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CANCER MORTALITY TRENDS IN A BLACKFOOT DISEASE ENDEMIC COMMUNITY OF TAIWAN FOLLOWING WATER SOURCE REPLACEMENT

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Blackfoot disease is an endemic peripheral vascular disease found among people in a limited area on the southwest coast of Taiwan, where artesian well water has a high concentration of arsenic and was used since the turn of this century. This is an important public health problem and was noted by the authorities, who began improving the water supply in such communities in 1956. This enabled us to test the relationship between arsenic and malignant tumors using a specific exposed community. Study subjects were divided into four groups according to age (under or over 40 yr) and gender. Two methods were used for the estimation of the age-adjusted mortality rate ratios. First, using the first time interval (1971–1973) as the standard, the mortality rate ratio for all malignant tumors was estimated from this interval through to the last interval (1992–1994) using Poisson regression. Cancers that were found to be related to arsenic in previous reports, such as liver, lung, bladder, kidney, and skin cancers, were examined and other malignant tumors except these cancers were also assessed. The same calculations were performed for all of Chiayi and Tainan counties, excluding the study areas, which were used as the local reference, and for the general population of Taiwan, which was used as a national reference group. Second, mortality rate ratios for the study area were compared to the local and national reference for the same time intervals for each disease category. From our results, significantly declining trends for mortality rate ratios of all malignant tumors with 1971–1973 as the standard were found for the study areas, especially in females. A decrease of mortality rate ratios from malignant cancers, compared to the local or national references, was found in those aged over 40 yr for both sexes. The decreases are mainly due to a fall in internal and skin cancer mortality rates. In conclusion, our results suggest that the improvement of drinking water supply to eliminate arsenic exposure from artesian well water decreased the mortality incidence of arsenic-related cancers in blackfoot disease endemic communities.

Blackfoot disease is an endemic peripheral vascular disease found in a limited area on the southwest coast of Taiwan, where artesian well water with a high concentration of arsenic has been used since the first decade of this century (Wu et al., 1961). Patients suffering from this disease experience symptoms beginning with numbness or coldness of one or more extremities and intermittent claudication, which progresses to black discoloration, ulceration, and gangrene (Tseng et al., 1961). In the end stage, patients commonly meet with the calamity of the spontaneous amputation of affected extremities. This is an important public health problem in these areas and was noted by the authorities in 1950s. The etiology of blackfoot disease, according to many previous studies, is asso-

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ciated with drinking water derived in endemic areas from artesian wells with a high concentration of arsenic, in addition to organic chlorides and ergot, which have also been identified in artesian well water (Chen & Wu, 1962; Lu, 1990). It is still a matter of controversy whether arsenic or humic acid may be responsible for this disease. However, it is certain that the use of artesian well water as drinking water should be prohibited as soon as possible. In some parts of these endemic areas, a tap-water supply was provided by the government in 1956, and all of the areas were almost completely supplied between 1966 and 1975 (Tseng, 1989). The detailed rates of tap-water supply from 1957 to 1981 are listed in Table 1.

In addition to the relationship between blackfoot disease and arsenic exposure, according to many observational epidemiological studies, exposure to arsenic from medicines, wine substitutes, or drinking water was related to skin, liver, lung, kidney, and bladder cancer (Tsuda et al., 1995). Actually, drinking water with arsenic in this blackfoot disease endemic area has been studied widely by Chen et al. (1985), who found significantly elevated standardized mortality ratios (SMRs) in both sexes for cancers of lung, bladder, kidney, and liver. Subsequently, retrospective studies (Chen et al.,

TABLE 1. Rate (%) of Tap-Water Supply in Blackfoot Disease (BFD) Community, 1957–1981

Year	Peimen	Hsuechia	Putai	Ichu
1957	44.19	41.17	16.65	0
1958	53.53	42.05	18.16	0
1959	52.85	41.10	24.60	0
1960	52.72	41.14	25.92	0
1961	54.09	40.78	31.78	0
1962	53.60	45.19	34.27	0
1963	55.84	45.93	47.57	0
1964	58.38	46.20	53.76	0
1965	74.93	46.98	54.17	0
1966	82.42	75.69	54.38	0
1967	85.17	78.63	55.22	25.47
1968	87.23	80.89	55.15	27.93
1969	88.20	82.22	54.27	32.52
1970	89.19	83.80	52.72	33.86
1971	90.76	84.07	53.43	37.60
1972	90.66	85.75	57.06	39.94
1973	91.59	86.49	57.65	42.36
1974	92.50	87.82	59.25	47.25
1975	93.05	91.86	61.00	51.68
1976	95.59	89.87	58.72	57.32
1977	97.31	88.35	60.47	61.08
1978	99.67	91.67	62.47	65.98
1979	99.32	92.92	66.91	72.09
1980	99.55	93.73	68.98	79.63
1981	95.47	93.95	71.09	85.02

Note. Data were acquired from Taiwan Water Supply Corp.

