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

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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 1100, 734, 320, 170, and 160, 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 areas. 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

BFD 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 ergot alkaloids 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 endemicty, 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 endemicity; 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 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 endemicity: 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,
marriage, divorce, and migration in the household registration offices, and the registered household information is annually checked through a home-visit interview by the registration office. Highly accurate and complete population and vital statistics are continuously produced, which makes reliable demographic data available since 1905 (13). The midyear population in Taiwan increased steadily from 13,682,588 in 1968 to 18,515,754 in 1982 with an annual natural increase rate of 21.6%, and only a small percentage of people migrated to foreign countries (0.54%). The population in the BFD-endemic area decreased from 141,733 in 1968 to 120,607 in 1982, with an average natural increase rate of 15.6% and an average emigration rate of 27.0%. Although youths and young adults tended to emigrate to metropolitan areas as in the case of other rural townships in Taiwan, those who aged 45 or more yr old emigrated to metropolitan areas with a much lower rate of 6.0%. Most of the residents in the BFD-endemic areas engaged in farming, fishery, and salt production. Their educational level and socioeconomic status were below the average as compared with the general population in Taiwan.

As cancer mortality rates from 1968 to 1982 were studied, the average population for each age-sex group during this period of time was used to calculate CMRs and SMRs. When age-adjusted mortality rates of cancers were computed, the 1976 world population was used as the standard population (14).

Mortality Analysis. As it is mandatory for local household registration offices to submit standardized certificates of each death to the Department of Health, the vital statistics are thus very complete in Taiwan (15). According to a recent report, all the cancers except liver cancer were more than 85% confirmed either histologically or cytologically (16). The crude death rate in Taiwan decreased from 5.38% in 1968 to 4.77% in 1983, mainly due to the decline of the infant mortality rate. The age-adjusted cancer mortality rate in Taiwan increased from 89.4/100,000 in 1968 to 107.4/100,000 in 1982, while it increased from 160.9/100,000 in 1968 to 225.5/100,000 in 1982 in the BFD-endemic area. In this study, all the certifications of cancer deaths obtained from the Information Center of the Taiwan Provincial Department of Health were further reviewed by the researchers.

Both SMRs (17) and CMRs (18) in the BFD-endemic area and Taiwan were compared for various cancers grouped according to the expansion 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 in both sexes with higher SMRs for females than males. The SMR for cancer of the small intestine was as high as 258 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

RESULTS

SMRs of Cancers in the BFD-endemic Area. The SMRs with their 95% confidence intervals of various cancers were classified according to the code 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 in both sexes with higher SMRs for females than males. The SMR for cancer of the small intestine was as high as 258 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 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 Endemicity. Chart 2 indicates sex-specific SMRs for cancers of the bladder, kidney, skin, lung, liver, and colon in townships of Peimen, Hsuechia, Putai, and Ichou 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, lung, and liver of the township. 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 hyperendemic, endemic, or nonendemic. A dose-response relationship was observed between BFD endemicity and SMRs of cancers of the bladder, kidney, skin, lung, and liver, but not between BFD endemicity 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.

DISCUSSION

The extraordinarily high prevalence of BFD in the limited area on the southwest coast of Taiwan has attracted researchers to explore its risk factors and etiological mechanism. Epidemiological studies did show that artesian well water was significantly associated with the disease. It has been reported that BFD patients, their family members, and healthy controls in the BFD-endemic area had much higher arsenic content in their hair and urine than residents of other areas in Taiwan (19).

Significantly high mortality rates of cancers in the BFD-endemic area might be due to some local risk factors which were either unique or in much greater quantity in this area than other areas of Taiwan. The exposure and/or effects of these local risk factors might be accumulated gradually over a long period of time and thus contribute to the increased difference in SMRs between the BFD-endemic area and Taiwan with the increase in age. Greater SMR discrepancy between the BFD-endemic area and Taiwan in females than in males might be attributable to the fact that males are exposed to more risk factors in addition to local ones than are females. The relative impact of the local risk factors...
Table 1

Standardized mortality ratios with their 95% confidence intervals for various cancers by sex in blackfoot disease-endemic area in Taiwan, 1968–1982

<table>
<thead>
<tr>
<th>Cancer (ICD codes)</th>
<th>Sex</th>
<th>Age-adjusted rate in Taiwan*</th>
<th>Number of deaths</th>
<th>Standardized mortality ratiob</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. observed</td>
<td>No. expected</td>
<td>Ratio</td>
</tr>
<tr>
<td>Bladder (188)</td>
<td>Male</td>
<td>2.71</td>
<td>167</td>
<td>15.2</td>
<td>1100</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>
</tr>
<tr>
<td>Kidney (189.0)</td>
<td>Male</td>
<td>0.85</td>
<td>42</td>
<td>5.4</td>
<td>772</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>
</tr>
<tr>
<td>Skin (172)</td>
<td>Male</td>
<td>1.49</td>
<td>48</td>
<td>8.6</td>
<td>534</td>
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<tr>
<td></td>
<td>Female</td>
<td>1.15</td>
<td>49</td>
<td>7.5</td>
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<tr>
<td>Lung (162)</td>
<td>Male</td>
<td>17.08</td>
<td>332</td>
<td>103.8</td>
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<td>Female</td>
<td>8.34</td>
<td>233</td>
<td>56.5</td>
<td>413</td>
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<tr>
<td>Liver (155)</td>
<td>Male</td>
<td>26.72</td>
<td>305</td>
<td>179.4</td>
<td>170</td>
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<td></td>
<td>Female</td>
<td>9.19</td>
<td>146</td>
<td>63.7</td>
<td>229</td>
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<tr>
<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>
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<tr>
<td>Small intestine (152)</td>
<td>Male</td>
<td>0.91</td>
<td>17</td>
<td>5.7</td>
<td>298</td>
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<td></td>
<td>Female</td>
<td>0.76</td>
<td>5</td>
<td>5.2</td>
<td>97</td>
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<tr>
<td>Esophagus (150)</td>
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<td>7.29</td>
<td>53</td>
<td>42.8</td>
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<td></td>
<td>Female</td>
<td>1.63</td>
<td>12</td>
<td>10.8</td>
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<tr>
<td>Nasopharynx (147)</td>
<td>Male</td>
<td>3.74</td>
<td>26</td>
<td>26.1</td>
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<td>1.55</td>
<td>17</td>
<td>11.3</td>
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<tr>
<td>Leukemia (204–208)</td>
<td>Male</td>
<td>3.36</td>
<td>45</td>
<td>31.6</td>
<td>142</td>
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<tr>
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<td>Female</td>
<td>2.72</td>
<td>22</td>
<td>24.6</td>
<td>90</td>
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<tr>
<td>Rectum (154)</td>
<td>Male</td>
<td>2.85</td>
<td>21</td>
<td>17.5</td>
<td>120</td>
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<tr>
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<td>Female</td>
<td>2.37</td>
<td>15</td>
<td>16.1</td>
<td>93</td>
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<tr>
<td>Stomach (151)</td>
<td>Male</td>
<td>22.17</td>
<td>112</td>
<td>132.5</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10.91</td>
<td>82</td>
<td>73.1</td>
<td>112</td>
</tr>
<tr>
<td>Thyroid (193)</td>
<td>Male</td>
<td>0.24</td>
<td>1</td>
<td>1.4</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.50</td>
<td>2</td>
<td>3.4</td>
<td>60</td>
</tr>
</tbody>
</table>

* Age-adjusted mortality rate per 100,000 using 1976 world population as standard population.

b 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.
High-Arsenic Artesian Well Water and Cancers

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 Blackfoot 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 socioeconomically 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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