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ABSTRACT

A significant dose-response relation between ingested arsenic and several cancers has recently been reported in four townships of the endemic area of blackfoot disease, a unique peripheral artery disease related to the chronic arsenic exposure in southwestern Taiwan. This study was carried out to examine ecological correlations between arsenic level of well water and mortality from various malignant neoplasms in 314 precincts and townships of Taiwan. The arsenic content in water of 83,656 wells was determined by a standard mercuric bromide stain method from 1974 to 1976, while mortality rates of 21 malignant neoplasms among residents in study precincts and townships from 1972 to 1983 were standardized to the world population in 1976. A significant association with the arsenic level in well water was observed for cancers of the liver, nasal cavity, lung, skin, bladder and kidney in both males and females as well as for the prostate cancer in males. These associations remained significant after adjusting for indices of urbanization and industrialization through multiple regression analyses. The multivariate-adjusted regression coefficient indicating an increase in age-adjusted mortality per 100,000 person-years for every 0.1 ppm increase in arsenic level of well water was 6.8 and 2.0, 0.7 and 0.4, 5.3 and 5.3, 0.9 and 1.0, 3.9 and 4.2, as well as 1.1 and 1.7, respectively, in males and females for cancers of the liver, nasal cavity, lung, skin, bladder and kidney. The multivariate-adjusted regression coefficient for the prostate cancer was 0.5. These weighted regression coefficients were found to increase or remain unchanged in further analyses in which only 170 southwestern townships were included.

INTRODUCTION

Although arsenic has been documented as a human carcinogen of skin and lung (1), the role of arsenic in the determination of other internal organ cancers remains to be elucidated (2). We reported a significantly high mortality from cancers of the skin, lung, liver, bladder, and kidney among residents of four townships in the endemic area of blackfoot disease, a unique peripheral artery disease associated with chronic arsenic exposure in southwestern Taiwan. The standardized mortality ratios for these cancers in different villages showed a dose-response relation to the endemicity of blackfoot disease (3). A recent case-control study of malignant neoplasms of the bladder, lung, and liver in this area also showed a significant association with the duration of high-arsenic artesian well water use (4). Furthermore, dose-response relations between the arsenic content in well water and mortality rates from cancers of the skin, lung, liver, bladder, kidney, and prostate were observed in 42 villages of the blackfoot disease endemic area (5, 6). Patients with blackfoot disease also had a higher mortality from these cancers than the general population in this area (7).

However, the associations between arsenic and cancers were inconclusive in populations other than that in the blackfoot disease endemic area. This study was carried out to examine ecological correlations between arsenic content in well water and mortality from various malignant neoplasms in 314 precincts and townships of Taiwan as a whole. Indices of urbanization and industrialization were also adjusted through multiple regression analyses in this study.

MATERIALS AND METHODS

Study Areas. To the southeast of mainland China, Taiwan includes a main island, Penghu Islets, Green Islet, Lanyue Islet, and Liuchiu Islet. There are >20 million inhabitants living in an area of 36,000 km². Most residents in Taiwan are Fukien and Hakka Taiwanese. Mainland Chinese who or whose parents migrated to Taiwan after the Second World War mostly live in cities, while most aborigines live in the mountainous area and Lanyue Islet. Among 361 administrative districts in Taiwan, 36 metropolitan precincts, 264 urban and rural townships, and 14 aboriginal townships where the arsenic content in well water was examined by the Taiwan Provincial Institute of Environmental Sanitation from 1974–1976 (8) were included in this study. Fig. 1 shows the map of Taiwan indicating 314 study precincts and townships including 4 townships in the endemic area of blackfoot disease. There are one urban and five rural townships in Penghu Islets which are located to the west of the main island. Aboriginal townships are clustered in central and eastern Taiwan.

Because it is mandatory to register any event of birth, marriage and divorce, employment, education, migration, and death in the household registration offices, the vital statistics in Taiwan are accurate and complete (9). The average population size in metropolitan precincts, urban townships, rural townships, and aboriginal townships was approximately 75,000, 50,000, 30,000, and 7,500, respectively. While the sex distribution was similar among residents in these study precincts and townships, those who lived in rural and aboriginal townships were older than those who lived in urban townships and metropolitan precincts.