1986a) and ecological studies (Chen & Wang, 1990) were launched and revealed that the years of use of artesian well water with arsenic and the well water arsenic levels, respectively, had dose-response relationships with internal cancer. Similar results have been reported in other high-arsenic areas in different countries. In Namiki-dor, an arsenic-polluted area of Japan, the mortality rates for lung and urinary-tract cancer were high when compared to general populations of the same prefecture (Tsuda et al., 1995). Bladder cancer and skin cancer related to arsenic in drinking water have been reported in Argentina and India (Hopenhayn-Rich et al., 1996; Das et al., 1995).

The consistency of the relationship between internal cancer and arsenic exposure via drinking water has been established by these observational epidemiological studies launched in different counties. The plausibility of a potential epidemiological association is enhanced if a similar disease can be simulated in experimental studies. Unfortunately, the carcinogenic effect of arsenic was challenged by experimental animal studies with oral exposure to arsenic. The reason for this discrepancy is suspected to be that the detoxification capacity of arsenic is different between humans and experimental animals (Thompson, 1993). Nevertheless, it is impossible to treat humans like experimental animals to test this hypothesis. The water supply in the blackfoot disease endemic area was improved between 1966 and 1975. This provided us an opportunity to examine whether the mortality of internal cancers would decrease with the intervention of the withdrawal of arsenic exposure. The purpose of this study was to elucidate the trend between the age-adjusted cancer mortality rates for all malignant tumors and time from 1971 to 1994 in these areas as compared to two reference groups, the population of Chiayi-Tainan County and the population of Taiwan. Skin and internal cancers, including lung, liver, bladder, and kidney, which were reported to be related to arsenic exposure, and total cancers, excluding the listed cancers, were also assessed.

MATERIALS AND METHODS

Study Area

The area covered in this study was limited to the four townships of Peimen and Hsuechia in Tainen County, and Putai and Ichu in Chiayi County. According to previous studies, blackfoot disease was highly prevalent in these areas at rates of 5.57, 3.87, 2.02, and 0.64 per 1000, respectively (Wu et al., 1961). These four neighboring townships are located on the southwest coast of Taiwan. The soil and water form shallow wells, which have a high salt content. For this reason, some inhabitants of the study area have used water from artesian wells for drinking, washing, agriculture, aquaculture, and livestock husbandry since the beginning of this century (Tseng, 1989), especially those living in villages along the

coast. Unfortunately, water from wells developed in these areas is usually poor in quality and quantity because of its geological uniqueness (Tseng et al., 1968), and arsenic concentration of soil in this area, according to previous reports, ranged from 5.3 to 11.2 mg/kg with a median of about 7.2 mg/kg (Lo, 1978). As a result, the arsenic content of the water derived from artesian wells ranged from 0.35 to 1.14 ppm with a median of 0.78 ppm reported in 1962 (Chen et al., 1962). A later study examining a total of 83,565 wells throughout Taiwan showed that 29.1% and 5.2% of the wells in study area contained arsenic at greater than 0.05 and 0.35 ppm, respectively, while only 5.7% and 0.3% of the wells in other areas of Taiwan had arsenic content greater than 0.05 and 0.35 ppm, respectively (Lo et al., 1977). The arsenic levels of artesian well water in the study area were reported to be stable by two surveys carried out by the Taiwan Provincial Institute of Environmental Sanitation (Lo et al., 1977). The tap water supplied for study area came from several small water reservoirs from 1956 to 1966 and a big water reservoir named Tzeng-Wen after 1966. The arsenic concentration of water in these reservoirs was less than 0.01 ppm (Chen & Chen, 1985).

Study Population

Since it is obligatory to register any event of birth, death, marriage and divorce, and migration in the household registration offices, the population statistics in Taiwan are highly accurate and complete. According to the Taiwan-Fukien Demographic Fact Book printed by Republic of China Ministry of Interior, most of the residents in the study area were engaged in farming, fishery, and salt production. The educational level and socioeconomic status were similar to the populations of Tainan and Chiayi counties, but below the average as compared with the general population in Taiwan. A nutrition survey carried out in 1960 indicated that residents had an insufficient intake of fresh vegetables and animal protein (Chen et al., 1986b). The smoking habits of the female residents are the same as for the general population of Taiwan. However, the males in this area smoke a little more when compared to the general population. In essence, the life style of the study area is similar to the local reference group and somewhat different from the national reference group. With respect to migration, it has been reported by the Department of Environmental Protection of Taiwan (1988) that more than 90% of local residents lived in the study area all their lives, especially the older people.

