Malignant Neoplasms among Residents of a Blackfoot Disease-endemic Area in Taiwan: High-Arsenic Artesian Well Water and Cancers

Chien-Jen Chen,2 Ya-Chien Chuang, Tong-Ming Lin, and Hsin-Yin Wu

ABSTRACT

The objective of this study is to elucidate the association between high-arsenic artesian well water and cancers in endemic area of blackfoot disease, a unique peripheral vascular disease related to continuous arsenic exposure. As compared with the general population in Taiwan, both the standardized mortality ratio (SMR) and cumulative mortality rate were significantly high in blackfoot disease-endemic areas for cancers of bladder, kidney, skin, lung, liver, and colon. The SMRs for cancers of bladder, kidney, skin, lung, liver, and colon were 1010, 764, 522, 310, 170, and 168, respectively, for males, and 2009, 1119, 652, 413, 229, and 168, respectively, for females. A dose-response relationship was observed between SMRs of the cancers and blackfoot disease prevalence rate of the villages and townships in the endemic area. SMRs of cancers were greater in villages where only artesian wells were used as the drinking water source than in villages using both artesian and shallow wells, and even greater than in villages using shallow wells only.

INTRODUCTION

BFD3 is an endemic peripheral vascular disorder confined to a limited area on the southwest coast of Taiwan (1). Clinically, the disease starts with numbness or coldness of one or more extremities and intermittent claudication which progresses to black discoloration, ulceration, and gangrene. In end stages of the disease, spontaneous amputation of the distal parts of the affected extremities is common (2). Although its etiology is still unclear, BFD has been related to drinking water derived from artesian wells in the endemic areas (3). Substances including organic chlorides and organoalkaloids have been identified in artesian well water; however, arsenic has been suggested as the most important determinant of BFD (4–6).

Previous studies have shown that the crude mortality rate of cancer was higher in BFD-endemic areas than the general population in Taiwan (7). It has also been found that the prevalence rate of skin cancer in a BFD-endemic area was as high as 10.6/1000 (8), and a dose-response relationship was observed between the prevalence rate of skin cancer and the arsenic concentration of the well water in villages of the endemic area (9). However, epidemiological characteristics of other cancers have never been studied.

In order to examine cancer mortality rates in BFD-endemic areas during the period from 1968 to 1982 and to explore their possible associations with artesian well water and BFD endemcity, the specific aims of this study include: (a) to compare SMRs and age-specific CMRs of various cancers in the BFD-endemic area with those in Taiwan; (b) to compare SMRs of cancers in townships with different BFD prevalence rates; (c) to compare SMRs of cancers in villages with different BFD endemcity; and (d) to compare SMRs of cancers in villages using artesian wells and/or shallow wells.

MATERIALS AND METHODS

Study Area. The area covered in this study was limited to the townships of Peimen, Hsuechia, Putai, and Ichu where previous studies have shown BFD to be distinctly prevalent with rates per 1000 of 5.57, 3.87, 2.02, and 0.64, respectively (1). These four neighboring townships are located on the southwest coast of Taiwan. The soil of this area has a high salt content, and the water from shallow wells (6 to 8 m in depth) of this area also has a high salinity. For this reason, some residents of this area have been using water from artesian wells (100 to 200 m deep), since the 1920s, especially those living in villages along the coast (4). Totally, there were 84 villages in the study area: 31 villages using only artesian wells; 27 using both artesian and shallow wells; 24 using only shallow wells; and 2 using surface water in the stream (3). Even after 1956 when the piped water was first supplied, some people still use the artesian well water for agriculture, pisciculture, and for drinking and washing (5).

It was noted in an early report that the arsenic content of artesian well water in BFD-endemic areas ranged from 0.35 to 1.14 ppm with a median of 0.78 ppm, while the shallow well water in BFD-endemic areas had arsenic content between 0.00 and 0.30 ppm with a median of 0.04 ppm (4). A more recent study in which a total of 83,565 wells from all over Taiwan was examined showed that 29.1% of the wells had an arsenic content greater than 0.05 ppm, and 5.2% of the wells had an arsenic content greater than 0.35 ppm with a highest value of 2.5 ppm in the BFD-endemic area, while only 5.7% of the wells had an arsenic content greater than 0.05 ppm; and 0.3% of the wells had an arsenic content greater than 0.35 ppm in other areas of Taiwan (10). The arsenic content of surface soil samples in BFD-endemic areas ranged from 5.3 mg/kg to 11.2 mg/kg with a median of 7.2 mg/kg, and farm products and fishes also had significantly high arsenic content in areas where artesian well water was extensively used for agriculture and pisciculture (11). It was estimated that the total daily arsenic ingested by residents in BFD-endemic areas was as high as 1 mg (12).

