Incidence of Internal Cancers and Ingested Inorganic Arsenic: A Seven-Year Follow-up Study in Taiwan

Hung-Yi Chiou, Yu-Mei Hsueh, Kuen-Fu Liaw, Shan-Far Horng, Ming-Hsi Chiang, Yeong-Shiau Pu, Johnny Shin-Nan Lin, Chun-Hsiung Huang, and Chien-Jen Chen

ABSTRACT

In order to elucidate the dose-response relationship between ingested inorganic arsenic and internal cancers, a total of 263 patients with blackfoot disease and 2293 healthy residents in the endemic area of arseniasis were recruited and followed up for 7 years. The information on consumption of high-arsenic artesian well water, sociodemographic characteristics, life-style and dietary habits, and personal and family history of cancers was obtained through standardized interviews. The occurrence of internal cancers among study subjects was determined through annual health examinations, home visit personal interviews, household registration data checks, and national death certification and cancer registry profile linkage. A dose-response relationship was observed between the long-term arsenic exposure from drinking artesian well water and the incidence of lung cancer, bladder cancer, and cancers of all sites combined after adjustment for age, sex, and cigarette smoking through Cox's proportional hazards regression analysis. Blackfoot disease patients had a significantly increased cancer incidence after adjustment for cumulative arsenic exposure.

INTRODUCTION

Arsenic is a ubiquitous element widely distributed in the environment. It is transported mainly in the environment by water. Humans are exposed to inorganic and organic arsenic through environmental, medicinal, and occupational exposures. Both inorganic and organic arsenic is present in food in different amounts. For example, seafood contains a high concentration of organic arsenic. However, organic arsenic is much less toxic than inorganic arsenic. Some drugs containing inorganic arsenic have been used to treat leukemia, psoriasis, and asthma. It has also been used as a tonic. Workers who are engaged in smelting and refining copper, gold, and lead ores; in producing and using agricultural pesticides; in using arsenic as pigments and dyes; and in manufacturing glass, semiconductors, and various pharmaceutical substances may have a high exposure to air-borne arsenic (1, 2). The main source of arsenic exposure for the general population is through ingestion of water that contains a high level of inorganic arsenic. The safety level for arsenic in drinking water set by the United States Environmental Protection Agency is 0.05 mg/liter. In the United States, it has been estimated that about 350,000 people may drink water containing more than this level of arsenic (3).

Arsenic has been well documented as one of the major risk factors for BFD, a unique peripheral vascular disease identified in the endemic area of arseniasis located on the southwestern coast of Taiwan where residents had used high-arsenic artesian well water for more than 50 years (4, 5). Clinically the disease starts with numbness or coldness of one or more extremities and intermittent claudication, progresses to ulceration due to minor traumas, and ends with gangrene and spontaneous amputations (6, 7). BFD patients have a high prevalence of arsenic-induced skin lesions including hyperpigmentation, hyperkeratosis, and skin cancers. They also have a high risk of dying from cancers of the lung, liver, bladder, kidney, and prostate, as well as ischemic heart disease.

An increasing mortality from lung cancer due to occupational exposures to inorganic arsenic through inhalation has been reported among copper smelter workers of two large cohorts in Anaconda, MT (8-10), and Tacoma, WA (11-13). Significant associations between lung cancer risk and ingested inorganic arsenic have been observed in patients treated with arsenic-containing medicine (14), in Moselle vintners exposed to arsenic pesticides (15), and in persons exposed to inorganic arsenic from artesian well water (5, 16-21). Liver cancers including hepatic angiosarcoma and hepatocellular carcinoma have been associated with the long-term exposure to ingested and inhaled inorganic arsenic. The main arsenic exposure sources included contaminated wine, drinking water, Fowler's solution and copper smelting (16-24). Increased risk of bladder cancer was observed among patients treated with Fowler's solution; in Moselle vintners; and in workers in nonferrous metal smelters, refineries, and mines, as well as persons who drank high-arsenic artesian well water (15-21, 25). In a series of studies in Taiwan, an increasing mortality from cancers of the lung, liver, and bladder has been documented among residents in the endemic area of BFD (16-18, 20). A significant dose-response relationship between the arsenic concentration in well water and the mortality from various cancers has also been reported (21). Consistent findings have also been observed in a large-scale ecological correlation study on the association between arsenic concentration in well water and age-adjusted mortality from cancers of the nasal cavity, lung, liver, bladder, kidney, and prostate in 314 townships across Taiwan (19).