Mortality Rate Ratio Analyses

In Taiwan, it is mandatory for physicians to submit standardized certificates for each death to the Department of Health. The vital statistics published by the National Health Department of Taiwan are thus very complete. Physicians confirmed the cause of death in vital statistics published by this office with a rate of 99%. In our study, all the death infor-

mation was obtained from vital statistics and the computer database for deaths was set up by the National Health Department. The underlying cause of death in the computer database was coded according to the eighth (before 1980) or ninth revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death. All the malignant tumors from 1971 to 1994 were included in this study. Furthermore, the malignant tumors were divided into two groups, the arsenic-related cancers and the others. The arsenic-related cancers include liver, lung, skin, bladder, and kidney cancers, which have been reported by Chen et al. (1985) with high standardized mortality ratios (SMRs) in study area for both sexes when compared to the Taiwan population. The 24 yr from 1971 to 1994 were divided into 8 intervals of 3 yr. Since the tap-water supplement was first setup in 1956, the deaths among males and females were divided into 2 study groups according to age under or over 40 yr. Liver cancer, which has been reported to be related to arsenic exposure, is included despite the mortality from hepatitis B-related liver cancer in people under 10 yr of age, which was reduced by the hepatitis B vaccination program setup in 1984 (Lee & Ko, 1997). Two methods were used for estimation of age-adjusted mortality rate ratios. The first method used the first time interval, 1971 to 1973, as the standard, the age-adjusted mortality rate ratios for all malignant tumors, the total of skin and internal cancers including lung, kidney, bladder, and liver, and the other cancers as estimated for the first interval, 1971–1973, through the last interval, 1992–1994, by Poisson regression from the SAS package. The same calculations were also undertaken for local and national reference groups. For the second method, the calculations of rate ratios for study area were compared to the local or national references at the same time intervals with Poisson regression from the SAS package. The Poisson model included the number of deaths as the response variable, the natural logarithm of person-time as an offset, indicators for calendar year as the main exposure variable, and indicators for age as a covariate. Person-time by sex and age group (0, 1–4, 5–9, . . ., 85 up) used in our study was obtained from the Taiwan-Fukien Demographic Fact Book published by the Ministry of the Interior. The Spearman correlation was used to assess the rate ratio–time trends for all groups.

RESULTS

The numbers of deaths, person-years, and crude mortalities from 1971 to 1994 for each of the disease categories by areas, sexes, and age groups are listed in Table 2. The crude mortalities show a dose response from highest in the study area to lowest in the national reference, for all disease categories in both sexes and age groups. The crude mortalities for the study area for all disease categories are about 2 to 3 times higher than the local reference and about 5 to 15 times higher than the national reference in people aged over 40 yr.

TABLE 2. Number of Deaths, Person-Years, and Crude Mortality (per 10^5) in Blackfoot Disease (BFD) Community

			Study area			Local reference			National reference		
Sex	Age (yr)	Death cause	Deaths	Person-time	Crude mortality	Deaths	Person-time	Crude mortality	Deaths	Person-time	Crude mortality
Male	<40	All malignant tumors	236		21.07	1671		12.79	21,877		9.63
		Internal[a] and skin cancers	107	1,119,950	9.55	591	13,062,408	4.52	7581	227,273,814	3.34
		Cancers except internal and skin	129		11.52	1080		8.27	14,296		6.29
	≥40	All malignant tumors	2538		652.99	15,622		313.46	204,339		97.51
		Internal[a] and skin cancers	1695	388,673	436.10	8112	4,983,715	162.77	98,237	209,548,487	46.88
		Cancers except internal and skin	843		216.89	7510		150.69	106,102		50.63
Female	<40	All malignant tumors	124		12.42	1246		11.01	16,654		7.33
		Internal[a] and skin cancers	36	998,588	3.61	211	11,313,320	1.87	2654	227,273,814	1.17
		Cancers except internal and skin	88		8.81	1035		9.15	14,000		6.16
	≥40	All malignant tumors	1905		469.01	9209		208.07	113,402		62.06
		Internal[a] and skin cancers	1150	406,171	283.13	3250	4,425,978	73.43	34,406	209,548,487	17.69
		Cancers except internal and skin	755		185.88	5959		134.64	78,996		44.38

[a]Lung, liver, bladder, and kidney.