The socioeconomic characteristics are different in precincts and townships. Both urbanization index and industrialization index were used to adjust for the possible confounding resulting from this discrepancy. The urbanization index was obtained from a governmental report (10); it was derived from 19 demographic, socioeconomic, educational, commercial, residential, environmental, and health service-related characteristics and was defined as an integrated indicator of the state of being urbanized for a given precinct or township. The industrialization index was obtained from the official statistics of various industries (11). It was defined as a summary indicator showing the density of various factories in a given precinct or township. In addition to their low socioeconomic status, residents in aboriginal townships and Penghu Islets also had life-styles and lived in natural environments different from those in other areas.

Arsenic Content in Well Water. Although the first public water supply system in Taiwan was implemented as early as 1898, its supply was limited to populated cities with a coverage of <20% before 1945 (12). Because Taiwan is a mountainous island where rivers are short with a great altitude change, underground water instead of surface water was the major water source until the late 1960s when several large reservoirs were constructed. In the areas that were not served by the public water supply system, most households used water from wells either owned by themselves or shared with other households in the same village. The
Public water supply system served only 50% of the total population in 1974–1976 when an island-wide survey of the arsenic concentration in well water was carried out in Taiwan. Because the water supply system primarily served metropolitan precincts, its coverage in urban and rural townships was as low as 30% in 1975 (13). Generally, most residents in Taiwan, especially those who lived in townships, had been using well water from either the public water supply system or private wells before 1970s.

The arsenic level in water of 83,656 wells was determined by a special survey team of the Taiwan Provincial Institute of Environmental Sanitation during 1974–1976. Because the coverage of the water supply system was complete in Taipei City and its water source was from a reservoir, all 16 precincts in the city were excluded from this survey. A total of 13 rural and 15 aboriginal townships in mountainous areas where residents used surface water instead of well water were not included either. Furthermore, one rural township in Green Islet and one in Luchiu Islet, as well as one aboriginal township in Lanyue Islet, were also excluded from the survey because of their small population size. The number of wells examined in each precinct or township ranged from 12–3160, depending on the population size, geographical area, and number of wells. The greater the population size, geographical area, or number of wells, the more wells were surveyed. More than 90% of precincts and townships had more than 50 wells examined, and the average number of wells examined in each precinct or township was as high as 265 (8). Because most precincts and townships except aboriginal townships have an area of <50 km², the coverage of this survey was considered complete.

The arsenic content of well water was determined on-site by the standard mercuric bromide stain method (14). Among 83,656 wells tested, there were 15,649 (18.7%) wells with an arsenic level ≥0.05 ppm which is the safety level set by the World Health Organization (15), and 2,224 (2.7%) wells had an arsenic level ≥0.35 ppm which was reported to be the minimal level to induce blackfoot disease (16). Among 314 study precincts and townships, 232 (73.9%) had <5% wells with an arsenic level of ≥0.05 ppm, 46 (14.7%) had 5–14% wells with an arsenic level of ≥0.05 ppm and 36 (11.5%) had ≥15% wells with an arsenic level of ≥0.05 ppm. As to the percentage of wells with an arsenic level of ≥0.35 ppm, 256 (81.5%) precincts and townships had a percentage of <1%, 40 (12.8%) had a percentage of 1–5%, and 18 (5.7%) had a percentage of ≥6%. Most administrative areas in Taiwan were defined by natural environmental boundaries such as rivers and mountains. Although some variation in the arsenic concentration of well water in the same precinct or township was observed, there was a significant intraarea homogeneity and interarea heterogeneity in arsenic concentration. Thus, the average level of arsenic in well water was used as the arsenic exposure index in this study. Precincts and townships with high arsenic level in well water were found to be clustered in the Lanyang Basin in the northeast and the coastal area in the southwest of Taiwan.

There was another small scale survey of arsenic content in well water carried out by the Taiwan Provincial Institute of Environmental Sanitation from 1971–1973 (17). Based on the data of wells repeatedly examined, a high correlation in the arsenic concentration was observed between water samples from the same wells tested in two different surveys. Furthermore, the arsenic content in well water samples of the blackfoot disease endemic area tested by the National Taiwan University College of Medicine from 1962–1964 (18) was also consistent with that of the same wells tested in two surveys in 1970s. It was considered that the arsenic concentration in well water was quite stable during the study period.