The BFD was first observed in this area in late 1920s after artesian wells were implemented, and none of these BFD cases was reported in villages where only shallow well water or surface water was used (3). There was a decreasing gradient of BFD prevalence rate following the order of villages using artesian wells only, villages using both types of wells, and villages using only shallow wells (3). Villages in the study area were grouped into three subareas according to their BFD endemcity: hyperendemic area including 21 villages with a BFD prevalence greater than 5.0/1000; endemic area including 25 villages with a BFD prevalence between 0.1 and 5.0/1000; and nonendemic area including 38 villages where no BFD case was reported (1).

Study Population. It is obligatory to register any event of birth, death, and marriage in Taiwan. The death certificates of Taiwan residents were collected in every death registration form. Information on the place of residence and date of death were recorded in every death certificate. Two computerized databases were used to store the data: the Taiwan Mortality Census Database and the Taiwan Population Census Database. The latter was used to compute the death rates and the former to compute the person-years of observation.

1 This study is supported by the Taiwan Provincial Department of Health.
2 To whom requests for reprints should be addressed, at Institute of Public Health, NTU College of Medicine, 1, Jen-AI Rd. Sec. 1, Taipei, Taiwan, Republic of China.
3 The abbreviations used are: BFD, blackfoot disease; SMR, standardized mortality ratio; CMR, cumulative mortality rate.
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Mortality rates of cancers of the esophagus, nasopharynx, bladder, kidney, skin, lung, liver, and colon in the BFD-endemic area and in Taiwan are illustrated in Chart 1. The CMRs of these cancers were higher in the BFD-endemic area than in Taiwan for all age groups. The older the age, the larger the difference in CMRs between the BFD-endemic area and Taiwan for these cancers except colon cancer. The differences in CMRs between the BFD-endemic area and Taiwan were greater in females than in males for all age groups. The CMRs of females in the BFD-endemic area were higher than those of males in Taiwan for all these cancers except for liver cancer.

SMRs of Cancers in Townships and Villages with Different BFD Endemcity. Chart 2 indicates sex-specific SMRs for cancers of the bladder, kidney, skin, lung, liver, and colon in townships of Peimen, Hsuechia, Putai, and Ichu following a declining gradient of BFD prevalence rate. The SMRs were higher in females than in males for all the cancers in all the townships besides the colon cancer in Putai. Generally speaking, the higher the BFD prevalence rate of a township, the greater the SMRs for cancers of bladder, kidney, skin, and lung of the townships. However, the declining gradient of SMRs was not in the order of the BFD prevalence rates of the townships for cancers of liver and colon. Chart 3 depicts age- and sex-adjusted SMRs in villages where BFD was hyper endemic, endemic, or non-endemic. A dose-response relationship was observed between BFD endemcity and SMRs of cancers of the bladder, kidney, skin, lung, and liver, but not between BFD endemcity and SMR of colon cancer. The villages without any BFD case still showed SMRs greater than 150 for these cancers.

SMRs of Cancers in Villages Using Different Types of Wells. SMRs of various cancers in villages with different types of wells are shown in Chart 4. The SMRs for cancers of the bladder, kidney, skin, lung, and liver were highest in villages where only artesian wells were used and lowest in villages where only shallow wells were used. However, villages using only shallow wells still had SMRs greater than 150 for these cancers.

**RESULTS**

**SMRs of Cancers in the BFD-endemic Area.** The SMRs with their 95% confidence intervals of various cancers were classified according to the codes of the eighth revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death shown in Table 1. The SMRs were significantly higher (P < 0.05) in the BFD-endemic area than in Taiwan for cancers of bladder, kidney, skin, lung, liver, and colon for both sexes with higher SMRs for females than males. The SMR for cancer of the small intestine was as high as 298 for males, but only 97 for females. Mortality rates of cancers of the esophagus, nasopharynx, leukemia, rectum, stomach, and thyroid were about the same in the BFD-endemic area and in Taiwan. The age-adjusted mortality rates for various cancers are also shown in the Table 1. The age-adjusted mortality rates for liver cancer and nasopharyngeal cancer were greater in Taiwan than in other countries of the world, while those for other cancers were within the normal range of the world.