Age-adjusted mortality rate ratios for all malignant tumors of the study group and the two reference groups are listed in Table 3. Relative to the first interval rate for males under 40 yr, significant decreases in the rate ratios of the study group were found at intervals 3 (1974–1976), 5 (1983–1985), and 7 (1992–1994). For females of the same age, the age-adjusted mortality rate ratios were significant at interval 7 (1989–1991). In the local reference group, rate ratios of age under 40 yr are significantly de-

TABLE 3. Age-Adjusted Mortality Rate Ratios for All Malignant Cancers in Blackfoot Disease (BFD) Community

Sex	Age (yr)	Year	BFD study area		Local reference, rate ratio	National reference, rate ratio	Study area/ local reference, rate ratio	Study area/ national reference, rate ratio
			Rate ratio	95% CI				
Male	<40	1971–1973	1.00		1.00	1.00	1.84[b]	1.85[b]
		1974–1976	1.28	(0.83–1.97)	0.96	0.99	2.45[b]	2.40[b]
		1977–1979	0.55	(0.32–0.96)[a]	0.92	0.94	1.10	1.09
		1980–1982	1.10	(0.69–1.75)	0.79[a]	1.00	2.61[b]	2.11[b]
		1983–1985	0.79	(0.75–0.84)[a]	0.80[a]	0.95	1.88[b]	1.60[b]
		1986–1988	0.86	(0.53–1.39)	0.86	0.90[a]	2.00[b]	1.97[b]
		1989–1991	0.49	(0.27–0.87)[a]	0.98	0.87[a]	0.96	1.10
		1992–1994	0.64	(0.38–1.09)	0.98	0.86[a]	1.27	1.46
	≥40	1971–1973	1.00		1.00	1.00	2.84[b]	2.27[b]
		1974–1976	0.86	(0.72–1.02)	0.98	1.00	2.46[b]	1.93[b]
		1977–1979	0.83	(0.69–0.98)[a]	1.12[a]	1.05[a]	2.06[b]	1.75[b]
		1980–1982	1.01	(0.85–1.19)	1.12[a]	1.11[a]	2.50[b]	2.02[b]
		1983–1985	1.08	(0.92–1.26)	1.26[a]	1.13[a]	2.40[b]	2.11[b]
		1986–1988	0.94	(0.80–1.11)	1.28[a]	1.13[a]	2.05[b]	1.83[b]
		1989–1991	0.94	(0.80–1.10)	1.29[a]	1.13[a]	2.00[b]	1.79[b]
		1992–1994	0.95	(0.81–1.12)	1.49[a]	1.19[a]	1.75[b]	1.72[b]
Female	<40	1971–1973	1.00		1.00	1.00	1.29	1.39
		1974–1976	1.08	(0.59–1.94)	0.89	0.96	1.56[b]	1.56[b]
		1977–1979	1.09	(0.60–1.99)	0.89	0.94	1.56	1.63[b]
		1980–1982	0.82	(0.42–1.61)	0.78[a]	0.92[a]	1.30	1.21
		1983–1985	0.73	(0.37–1.47)	0.85	0.90[a]	1.13	1.19
		1986–1988	0.79	(0.40–1.55)	0.83	0.83[a]	1.27	1.36
		1989–1991	0.26	(0.10–0.68)[a]	0.88	0.82[a]	0.42	0.49
		1992–1994	0.71	(0.35–1.43)	1.20	0.81[a]	0.82	1.29
	≥40	1971–1973	1.00		1.00	1.00	2.72[b]	2.19[b]
		1974–1976	1.15	(0.95–1.39)	0.98	1.01	3.22[b]	2.49[b]
		1977–1979	1.11	(0.92–1.35)	0.98	1.04[a]	3.10[b]	2.36[b]
		1980–1982	1.03	(0.84–1.25)	1.01	1.06[a]	2.81[b]	2.13[b]
		1983–1985	1.01	(0.84–1.22)	1.10[a]	1.06[a]	2.54[b]	2.11[b]
		1986–1988	0.91	(0.75–1.10)	1.13[a]	1.04[a]	2.21[b]	1.90[b]
		1989–1991	0.86	(0.71–1.04)	1.07	1.02	2.16[b]	1.80[b]
		1992–1994	0.80	(0.66–0.96)[a]	1.89[a]	1.07[a]	1.15[b]	1.63[b]

[a]Statistically significant ($p < .05$) compared to first interval (1971–1973).
[b]Statistically significant ($p < .05$) between different groups at the same interval.

creased at intervals 4 (1980–1982) and 5 (1983–1985) for males and interval 3 for females. The rate ratios of the national reference were significantly decreased in recent years. For those aged over 40 yr from the study group, there are no significant changes except for interval 3 (1977–1979) in males and interval 8 in females. For both the local and national references, the mortality rate ratios for both sexes over 40 yr of age were significantly increased in recent years. Rate ratios for the study area related to the reference groups showed that it is statistically significant for both sexes of age greater than 40 yr for all study intervals and significant in early intervals for those aged less than 40 yr.