However, most previous studies were either ecological correlation studies or case-control studies. The former may have the problem of ecological fallacy, and the latter may be subject to the bias resulting from differential recall bias. Mortality rates rather than incidence rates were used to evaluate internal cancer risk induced by ingested inorganic arsenic in previous studies, but incidence rates are better than mortality rates for elucidating risk factors. Also, there has been no reported prospective follow-up study of the association between the long-term arsenic exposure through drinking artesian well water and the incidence of internal cancers. The aim of this study is to assess the dose-response relationship between cumulative exposure to ingested inorganic arsenic and incidence rate of cancers among residents in the BFD-endemic area.

MATERIALS AND METHODS

Study Area. The area covered in this study was limited to four BFD-endemic townships of Peimen, Hsuechua, Putai, and Ichu located on the southwestern coast of Taiwan. The prevalence of BFD in these four neighboring townships was 5.57, 3.87, 2.20, and 0.64/1000, respectively (26). Because
of the high salinity of shallow well water (6–8 m deep), residents in the area had used artesian well water (100–300 m deep) for more than 50 years. Artesian well water in the BFD-endemic area was found to have a high arsenic content ranging from 0.35 to 1.14 mg/liter with a median of 0.78 mg/liter, while the shallow well water in the BFD-endemic area had an arsenic content between nondetectable and 0.30 mg/liter with a median of 0.04 mg/liter (27).

It was estimated that the total amount of arsenic ingested daily by local residents was as high as 1 mg, mainly from drinking water (28).

Study Cohort. Study subjects were recruited from two independent studies. In our previous case-control study on multiple risk factors of BFD (5), a total of 249 BFD patients and 759 healthy community controls who were group matched on age, sex, and residential township had been recruited. Structured questionnaires were used to obtain information on possible risk factors of BFD and cancers through a standardized personal interview. Study subjects were then followed up to examine their occurrence of cancers and cardiovascular diseases. During the follow-up period, there were six healthy community controls affected with newly developed BFD. In the same time, another two

Cancer Mortality and BFD. In our previous case-control study on multiple risk factors of BFD (5), a total of 249 BFD patients and 759 healthy community controls who were group matched on age, sex, and residential township had been recruited. Structured questionnaires were used to obtain information on possible risk factors of BFD and cancers through a standardized personal interview. Study subjects were then followed up to examine their occurrence of cancers and cardiovascular diseases. During the follow-up period, there were six healthy community controls affected with newly developed BFD. In the same time, another two

BFD cases were hyperendemic in these three villages with a prevalence of 13.6, 9.6, and 10.3/1000, respectively. The median arsenic concentration in well water of these three villages ranged from 0.70 to 0.93 mg/liter (30). All study subjects from the 3 villages were interviewed at home using a structured questionnaire, and there were 6 BFD patients identified among them. Combining these two study cohorts together, there were 2256 study subjects including 263 BFD patients and 2293 health community residents in this study.

Questionnaire Interview. A standardized personal interview based on a structured questionnaire was carried out by public health nurses who were well trained in interview techniques and questionnaire details. The information obtained from questionnaire interviews included sociodemographic characteristics; residential and occupational history; history of drinking high-arsenic artesian well water; life-style variables including cigarette smoking and alcohol drinking; duration of sunlight exposure and physical activity at work; as well as personal and family history of hypertension, diabetes, vascular diseases, and various cancers. Detailed histories of residential address and duration of drinking artesian well water were used to derive cumulative arsenic exposure from drinking artesian well water for each study subject. The median arsenic level in artesian well water of each village where study subjects had lived was derived from previous studies carried out in the early 1960s (29). The cumulative arsenic exposure from drinking artesian well water in mg/liter × year for each study subject was calculated as the sum of the products, derived by multiplying the arsenic concentration in artesian well water (mg/liter) by the duration of drinking artesian well water (year) during consecutive periods of living in different villages, i.e.,