**CMRs of Cancers in the BFD-endemic Area.** The age-specific CMRs for cancers of the bladder, kidney, skin, lung, liver, and colon in the BFD-endemic area and in Taiwan are illustrated in Chart 1. The CMRs of these cancers were higher in the BFD-endemic area than in Taiwan for all age groups. The older the age, the larger the difference in CMRs between the BFD-endemic area and Taiwan for these cancers except colon cancer. The differences in CMRs between the BFD-endemic area and Taiwan were greater in females than in males for all age groups. The CMRs of females in the BFD-endemic area were higher than those of males in Taiwan for all these cancers except for liver cancer.
### Table 1

<table>
<thead>
<tr>
<th>Cancer (ICD codes)</th>
<th>Sex</th>
<th>Age-adjusted rate in Taiwan&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. observed</th>
<th>No. expected</th>
<th>Standardized mortality ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% confidence interval</th>
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<td></td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td>Ratio</td>
<td></td>
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<tr>
<td>Bladder (188)</td>
<td>Male</td>
<td>2.71</td>
<td>167</td>
<td>15.2</td>
<td>1100</td>
<td>933-1267</td>
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<tr>
<td></td>
<td>Female</td>
<td>1.26</td>
<td>165</td>
<td>8.2</td>
<td>2009</td>
<td>1702-2316</td>
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<td>Kidney (189.0)</td>
<td>Male</td>
<td>0.85</td>
<td>42</td>
<td>5.4</td>
<td>772</td>
<td>537-1007</td>
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<tr>
<td></td>
<td>Female</td>
<td>0.81</td>
<td>62</td>
<td>5.5</td>
<td>1119</td>
<td>838-1400</td>
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<tr>
<td>Skin (172)</td>
<td>Male</td>
<td>1.49</td>
<td>48</td>
<td>8.6</td>
<td>534</td>
<td>379-689</td>
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<tr>
<td></td>
<td>Female</td>
<td>1.15</td>
<td>49</td>
<td>7.5</td>
<td>652</td>
<td>469-835</td>
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<td>Lung (162)</td>
<td>Male</td>
<td>17.08</td>
<td>332</td>
<td>103.8</td>
<td>330</td>
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<td></td>
<td>Female</td>
<td>8.34</td>
<td>233</td>
<td>55.6</td>
<td>413</td>
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<tr>
<td>Liver (155)</td>
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<td>26.72</td>
<td>305</td>
<td>179.4</td>
<td>170</td>
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<td>9.19</td>
<td>146</td>
<td>63.7</td>
<td>229</td>
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<td>Colon (153)</td>
<td>Male</td>
<td>5.49</td>
<td>54</td>
<td>33.8</td>
<td>160</td>
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<tr>
<td></td>
<td>Female</td>
<td>5.38</td>
<td>61</td>
<td>36.3</td>
<td>168</td>
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<td>Small intestine (152)</td>
<td>Male</td>
<td>0.91</td>
<td>17</td>
<td>5.7</td>
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<td></td>
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<td>0.76</td>
<td>5</td>
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<td>Esophagus (150)</td>
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<td>7.29</td>
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<td>42.8</td>
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<td>1.63</td>
<td>12</td>
<td>10.8</td>
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<td>Nasopharynx (147)</td>
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<td>1.55</td>
<td>17</td>
<td>11.3</td>
<td>151</td>
<td>79-223</td>
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<td>Leukemia (204–208)</td>
<td>Male</td>
<td>3.36</td>
<td>45</td>
<td>31.6</td>
<td>142</td>
<td>100-184</td>
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<tr>
<td></td>
<td>Female</td>
<td>2.72</td>
<td>22</td>
<td>24.6</td>
<td>90</td>
<td>53-127</td>
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<td>Rectum (154)</td>
<td>Male</td>
<td>2.85</td>
<td>21</td>
<td>17.5</td>
<td>120</td>
<td>69-171</td>
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<td>15</td>
<td>16.1</td>
<td>93</td>
<td>46-140</td>
</tr>
<tr>
<td>Stomach (151)</td>
<td>Male</td>
<td>2.28</td>
<td>112</td>
<td>132.5</td>
<td>85</td>
<td>69-101</td>
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<tr>
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<td>73.1</td>
<td>112</td>
<td>88-196</td>
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<tr>
<td>Thyroid (193)</td>
<td>Male</td>
<td>0.24</td>
<td>1</td>
<td>1.4</td>
<td>69</td>
<td>-71-209</td>
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<tr>
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<td>Female</td>
<td>0.50</td>
<td>2</td>
<td>3.4</td>
<td>60</td>
<td>-22-142</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Age-adjusted mortality rate per 100,000 using 1976 world population as standard population.

<sup>b</sup> Age-specific mortality rates in Taiwan were used as standard rates to calculate the standardized mortality ratio; i.e., SMR for each cancer in Taiwan is 100.

Factors is thus much more reduced in males than in females of the BFD-endemic area.