With respect to the total of lung, liver, kidney, bladder, and skin cancer, mortality rate ratios are listed in Table 4. The rate ratios for the study area over time for both sexes were nonsignificant, with one exception: A significant decrease was noted for females under 40 yr at interval 7 (1989–1991). However, the rate ratios of local and national reference for age above 40 yr in both sexes were significantly increased in recent years. The rate ratios between different areas are similar for all malignant tumors. Significantly increased rate ratios were found for those aged over 40 yr in both sexes at all study intervals and at early intervals for those aged under 40 yr.

As for the other cancers, the study area showed significantly decreased rate ratios with the first interval as a standard for those aged under 40 yr at intervals 2, 7, and 8 for males and interval 7 for females. For those aged over 40 yr, there is no marked difference for both sexes. The local reference area showed a significant increase at interval 8 for age above 40 yr in both sexes. Use of the national reference area gave different results. Significant decreases were found at late intervals for both sexes and age groups. The results of rate ratios between various areas were different from other disease categories. Even the rate ratios between local and national reference are not parallel. These results are shown in Table 5.

The Spearman coefficients of trend in terms of the correlation between mortality rate ratios related to the first interval for all malignant tumors, internal and skin cancers, and other cancers with time, sex, and age are shown in Table 6. The total malignant cancers and internal and skin cancers were significantly decreased in females in the study area. These results are different from the local and national reference. There is no significant decrease found in males of the study area, and even a significant increase in internal and skin cancer for those aged above 40 yr. The increase over time of these diseases was greater in the local and national reference population aged over 40 yr. The results for other cancers for the study area are similar to the national reference, which were decreased for both sexes and age groups, but different from the local reference, which increased.

The Spearman coefficients of trend in terms of the correlation between mortality rate ratios related to the reference groups of all malignant tumors, internal and skin cancers, and the other cancers with time, sex, and age are shown in Table 7. The coefficients are negative for total

TABLE 4. Age-Adjusted Mortality Rate Ratios for Lung, Liver, Bladder, Kidney, and Skin Cancers in Blackfoot Disease (BFD) Community

Sex	Age (yr)	Year	BFD study area		Local reference, rate ratio	National reference, rate ratio	Study area/ local reference, rate ratio	Study area/ national reference, rate ratio
			Rate ratio	95% CI				
Male	<40	1971–1973	1.00		1.00	1.00	2.07	2.08[b]
		1974–1976	1.53	(0.75–3.10)	0.82	0.96	3.84[b]	3.39[b]
		1977–1979	0.78	(0.33–1.83)	1.03	0.94	1.48	1.69
		1980–1982	1.47	(0.70–3.08)	0.79	1.07	3.64[b]	2.94[b]
		1983–1985	1.15	(0.53–2.53)	0.97	1.02	2.47[b]	2.41[b]
		1986–1988	0.89	(0.40–1.96)	1.02	0.94	1.96[b]	2.18[b]
		1989–1991	0.66	(0.28–1.57)	0.96	0.92	1.46	1.59
		1992–1994	1.05	(0.50–2.19)	1.05	0.90[a]	2.27[b]	2.70[b]
	≥40	1971–1973	1.00		1.00	1.00	4.10[b]	3.55[b]
		1974–1976	0.84	(0.67–1.05)	1.12	1.07[a]	3.04[b]	2.77[b]
		1977–1979	0.94	(0.76–1.17)	1.20[a]	1.15[a]	3.16[b]	2.83[b]
		1980–1982	0.99	(0.80–1.22)	1.30[a]	1.29[a]	3.06[b]	2.66[b]
		1983–1985	1.18	(0.97–1.43)	1.50[a]	1.37[a]	3.17[b]	3.00[b]
		1986–1988	1.01	(0.83–1.24)	1.54[a]	1.38[a]	2.67[b]	2.53[b]
		1989–1991	1.01	(0.83–1.24)	1.58[a]	1.39[a]	2.54[b]	2.45[b]
		1992–1994	1.07	(0.88–1.29)	1.93[a]	1.53[a]	2.11[b]	2.28[b]
Female	<40	1971–1973	1.00		1.00	1.00	2.50[b]	2.69[b]
		1974–1976	1.13	(0.40–3.22)	1.04	0.92	2.63[b]	3.13[b]
		1977–1979	0.87	(0.27–2.75)	0.77	0.83[a]	2.60	2.65[b]
		1980–1982	1.07	(0.36–3.23)	0.84	0.89	3.11[b]	3.21[b]
		1983–1985	0.61	(0.16–2.40)	1.02	0.85[a]	1.37	1.75
		1986–1988	0.74	(0.21–2.55)	0.63	0.70[a]	2.70	2.67[b]
		1989–1991	0.17[a]	(0.13–0.20)	0.79	0.69[a]	0.53	0.66
		1992–1994	0.47	(0.12–1.87)	1.13	0.74[a]	1.11	1.75
	≥40	1971–1973	1.00	1.00		1.00	4.61[b]	4.59[b]
		1974–1976	1.24	(0.96–1.59)	1.03	1.03	5.54[b]	5.48[b]
		1977–1979	1.16	(0.90–1.49)	0.93	1.08[a]	5.79[b]	4.91[b]
		1980–1982	1.17	(0.92–1.51)	1.00	1.17[a]	5.59[b]	4.65[b]
		1983–1985	1.19	(0.93–1.52)	1.20[a]	1.23[a]	4.68[b]	4.47[b]
		1986–1988	1.03	(0.81–1.33)	1.18[a]	1.25[a]	4.13[b]	3.79[b]
		1989–1991	0.93	(0.72–1.19)	1.29[a]	1.22[a]	3.36[b]	3.40[b]
		1992–1994	0.83	(0.65–1.07)	2.24[a]	1.37[a]	1.75[b]	2.76[b]

