synergistic effect and have promoted the development of BO syndrome. If we assumed that insomnia was induced by caffeine supplement, our results showed that insomnia occurred in 51.8 percent of cases and 48.1 percent of self-referred patron controls. It is intriguing to note that the rate of insomnia in the cases and controls who made the uncooked *S. androgynus* juice themselves was 50.9 percent, which was not statistically different from the rate (47.4 percent) of the patients who bought the uncooked *S. androgynus* juice from vendors. It is our speculation that some unidentified constituents of *S. androgynus*, not only supplements added by vendors, may be responsible for the pathogenesis and clinical symptoms.

The dose-response relation was clearly demonstrated between the total quantity of *S. androgynus* consumption and BO syndrome but was not established between the average daily consumption and BO syndrome in our study. This suggested that *S. androgynus* patrons ingested almost the same *S. androgynus* amount per day as cases ingested. If they had not been persuaded to interrupt ingesting *S. androgynus*, they would have accumulated enough *S. androgynus* and would have developed BO syndrome the following day. A total of two alleged *S. androgynus*-related deaths were observed in our hospital. Additionally, it is also interesting to note that there were five self-referred patron controls who ingested large amounts of *S. androgynus* (4,501–15,525 g) yet did not develop any respiratory symptoms. Genetic predisposition might play a significant role in *S. androgynus*-associated BO syndrome, as in diffuse panbronchiolitis (21).

The number of BO syndrome cases was increased distinctly in Taiwan after local or national publicity began. Selection bias can result because the experience of *S. androgynus* consumption might affect the probability of a case being enrolled in our case-control study. We had tried to avoid selection bias by systematically investigating all previous pathologic reports of open lung biopsy and by interviewing all of the senior lung specialists to collect the BO or BO syndrome cases before late July 1995 at our hospital (before any association between *S. androgynus* and BO had been covered extensively by the mass media). However, only eight patients with BO syndrome were confirmed before late July 1995. These eight patients were the initially eligible cases who were confirmed in our study between late April and mid-July 1995. There were no other confirmed cases with BO syndrome before late April 1995 at our hospital. Reasons for this may be that BO is a very rare disease (the incidence is 2.38 per 100,000 (22)) and that our hospital is a new medical center (it opened in October 1990). Additionally, 10 patients with BO syndrome were confirmed at Chang-Gung Memorial Hospital-Kaohsiung and two other patients were confirmed at National Chen-Kung University Hospital before publicity of *S. androgynus*-associated BO syndrome. All of these 20 patients had a history of *S. androgynus* consumption. Therefore, our findings were not completely affected by the publicity.

We could not keep the interviewer blinded to case/neighborhood control/physical check-up control status in the actual field operation because most cases had severe pulmonary obstructive symptoms and the locations of their interviews were different in these three groups. Information bias (recall and interviewer bias) may have occurred despite our use of a standardized questionnaire combined with intensive interviewer training of impartial questioning techniques. Additionally, dietary histories are notorious for error (4). However, from our experiences, we found that most respondents were young and could remember their *S. androgynus* consumption history, and especially the uncooked *S. androgynus* juice consumption, clearly. This was because the taste of uncooked *S. androgynus* juice was repulsive (most consumers added fragrant fruit to improve the taste) and because *S. androgynus* was expensive (46 US dollars per 1,000 g) compared with other regular vegetables (which averaged 2 US dollars per 1,000 g).
To avoid diagnosis bias, our cases and self-referred patron controls were identified at our hospital (in their local sites of occurrence), and the roentgenologist and lung specialist were blinded to the amount of *S. androgyrus* consumption. If any BO syndrome misclassification had arisen, due to the fact that the physicians were blinded at the time of diagnosis, the values of the exposure variables would have resulted in odds ratio estimates closer to unity.

After media coverage in late July, more than 90 newly diagnosed cases were identified in the next 4 months at VGH-K alone. Subsequently, there were no more newly diagnosed cases identified after November 1995 at VGH-K and in other parts of Taiwan (Dr. D. H. Hsieh, personal communication, 1996). It appears that the *S. androgyrus*-associated BO syndrome outbreak was interrupted by successful public education of cessation of *S. androgyrus* consumption through the mass media. However, additional studies are necessary to identify the active constituents of *S. androgyrus* that induces BO syndrome directly or promotes BO syndrome with other unknown agents.

In conclusion, our results clearly support the association of *S. androgyrus* ingestion with BO syndrome. Larger total amounts of *S. androgyrus* consumption, preparation of *S. androgyrus* food without cooking, and ingestion of *S. androgyrus* food prepared by vendors were the significant risk factors associated with BO syndrome.

ACKNOWLEDGMENTS

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