\[ \sum (C_i \times D_i) \]

where \( C_i \) was the median arsenic concentration in artesian well water of the village where a given study subject lived during the period \( i \), and \( D_i \) was the duration of drinking artesian well water in the village during the same period \( i \). In other words, this cumulative index equates the level of arsenic in artesian well water with the duration of drinking the water. The average arsenic concentration in drinking water was derived by the formula

\[ \frac{\sum (C_i \times D_i)}{\sum (D_i)} \]

Both cumulative arsenic exposure from drinking artesian well water and average arsenic concentration in drinking water were available only for those subjects for whom there was complete information on arsenic exposure from drinking artesian well water throughout their lifetime. These two arsenic exposure indices of a given subject were classified as unknown if the median arsenic level in artesian well water of any residential village through his/her lifetime was not available. The duration of living in the BFD-endemic area was calculated as the sum of years living in villages where the prevalence of BFD was >0.

Follow-up of Cancer Incidence. The study subjects were followed up regularly after recruitment. The occurrence of internal cancers among study subjects was determined through four channels including annual health examination, home visit personal interview, household registration data check, and national death certification and cancer registry profile linkages. By the end of January 1993, a total of 120 newly diagnosed internal cancer cases occurred during the follow-up period. The follow-up period ranged from 0.05 to 7.69 years [4.97 ± 1.72 (SD) years].

Data Analysis and Statistical Method. All the 120 newly diagnosed internal cancer cases including 27 lung cancer and 29 bladder cancer cases were involved in the assessment of cancer incidence induced by inorganic arsenic in artesian well water. Because BFD has been reported to be related to long-term arsenic exposure, the cancer risk associated with BFD and chronic arsenic exposure analysis was performed in three separate models: one included BFD status, age, sex, and cigarette smoking to evaluate cancer risks of BFD patients; another included long-term arsenic exposure, age, sex, and cigarette smoking in order to assess cancer risk associated with arsenic exposure; the third included long-term arsenic exposure, BFD status, age, sex, and cigarette smoking in order to explore relative risk of developing cancers for BFD status after adjustment for long-term arsenic exposure. Non-zero levels of arsenic exposure indices were categorized into relatively equal groups to avoid unstable estimation due to unequal categorization. Cox's proportional hazards regression analysis was used to estimate the multivariate-adjusted relative risk and its 95% confidence interval (31, 32). The statistical significance of a multivariate-adjusted relative risk was examined by the significance test of regression coefficient. Diseases related to long-term arsenic exposure were also included in the multiple regression model to examine their relative risk of developing internal cancers.

RESULTS

Table 1 shows the results of Cox’s proportional hazards regression analysis of cancer incidence for arsenic exposure indices and blackfoot disease status separately after adjustment for age, sex, and cigarette smoking. The duration of residing in BFD-endemic area was significantly associated with the incidence of all cancer sites combined and bladder cancer; the duration of drinking artesian well water was significantly associated with the incidence of all cancer sites combined and lung and bladder cancer. While the average arsenic concentration in drinking water was significantly associated with the incidence of bladder cancer only, the cumulative arsenic exposure of drinking artesian well water was significantly associated with the incidence of all sites combined and lung and bladder cancer. BFD patients had a significantly higher incidence of all cancer sites combined and lung and bladder cancer than did healthy residents.

The multivariate-adjusted relative risk of developing cancers of all sites combined and cancers of the lung and bladder among BFD patients and healthy residents are illustrated in Tables 2–4. There was a significant dose-response relationship among the incidence of all cancer sites combined, lung cancer and bladder cancer, and the cumulative arsenic exposure from drinking artesian well water. After adjustment for cumulative arsenic exposure and other risk factors, BFD patients still had a significantly higher incidence of various cancers than healthy residents. Cigarette smoking was also significantly associated with cancers of all sites combined and lung cancer. Men had a higher incidence of all cancer sites combined and bladder cancer than women, while women had a higher lung cancer incidence than men.