[a]Statistically significant ($p < .05$) compared to first interval (1971–1973).
[b]Statistically significant ($p < .05$) between different groups at the same interval.

malignant cancers, internal and skin cancers, and other cancers except for internal and skin cancers for males aged under 40 yr compared to the national reference. There are significant decreases for females aged over 40 yr for all these disease categories. For males aged over 40 yr, significant decreases were found in internal and skin cancers for different reference and total cancers for local reference group. Compared to those aged over 40 yr, significant coefficients for those aged under 40 yr were limited to females. Significant decreases were found in the local reference popu-

TABLE 5. Age-Adjusted Mortality Rate Ratios for the Other Cancers in Blackfoot Disease (BFD) Community

Sex	Age (yr)	Year	BFD study area		Local reference, rate ratio	National reference, rate ratio	Study area/ local reference, rate ratio	Study area/ national reference, rate ratio
			Rate ratio	95% CI				
Male	<40	1971–1973	1.00		1.00	1.00	1.73[b]	1.75[b]
		1974–1976	1.16	(0.67–1.99)	1.03	1.01	1.95[b]	1.99[b]
		1977–1979	0.43[a]	(0.21–0.91)	0.87	0.94	0.89	0.83
		1980–1982	0.92	(0.51–1.66)	0.79	0.96	2.12[b]	1.72[b]
		1983–1985	0.61	(0.31–1.20)	0.72[a]	0.92[a]	1.52	1.20
		1986–1988	0.84	(0.46–1.54)	0.79	0.87[a]	2.03[b]	1.86[b]
		1989–1991	0.38[a]	(0.17–0.85)	1.00	0.84[a]	0.69	0.81
		1992–1994	0.36[a]	(0.15–0.85)	0.95	0.84[a]	0.63	0.71
	≥40	1971–1973	1.00		1.00	1.00	1.86[b]	1.40[b]
		1974–1976	0.88	(0.67–1.17)	0.88	0.95	1.88[b]	1.30[b]
		1977–1979	0.84	(0.62–1.15)	1.06	0.98	1.09	0.88
		1980–1982	1.04	(0.79–1.35)	0.99	0.98	1.91[b]	1.44[b]
		1983–1985	0.90	(0.69–1.18)	1.07	0.97	1.54[b]	1.26[b]
		1986–1988	0.82	(0.62–1.08)	1.08	0.95[a]	1.36[b]	1.14
		1989–1991	0.81	(0.62–1.06)	1.06	0.95[a]	1.36[b]	1.13
		1992–1994	0.77	(0.59–1.01)	1.13[a]	0.96[a]	1.27[b]	1.11
Female	<40	1971–1973	1.00		1.00	1.00	1.06	1.14
		1974–1976	1.05	(0.51–2.15)	0.86	0.97	1.32	1.27
		1977–1979	1.19	(0.58–2.41)	0.91	0.96	1.40	1.45
		1980–1982	0.70	(0.29–1.65)	0.76[a]	0.93	0.91	0.82
		1983–1985	0.78	(0.35–1.77)	0.82	0.91[a]	1.08	1.08
		1986–1988	0.81	(0.36–1.83)	0.87	0.85[a]	1.05	1.14
		1989–1991	0.30[a]	(0.10–0.91)	0.90	0.84[a]	0.40	0.46
		1992–1994	0.83	(0.37–1.87)	1.21	0.48[a]	0.76	1.19
	≥40	1971–1973	1.00		1.00	1.00	1.82[b]	1.34[b]
		1974–1976	1.05	(0.79–1.40)	0.95	1.00	2.02[b]	1.41[b]
		1977–1979	1.06	(0.80–1.41)	1.01	1.02	1.92[b]	1.40[b]
		1980–1982	0.85	(0.63–1.14)	1.02	1.02	1.52[b]	1.11
		1983–1985	0.79	(0.59–1.07)	1.06	1.00	1.37[b]	1.06
		1986–1988	0.75	(0.56–1.02)	1.11	0.97	1.22	1.01
		1989–1991	0.77	(0.57–1.03)	0.97	0.95[a]	1.38[b]	1.03
		1992–1994	0.76	(0.57–1.01)	1.72[a]	0.85[a]	0.77[b]	1.01