Age-adjusted Mortality from Malignant Neoplasms. The death registration system in Taiwan has been significantly improved; the International Classification of Diseases, Injuries, and Causes of Death (19) is used to code the cause of death and the system has been completely computerized since 1972. Information concerning both death number and midyear population by age, sex, calendar year, and administrative district during 1972–1983 was obtained from the Information Center of the Taiwan Provincial Department of Health which is in charge of the death registration system in Taiwan. Precincts and townships were the smallest administrative units coded on death certificates. In order to yield an adequate number of deaths and subsequently a stable mortality rate by age, sex, administrative district, and cause of death from malignant neoplasms, death number and midyear population for each calendar year from 1972–1983 were summed first. Age-specific mortality rates from various malignant neoplasms were then calculated for males and females in each township by dividing the corresponding sum of death numbers by the sum of midyear populations. As the age distribution was not comparable among 314 precincts and townships, the direct adjustment using the world population in 1976 as the standard population (20) was used to derive age-adjusted mortality for comparison.

Totally, there were 21 malignant neoplasms studied. They were cancers of the nasopharynx (ICD 147), esophagus (ICD 150), stomach (ICD 151), small intestine (ICD 152), colon (ICD 153), rectum, rectosigmoid junction and anus (ICD 154), liver and intrahepatic bile ducts (ICD 155), pancreas (ICD 157), nasal cavity, middle ear and accessory sinuses (ICD 160), larynx (ICD 161), trachea, bronchus, and lung (ICD 162), bone and articulate cartilage (ICD 170), skin except melanoma (ICD 173), breast (ICD 174), cervix uteri (ICD 180), ovary and other uterine adhexa (ICD 183), prostate (ICD 185), bladder (ICD 188), kidney and other unspecified urinary organs (ICD 189), and brain (ICD 191) as well as leukemia (ICD 204–208).

Statistical Analysis. Pearson's product-moment correlation weighted by a factor proportional to the square root of person-years at risk for each study area (21) was used to examine the association between average arsenic level in well water and age-adjusted mortality from various malignant neoplasms. The correlation matrix for age-adjusted mortality rates of various cancers was derived in the same way for males and females. The correlation between age-adjusted mortality rates of males and females was also assessed for various cancers.

Both simple and multiple regression analyses using the square root of person-years as a weighting factor were carried out (21). The average arsenic level in well water was used as the independent variable in order to estimate the increase in age-adjusted mortality/100,000 person-years for every 0.1-ppm increase in the arsenic concentration of well water. In addition to the average arsenic level in well water, both urbanization index and industrialization index were included in the multiple regression analysis to adjust for their possible influence on cancer mortality and to obtain a better estimation of the role of arsenic.

These analyses were carried out in a stepwise way. First, all of the

3 The abbreviation used is: ICD, International Classification of Diseases, Injuries, and Causes of Death.
RESULTS

Age-adjusted Mortality. The percentiles of age-adjusted mortality rates of various malignant neoplasms among males and females in 314 precincts and townships are shown in Table 1. The 10 leading malignant neoplasms for males included cancers of the liver, stomach, lung, esophagus, colon, nasopharynx, rectum, bladder and pancreas, and leukemia. Cancers of the stomach, liver, lung, cervix uteri, colon, breast, rectum, esophagus, pancreas, and nasopharynx were the 10 leading malignant neoplasms for females. Males and females had similar mortality from cancers of the small intestine, colon, rectum, pancreas, bone and cartilage, skin, kidney, and brain as well as leukemia. The male to female ratio of age-adjusted mortality was \( \geq 3.0 \) for cancers of the esophagus and liver, 2.0 for cancers of the nasopharynx, stomach, larynx, lung, and bladder, and 1.5 for nasal cavity cancer. The ratio between the 75th and 25th percentiles of the age-adjusted mortality from various malignant neoplasms ranged from 1.6 for liver cancer to 3.2 for small intestine cancer in males and from 1.7 for liver cancer to 2.8 for skin cancer in females.

Among the 21 malignant neoplasms studied, a significantly positive association with arsenic level in well water was observed for cancers of the liver, nasal cavity, lung, skin, bladder, and kidney among both males and females as well as prostate cancer among males. None of 14 other cancers was significantly associated with arsenic level in well water. Detailed results of correlation and regression analyses are shown in Tables 2–4 for cancers of the liver, nasal cavity, lung, skin, bladder, kidney, and prostate only.

Ecological Correlation. Table 2 shows the weighted correlations between age-adjusted mortality from various malignant neoplasms among males and females. There was a significant correlation between males and females with a weighted correlation coefficient of 0.5, 0.3, 0.5, 0.3, 0.8, and 0.6 for cancers of the liver, nasal cavity, lung, skin, bladder, and kidney, respectively, in the analysis including all 314 study precincts and townships. The correlations remained significant in further analyses in which 20 townships in the aboriginal area and Penghu Islets, 36 metropolitan precincts, and 88 townships not in southwestern Taiwan were eliminated in a stepwise manner. The weighted correlation coefficients changed only slightly in each step for all cancers.