DISCUSSION

Compared with the general population in Taiwan, an increased mortality from cancers of the lung, liver, bladder, and skin has been reported among BFD patients and residents in the BFD-endemic area (5, 16). A case-control study carried out in the endemic area also
ARSENIC AND INTERNAL CANCERS

Table 1 Univariate analysis of relative risk of various cancers among blackfoot disease patients and healthy residents in the endemic area of arseniasis by arsenic exposure index and blackfoot disease status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Person yr</th>
<th>Case</th>
<th>ARR* (95% CI)</th>
<th>Case</th>
<th>ARR* (95% CI)</th>
<th>Case</th>
<th>ARR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of living in the endemic area (yr)</td>
<td>≤35</td>
<td>4,601</td>
<td>22</td>
<td>1.0</td>
<td>8</td>
<td>1.0</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>36–55</td>
<td>5,012</td>
<td>38</td>
<td>2.2 (1.3-3.8)</td>
<td>7</td>
<td>1.3 (0.5-3.8)</td>
<td>8</td>
<td>5.2 (1.1-25.1)</td>
</tr>
<tr>
<td></td>
<td>56+</td>
<td>3,100</td>
<td>60</td>
<td>3.1 (1.9-5.2)</td>
<td>12</td>
<td>1.6 (0.6-4.0)</td>
<td>19</td>
<td>12.8 (2.9-57.7)</td>
</tr>
<tr>
<td>Duration of drinking artesian well water (yr)</td>
<td>≤15</td>
<td>4,290</td>
<td>24</td>
<td>1.0</td>
<td>3</td>
<td>1.0</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>16–29</td>
<td>4,265</td>
<td>23</td>
<td>1.5 (0.9-2.6)</td>
<td>5</td>
<td>2.0 (0.5-8.4)</td>
<td>7</td>
<td>2.8 (0.7-10.8)</td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>4,159</td>
<td>64</td>
<td>2.0 (1.2-3.2)</td>
<td>19</td>
<td>4.6 (1.3-16.0)</td>
<td>19</td>
<td>5.1 (1.5-17.7)</td>
</tr>
<tr>
<td>Av. arsenic concentration in drinking artesian well water (mg/liter)</td>
<td>≤0.05</td>
<td>3,069</td>
<td>32</td>
<td>1.0</td>
<td>5</td>
<td>1.0</td>
<td>6</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.05–0.70</td>
<td>2,733</td>
<td>35</td>
<td>1.5 (0.9-2.4)</td>
<td>7</td>
<td>2.1 (0.7-6.8)</td>
<td>7</td>
<td>1.8 (0.6-5.3)</td>
</tr>
<tr>
<td></td>
<td>0.71+</td>
<td>2,672</td>
<td>23</td>
<td>1.4 (0.8-2.5)</td>
<td>7</td>
<td>2.7 (0.7-10.2)</td>
<td>7</td>
<td>3.3 (1.0-11.1)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>4,240</td>
<td>30</td>
<td>0.7 (0.4-1.2)</td>
<td>10</td>
<td>1.5 (0.5-4.3)</td>
<td>9</td>
<td>1.2 (0.4-3.4)</td>
</tr>
<tr>
<td>Cumulative arsenic exposure of drinking artesian well water (mg/liter × yr)</td>
<td>≤0.05</td>
<td>2,748</td>
<td>25</td>
<td>1.0</td>
<td>3</td>
<td>1.0</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.1–19.99</td>
<td>3,918</td>
<td>36</td>
<td>1.6 (1.0-2.7)</td>
<td>7</td>
<td>3.1 (0.8-12.2)</td>
<td>7</td>
<td>2.1 (0.6-7.2)</td>
</tr>
<tr>
<td></td>
<td>20+</td>
<td>1,808</td>
<td>29</td>
<td>2.0 (1.2-3.6)</td>
<td>7</td>
<td>4.7 (1.2-18.9)</td>
<td>9</td>
<td>5.1 (1.5-17.3)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>4,240</td>
<td>30</td>
<td>0.8 (0.5-1.4)</td>
<td>10</td>
<td>2.2 (0.6-8.1)</td>
<td>19</td>
<td>1.6 (0.5-5.3)</td>
</tr>
<tr>
<td>Status of blackfoot disease</td>
<td>No</td>
<td>11,265</td>
<td>83</td>
<td>1.0</td>
<td>18</td>
<td>1.0</td>
<td>16</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1,449</td>
<td>37</td>
<td>2.7 (1.9-4.1)</td>
<td>9</td>
<td>2.8 (1.2-6.2)</td>
<td>13</td>
<td>4.9 (2.3-10.2)</td>
</tr>
</tbody>
</table>