[a]Statistically significant ($p < .05$) compared to first interval (1971–1973).
[b]Statistically significant ($p < .05$) between different groups at the same interval.

lation for total cancers and other cancer categories and the national reference population for internal and skin cancer.

DISCUSSION

The inclusion of liver cancer in our study could cause a bias in the analyses. Taiwan started a large-scale hepatitis B vaccination program in 1984 owing to the high prevalence of hepatitis B. The mortality from hepa-

TABLE 6. Spearman's Coefficients Between Mortality Rate Ratio of Diseases, Compared to 1971–1973, and Time 1971–1994 in Blackfoot Disease (BFD) Study Area, Local Reference, and National Reference, by Sex and Age

		Total malignant cancers			Internal and skin cancer			Other cancers		
Sex	Age (yr)	Study area	Local reference	National reference	Study area	Local reference	National reference	Study area	Local reference	National reference
Male	<40	–0.54	0.39	–0.82[a]	–0.50	0.46	–0.71	–0.75	–0.11	–0.96[a]
	≥40	0.39	1.00[a]	0.89[a]	0.79[a]	1.00[a]	1.00[a]	–0.71	0.86[a]	–0.46
Female	<40	–0.89[a]	0.11	–1.00[a]	–0.89[a]	0.07	–0.79[a]	–0.46	0.46	–1.00[a]
	≥40	–1.00[a]	0.89[a]	0.50	–0.86[a]	0.86[a]	0.89[a]	–0.86[a]	0.64	–0.86[a]

[a]Statistically significant ($p < .05$), for null hypothesis: $r = 0$.

TABLE 7. Spearman's Coefficients Between Mortality Rate Ratio of Diseases for Blackfoot Disease (BFD) Study Area, Compared to Local and National Reference, and Time 1971–1994, by Sex and Age

		Total malignant cancers		Internal and skin cancer		Other cancers	
Sex	Age (yr)	Study area/ local reference	Study area/ national reference	Study area/ local reference	Study area/ national reference	Study area/ local reference	Study area/ national reference
Male	<40	–0.33	–0.38	–0.31	0.46	–0.48	–0 64
	≥40	–0.88[a]	–0.62	–0.79[a]	–0.84[a]	–0.50	–0.52
Female	<40	–0.81[a]	–0.64	–0.45	–0.71[a]	–0.71[a]	–0.29
	≥40	–0.86[a]	–0.92[a]	–0.71[a]	–0.86[a]	–0.86[a]	–0.86[a]

[a]Statistically significant ($p < .05$), for null hypothesis: $r = 0$.

tocellular carcinoma was decreased after 1984 for children under 10 yr of age (Lee & Ko, 1997). According to our further analyses, there were only a few deaths from this disease for this age group. The effect of the decrease due to this reason was limited.

The inhabitants of the study area were exposed to arsenic mainly via drinking artesian well water. In addition to drinking, the artesian well water has been used for washing and agriculture. Agricultural products and fish have been reported to contain high concentrations of arsenic (Lo, 1978). The soil of endemic areas also has an arsenic content, up to 11.2 mg/kg. As a result, it was estimated in 1959 that the daily arsenic ingested by the residents of this study area was as high as 1 mg (Blackwell, 1961). At the beginning of the improvement of the water supply in 1965, some people still used the artesian well water for drinking and washing as well as for agriculture and pisciculture (Lu, 1975). However, after the mid-1970s, artesian well water was not used for cooking or washing anymore. It is worth mentioning that there were no new cases of blackfoot disease found among the inhabitants who were born after the tap-water supply was established (Tseng, 1989). According to the Young and Wu (1983) study on arsenic concentration in hair for blackfoot disease endemic area, the hair concentration of young cohorts who were born after 1956 without drinking artesian well water was significantly less than that in the same age group who still used artesian well water. The replacement of water source did withdraw arsenic exposure in the study area. Besides arsenic, mercury and manganese in artesian well water were also identified as higher than in other nonendemic area (Yeh & Young, 1980). However, further study showed that the concentration of these elements in blood and urea was not significantly different between blackfoot disease patients and healthy people living in other areas (Yeh et al., 1982). Thus, exposure to these elements does not seem to be influenced by water replacement