Most intercorrelations among age-adjusted mortality rates for cancers of the liver, nasal cavity, lung, skin, bladder, and kidney in 314 precincts and townships were statistically significant. Almost all of the correlations for females were greater than those for males. Further analysis of mortality rates in 170 southwestern towns showed an increase in almost all correlations among various cancers for both males and females as shown in Table 3 in which the correlation matrix for males is shown above the diagonal and for females below the diagonal. A significant association with the average arsenic level in well water was observed for cancers of the liver, nasal cavity, lung, skin, bladder, and kidney in both males and females. The correlations between arsenic level in well water and cancer of the liver, nasal cavity, lung, skin, bladder, and kidney were 0.28, 0.22, 0.20, 0.25, 0.41, and 0.34, respectively, in males and 0.21, 0.20, 0.31, 0.28, 0.43, and 0.42, respectively, in females. The correlations increased or remained unchanged in further analyses of 20 towns in the aboriginal area and Penghu Islets, 36 metropolitan precincts, and 88 towns not in southwestern Taiwan eliminated by step. In the analysis of mortality rates in 170 southwestern towns, the correlations for cancer of the liver, nasal cavity, lung, skin, bladder, and kidney were 0.39, 0.30, 0.38, 0.27, 0.40, and 0.39, respectively, in males and 0.32, 0.24, 0.42, 0.27, 0.44, and 0.43 in females. The correlation for prostate cancer was also significant with a coefficient of 0.18.

Weighted Regression Analyses. Results of simple and multi-
ple regression analyses were similar and only those for multiple regression analysis are shown in Table 4. In the analyses including 314 precincts and townships, significant weighted regression coefficients, which indicate the increase in age-adjusted mortality/100,000 person-years for every 0.1-ppm increase in arsenic level of well water, were observed for cancers of the liver, nasal cavity, lung, skin, bladder, and kidney in both males and females and for prostate cancer in males after adjusting for the urbanization index and industrialization index. Males and females had similar risk associated with the arsenic level in well water for all of these cancers except liver cancer. Almost all weighted regression coefficients increased slightly in further multiple regression analyses in which only 170 southwestern townships were included. The multivariate-adjusted coefficients for cancers of the liver, nasal cavity, lung, skin, bladder, and kidney were 7.0, 0.8, 5.9, 0.9, 3.7, and 1.2, respectively, in males and 2.3, 0.5, 5.9, 1.0, 4.5, and 1.7, respectively, in females. The increased risk associated with the arsenic level in well water was similar in males and females for all cancers except liver cancer. The coefficient for prostate cancer was 0.6.

### DISCUSSION

Studies on the ecological correlation between mortality and environmental exposures have been widely used to generate and falsify epidemiological hypotheses, despite their inherent limitations. The completeness and accuracy of death registration system should be evaluated before any conclusion based on the mortality analysis is made. Because it is mandatory to register death certificates at local household registration offices and the household registration information is verified annually through a door-to-door survey, the death registration in Taiwan is quite complete. Although causes of death may be misdiagnosed and/or or misclassified, the problem has been minimized through the improvement in the verification and classification of causes of death in Taiwan since 1972. Furthermore, malignant neoplasms have been reported to be one of the most unequivocally classified causes of death in Taiwan, the same as in other countries (22).