*RR, relative risk; CI, confidence interval.

Table 2 Multivariate-adjusted relative risk of cancers of all sites combined among blackfoot disease patients and healthy residents in the endemic area of arseniasis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>RR* 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Every-1-yr increment</td>
<td>1.05 (1.03-1.06)</td>
</tr>
<tr>
<td>Sex</td>
<td>Men</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.72 (0.43-1.18)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.52 (1.00-2.48)</td>
</tr>
<tr>
<td>Status of blackfoot disease</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.69 (1.80-4.01)</td>
</tr>
<tr>
<td>Cumulative arsenic exposure of drinking artesian well water (mg/liter × yr)</td>
<td>0.1–19.99</td>
<td>1.39 (0.82-2.37)</td>
</tr>
<tr>
<td></td>
<td>20+</td>
<td>1.76 (1.01-3.06)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>0.72 (0.42-1.22)</td>
</tr>
</tbody>
</table>

*RR, relative risk; CI, confidence interval. 

Because the arsenic concentration in drinking artesian well water of villages where study subjects had lived was not always available, the cumulative arsenic exposure of drinking artesian well water level was unknown for some study subjects. As shown in Table 1, the adjusted relative risks of developing cancers of all sites combined and cancer of the lung and bladder for study subjects with an unknown cumulative arsenic exposure from drinking artesian well water were between those shown for the lowest and highest exposure groups. The absence of cumulative arsenic exposure from drinking artesian well water levels for about 33% of the study subjects does not affect the assessment of association between long-term exposure to arsenic and incidence from internal cancers.

Physical and chemical characteristics of drinking water, such as pH value and levels of arsenic, sodium, calcium, magnesium, manganese, iron, mercury, chromium, lead, nitrite and nitrate nitrogen, fluoride, and bicarbonate, have been intensively studied in the BFD-endemic and nonendemic areas (27, 33). Arsenic level was found to be the only item that was significantly higher than maximum allowable limit and strikingly different in water from shallow wells and artesian wells. Arsenic is thus the main chemical in the water responsible for the increased incidence of internal cancer. Fluorescent substances, especially humic substances, have also been suspected to be associated with development of BFD (34). However, there was no evidence of human carcinogenicity of humic substances in epidemiological stud-

Table 3 Multivariate-adjusted relative risk of lung cancer among blackfoot disease patients and healthy residents in the endemic area of arseniasis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>RR* 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Every-1-yr increment</td>
<td>1.06 (1.02-1.10)</td>
</tr>
<tr>
<td>Sex</td>
<td>Men</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1.79 (0.44-7.32)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4.31 (1.08-17.20)</td>
</tr>
<tr>
<td>Status of blackfoot disease</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.45 (1.07-5.57)</td>
</tr>
<tr>
<td>Cumulative arsenic exposure of drinking artesian well water (mg/liter × yr)</td>
<td>0.1–9.9</td>
<td>2.74 (0.69-11.0)</td>
</tr>
<tr>
<td></td>
<td>20+</td>
<td>4.01 (1.00-16.12)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2.01 (0.55-7.36)</td>
</tr>
</tbody>
</table>

*RR, relative risk; CI, confidence interval. 