or to affect cancer mortality incidence. The humic substances identified from artesian well water could be a putative confounding factor for cancer mortality, as these compounds exhibited inhibitory activity on cellular mitosis and induced chromosome aberrations in cultured human lymphocytes (Lu et al., 1982). This hypothesis seems unlikely because humic compounds are the decay of plant matter and are widespread in water supplies (Bates et al., 1992). There was no correlation of humic concentration with arsenic levels, blackfoot disease, or with any cancers. Briefly, the greatest advantage for this study area for water source replacement is to eliminate arsenic exposure.

Data support a correlation between internal and skin cancers and arsenic exposure. Withdrawal of the arsenic exposure by improvement in the water supply actually decreased the trend of mortality rate ratios attributed to all malignant tumors from 1971 to 1994 relative to the first interval, 1971–1973, in females over 40 yr. For males over 40 yr, the trend is a significant increase in internal and skin cancer. The reference group cancers are even more prominently increased in this age group. The discrepancy between males and females over 40 yr is probably due to males being affected by other risk factors related to cancers in addition to arsenic exposure in endemic area, including dust, air pollutants, etc.

Those aged less than 40 yr were born after the water supply was set up although not yet complete. Exposure to arsenic in this cohort is less than for those aged over 40 yr. From our analyses in Spearman coefficients for skin and internal cancers, there is a significant decrease in the mortality rate ratio when compared to the first interval for females. A possible explanation for these results is that the incubation time of arsenic-related internal cancers is long and thus the cancers occur in later life. It is difficult to identify the effect of withdrawing arsenic exposure in such a cohort because the incidence was low whether the water supply was or was not improved. The hazard of arsenic could be involved in many other cancers in addition to internal cancers, and the mortality rate ratio for all malignant tumors among female was significantly decreased for both age groups.

The total numbers of malignant tumors were decreased in the study area, mainly due to the decrease in internal and skin cancers. The other cancers were also decreased, but the effects are less than for internal and skin cancers. These findings emphasize the relationship between chronic arsenic exposure and internal and skin cancers. The possibility of a relationship between chronic arsenic exposure and other cancers cannot be excluded.

There are some factors other than improvement of water supply that involve change in cancer mortality, such as (1) changes in diagnostic or recording practices of cancer, (2) improvement of medical service, or (3) a change in migration, life style, occupational exposure, or nutrient state in the study area. It is felt that there have been no changes in the diagnostic

or recording practices for cancer. Furthermore, liver, lung, kidney, bladder, and skin cancer are diagnosed carefully by physicians in the study area, since chronic arsenic exposure has been reported to be related to internal cancers by Chen et al. (1985). The leading cause of death must be recorded by physicians on all death certificates forwarded to the National Health Department, and this requirement has remained the same throughout the years of our study. The mortality of young cohorts was decreased in both the study and reference groups, which could partially result from the improvement of medical services. The decrease in the older group cannot be explained by improvement of medical service as compared to the reference groups, for whom skin and internal cancer mortality increased steadily. Actually, the medical services in the study area and the local reference area are below average compared to Taiwan. With respect to migration, life style, and occupational exposure, most of the residents in the study area engaged in farming, fishery, and salt production and have lived there all their life. The only change in their life style was the change in the water supply. In regard to the nutrient state, the improvement of nutrient state in our study area with time could affect the mortality due to cancers related to arsenic exposure, as insufficient nutrition might enhance carcinogenesis by reducing the level of detoxifying enzymes (Bates et al., 1992). Although the nutritional status of our study area was similar to the local reference group, the mortality from cancers between both groups was different. Even though the nutritional status of study area was improved, the decrease in mortality from cancers in this study area cannot be explained only by this factor. It is clear that the withdrawal of arsenic exposure decreased the mortality for internal and skin cancers. As mentioned earlier, the significant decrease in all malignant tumors in females over 40 yr suggests that arsenic might exert a carcinogenic effect on the whole body.

In conclusion, our results support the hypothesis that the withdrawal of arsenic exposure can decrease the incidence of benign internal and skin cancers as well as all malignant tumors. In the blackfoot disease endemic area, a continued decrease in mortality from these cancers is predicted. These results can provide some guidelines to governments to enforce stricter standards for maximum contaminant levels of arsenic in drinking water.

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