<table>
<thead>
<tr>
<th>Cancer (ICD code) and sex</th>
<th>All precincts and townships (n = 314)</th>
<th>Southwestern townships (n = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (155)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6.8 (1.3)</td>
<td>7.0 (1.3)</td>
</tr>
<tr>
<td>Female</td>
<td>2.0 (0.5)</td>
<td>2.3 (0.6)</td>
</tr>
<tr>
<td>Nasal cavity (160)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.7 (0.2)</td>
<td>0.8 (0.2)</td>
</tr>
<tr>
<td>Female</td>
<td>0.4 (0.1)</td>
<td>0.5 (0.2)</td>
</tr>
<tr>
<td>Lung (162)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5.3 (0.9)</td>
<td>5.9 (1.0)</td>
</tr>
<tr>
<td>Female</td>
<td>5.3 (0.7)</td>
<td>5.9 (0.9)</td>
</tr>
<tr>
<td>Skin (173)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.9 (0.2)</td>
<td>0.9 (0.3)</td>
</tr>
<tr>
<td>Female</td>
<td>1.0 (0.2)</td>
<td>1.0 (0.3)</td>
</tr>
<tr>
<td>Bladder (188)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.9 (0.5)</td>
<td>3.7 (0.7)</td>
</tr>
<tr>
<td>Female</td>
<td>4.2 (0.5)</td>
<td>4.5 (0.7)</td>
</tr>
<tr>
<td>Kidney (189)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.1 (0.2)</td>
<td>1.2 (0.2)</td>
</tr>
<tr>
<td>Female</td>
<td>1.7 (0.2)</td>
<td>1.7 (0.3)</td>
</tr>
<tr>
<td>Prostate (185)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.5 (0.2)</td>
<td>0.6 (0.2)</td>
</tr>
</tbody>
</table>

* Only cancers significantly correlated with average arsenic level in well water are shown.

* B, regression coefficient indicating an increase in age-adjusted mortality/100,000 person-years for every 0.1-ppm increase in arsenic level of well water after adjusting for indices of industrialization and urbanization.

Correlations between specific environmental exposures and age-adjusted mortality rates should be assessed under the circumstances of similar life-style, living environment, and medical accessibility among study areas. Because Taiwan is a small island with a convenient communication network, the accessibility of medical service facilities, especially those for critical diseases such as malignant neoplasms, is comparable among study precincts and townships. In order to control possible variation which might result from differences in life-style and living environment, the analysis of ecological correlation was carried out in a stepwise way to eliminate 20 townships in the aboriginal area and Penghu Islets, 36 metropolitan precincts in national and provincial cities, and, finally, 88 townships not in southwestern Taiwan from the analysis. The ecological correlation was observed to increase or remain unchanged in these step by step analyses. In the multiple regression analysis, urbanization index and industrialization index were further adjusted. The weighted regression coefficients differed slightly between simple and multiple regression analyses.

Ecological fallacy which suggests the association observed at the precinct and township level may not hold at the village or even the individual level should also be assessed. Most malignant neoplasms have a multifactorial etiology. In addition to the arsenic level in well water, various factors such as life-style, living environment, and occupational exposure are involved in the development of malignant neoplasms studied here. It is considered that the ecological correlation between arsenic and cancers may thus be underestimated rather than overestimated. Under such conservative circumstances, we still found a significant association with the arsenic level in well water for the age-adjusted mortality from cancers of the liver, nasal cavity, lung, skin, bladder, and kidney. The findings from this study including all 314 precincts and townships in Taiwan are in concordance with those reported previously in only four townships of the blackfoot disease endemic area (3–7). In our previous studies, we observed a significant dose-response relation between ingested arsenic and cancers of the liver, lung, skin, bladder, kidney, and prostate at individual and village levels. Such a consistency further supports the findings of this study.

The association between skin cancer and arsenic through environmental, occupational, and medicinal exposures has long been documented, and the dose-response relation between ingested arsenic and skin cancer observed in Taiwan has been used to estimate the safety level of arsenic in water (2, 15). The association between inhaled arsenic and lung cancer has also been reported among workers at copper smelters (23, 24). However, the associations between arsenic and cancers of other internal organs were inconsistent (1, 2, 15). Based on the consistent results in this study and those observed previously in the endemic area of blackfoot disease, it is concluded that ingested arsenic may play an important role in the determination of cancers of the liver, bladder, kidney, and prostate. Small population size, different routes of entry, and various exposures to environmental cofactors may at least partly explain the inconsistent findings in previous occupational studies.

Arsenic seems involved in the development of several cancers in humans without showing any organotropism. However, limited evidence shows the carcinogenicity of arsenic to experimental animals (25, 26). Yet, sodium arsenate and sodium arsenite induce morphological transformation of cultured cells, but they are inactive or extremely weak to induce gene mutations at specific genetic loci (27). Arsenic causes chromosomal aberration and sister chromatid exchanges, but it seems to induce DNA damage in a rec assay of Escherichia coli only
(28). Its ability to induce gene amplification was recently documented (29). However, the exact mechanism of arsenic-induced carcinogenicity remains to be elucidated. In order to further elucidate the effect of arsenic on the induction of internal organ cancers, an extensive cohort study is being carried out in Taiwan.

REFERENCES