**documented a significant dose-response relationship between mortality from cancers of the lung, bladder, and liver and the duration of drinking high-arsenic artesian well water (17). The dose-response relationship between arsenic concentration in drinking water and mortality from various malignant neoplasms at village level was also observed in an ecological correlation study on cancer risk among residents in the BFD-endemic area (20). The association between arsenic concentration in well water and age-adjusted mortality from cancers has also been found in a large-scale ecological correlation study including 314 townships in Taiwan (19). However, there may exist some limitations in both ecological correlation studies and case-control studies aimed at exploring the causal relation between risk factors and health outcomes. Ecological correlation studies may have the problem of ecological fallacy while case-control studies may be subject to recall bias which may either underestimate or overestimate the association between risk factors and diseases. In order to elucidate associations between cancer risk and ingested inorganic arsenic from drinking artesian well water it would be better to use incidence rate rather than mortality rate as the health outcome. To the best of our knowledge, this is the first cohort study aimed to evaluate the dose-response relationship between the long-term exposure to arsenic in artesian well water and the incidence of internal cancers at the individual level.**
ies (35). Humic substances resulting from the decomposition of organic matter, particularly dead plants, are widespread contaminants of water supplies. No correlation between humic substances and cancers has ever been documented.

BFD has been considered to be related to long-term arsenic exposure. Table 1 shows that BFD patients had a significantly higher risk to develop various cancers after adjustment for age, sex, and cigarette smoking. However, even in multivariate-adjusted models including cumulative arsenic exposure from drinking artesian well water, as shown in Tables 2–4, a significantly higher cancer incidence was still observed in patients with BFD compared to healthy residents in the BFD-endemic area.

The observation that blackfoot disease is an independent risk factor for cancer even after controlling for the long-term exposure to arsenic may be the result of the greater amounts of water consumed by these patients, higher levels of arsenic in their personal wells, or an individual susceptibility to arsenic.

Cigarette smoking is a well-documented cause of cancer. After adjustment for the cumulative arsenic exposure from drinking artesian well water, age, sex, and status of BFD, cigarette smoking was significantly associated with the incidence of all cancers sites combined and lung cancer. In other words, among residents in the BFD-endemic area, cigarette smokers have a higher risk of developing cancer than do nonsmokers. Arsenic has been suggested to play a role in the promotion or progression of cancer development (36–38), although its effect on the early carcinogenesis cannot be ruled out. Cigarette smoking might be at least an initiator in arsenic-induced cancers.

Inorganic arsenic which enters the body through ingestion is quickly absorbed into the blood stream. Most inorganic arsenic in the body is transported to the liver and converted into various species of different oxidation states and organometalloidal forms through methylation processes. Although most methylated arsenic species are efficiently excreted in the urine, some of them may be deposited in tissues of the lung, liver, kidney, hair, and nails. In other words, systemic toxicity of ingested inorganic arsenic might be due to its systematic distribution in humans.

Arsenic is a well-documented human carcinogen of skin and lung. It is also involved in the development of other cancers, especially in the liver and the urinary system. However, limited evidence supports the carcinoogenicity of inorganic arsenic in experimental animals. The discrepancy between animal and human studies might be due to the higher capability of inorganic arsenic methylation in animals than in humans. In other words, humans are more sensitive to inorganic arsenic than animals. Inorganic arsenic compounds induce cultured cell transformation, chromosomal aberration, increased frequency of sister chromatid exchanges, and gene amplification (39–41), but they are inactive or extremely weak to induce gene mutations at specific loci (24, 42). The role of inorganic arsenic in carcinogenesis has been suggested as a promoter or progressor but not an initiator (36–38). However, the exact mechanism by which inorganic arsenic induces internal cancers in humans remains unclear. Further studies are needed to elucidate possible mechanisms of arsenic-induced carcinogenicity.

REFERENCES

30. Kuo, T. L. Arsenic content of artesian well water in endemic area of chronic arsenic
Incidence of Internal Cancers and Ingested Inorganic Arsenic: A Seven-Year Follow-up Study in Taiwan

Hung-Yi Chiou, Yu-Mei Hsueh, Kuen-Fu Liaw, et al.


**Updated version**  
Access the most recent version of this article at:  
[http://cancerres.aacrjournals.org/content/55/6/1296](http://cancerres.aacrjournals.org/content/55/6/1296)

**E-mail alerts**  
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**  
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**  
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.