The dose-response relationships between the BFD prevalence rate and cancer mortality rates suggested that BFD and these cancers might share some common local risk factors. The association between artesian well water and cancers was also suggested by the declining gradient of cancer mortality following the order of villages using artesian well only, villages using both types of wells, and villages using shallow wells only.

A high content of arsenic in artesian well water might be one of the most important determinants of cancers in BFD-endemic areas, as the artesian well water was used not only for drinking but also for daily washing, agriculture, and pisciculture. The surface soil and farm products in the BFD-endemic area have been found to have a high arsenic content. There were possibilities for residents of the BFD-endemic area to be exposed to arsenic by either skin contact or respiratory deposition in addition to gastrointestinal absorption. The p.o. and i.v. administration of radiolabeled arsenic to mice, rabbits, guinea pigs, hamsters, chickens, and monkeys did show wide distribution of the isotope in the body. The highest levels of arsenic were observed in liver, kidney, skin, lung, large intestine, and spleen (20–24). Following injection of radiolabeled arsenic in patients terminally ill with malignant diseases, the isotope was found to be widely distributed in the body just as in the case of experimental animals (25).

Although long-term animal tests for the carcinogenicity of arsenic did not show positive results (26, 27), occupational, environmental, and medicinal exposures to inorganic arsenics were related to lung cancer, skin cancer, and liver cancer (9, 28, 29). The association between arsenic exposure and cancers of lung and skin has long been documented. It is obvious that the increase in mortality rates of these two cancers in the BFD-endemic area is related to arsenic exposure. The arsenic compounds were found to be associated with hepatic angiosarcoma of the liver (30, 31), but most liver cancers in Chinese are hepatocellular carcinoma with cirrhosis which has been related to the hepatitis B viral infection (32). It thus remains to be elucidated whether or not the development of liver cancer in the BFD-endemic area has resulted from the interactive effects of exposures to arsenic, hepatitis B virus, and aflatoxin.

The association between arsenic exposure and bladder cancer, kidney cancer, and colon cancer has not been documented. Most residents of BFD-endemic areas engaged in farming, fishery, and salt production, and schistosomiasis has never been reported in this area. Neither the occupational exposure nor the Schistosoma haematobium infection seems likely to be an im-
Chart 1. Age-specific cumulative mortality rates of bladder cancer, kidney cancer, skin cancer, lung cancer, liver cancer, and colon cancer for males and females in the BFD-endemic area and in Taiwan. Age-specific curves are shown for four groups: males in the BFD-endemic area (bold solid line); females in the BFD-endemic area (bold broken line); males in Taiwan (fine solid line); and females in Taiwan (fine broken line).

Chart 2. Sex-specific SMRs for cancers of bladder, kidney, skin, lung, liver, and colon in the townships of Reimen, Hsuechia, Putai, and Ichu where foot disease prevalence rates were 5.57, 3.87, 2.02, and 0.64/1000, respectively. Age-specific mortality rates of these cancers in Taiwan were used as standard rates. (Scale of SMR is in logarithm.)

Chart 3. SMRs for cancers of the bladder, kidney, skin, lung, liver, and colon in three areas with different endemicity of BFD: hyperendemic area where the BFD prevalence rate was greater than 5.0/1000; endemic area where the BFD prevalence rate was between 0.1 and 5.0/1000; and nonendemic area where no BFD case was reported. Age- and sex-specific mortality rates of these cancers in Taiwan were used as standard rates. (Scale of SMR is in logarithm.)

Chart 4. SMR for cancers of the bladder, kidney, skin, lung, liver, and colon in three areas where different types of wells were used as drinking water source: area where only artesian wells were used; area where both artesian and shallow wells were used; and area where only shallow wells were used. Age- and sex-specific mortality rates of these cancers in Taiwan were used as standard rates. (Scale of SMR is in logarithm.)

Important reason for the high mortality rate of bladder cancer in this area. Cigarette smoking has been related to cancers of kidney and bladder, but the extraordinarily high SMRs of these two cancers were not readily explained by the relatively higher cigarette smoking rate in the BFD-endemic area than in Taiwan (40% versus 32%). The dietary pattern of residents in the BFD-endemic area was not different from that of the general population in Taiwan. They even consume more vegetables, fiber, and complex carbohydrates than do residents of other sociologically better developed areas in Taiwan. The only significant difference in environment between the BFD-endemic areas and
other areas is the arsenic content of the drinking water, surface soil, and farm products derived from artesian well water. The high mortality rates of cancers of the bladder, kidney, and colon in the BFD-endemic area are thus most probably attributable to the high-arSENic artesian well water of the areas. However, further investigations through prospective study of cancers among residents in the BFD-endemic area are needed to confirm the relationship between artesian well water and cancers.

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