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DOSE-RESPONSE RELATION BETWEEN ARSENIC CONCENTRATION IN WELL WATER AND MORTALITY FROM CANCERS AND VASCULAR DISEASES

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Wu, M.-M., T.-L. Kuo, Y-H. Hwang, and C.-J. Chen (Div. of Environmental Sciences, School of Public Health, Columbia U., New York, NY 10032). Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol* 1989;130:1123–32.

Age-adjusted mortality rates were analyzed to examine the dose-response relation between ingested arsenic levels and risk of cancers and vascular diseases among residents in the endemic area of blackfoot disease, a unique peripheral vascular disease associated with long-term exposure to high-arsenic artesian well water and confined to the southwestern coast of Taiwan. The arsenic levels in well water determined in 1964–1966 were available in 42 villages of the study area, while mortality and population data during 1973–1986 were obtained from the local household registration offices and Taiwan Provincial Department of Health. Age-adjusted mortality rates from various cancers and vascular diseases by sex were calculated using the 1976 world population as the standard population. A significant dose-response relation was observed between arsenic levels in well water and cancers of the bladder, kidney, skin, and lung in both males and females, and cancers of the prostate and liver in males. However, there was no association for cancers of the nasopharynx, esophagus, stomach, colon, and uterine cervix, and for leukemia. Arsenic levels in well water were also associated with peripheral vascular diseases and cardiovascular diseases in a dose-response pattern, but not with cerebrovascular accidents. The dual effect of arsenic on carcinogenesis and arteriosclerosis and the interrelation between these two pathogenic mechanisms deserve more intensive study.

arsenic; neoplasms; vascular diseases; water supply

Arsenic is a ubiquitous mineral in nature and its acute toxicity has been well documented (1–3). Significant excess mortality in respiratory cancer has been reported for workers after long-term occupational exposure to arsenic (4, 5). Skin cancer or its precursor lesions were found among psoriatic patients treated with arsenic (6). Epidemiologic studies in West Germany (7), Argentina (7), Chile (8), and Taiwan (9) also indicated a positive association between the arsenic content of drinking water

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Abbreviation: ICD-8, Eighth Revision of the *International Classification of Diseases*.

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and the prevalence of skin cancer. Malignant neoplasms of internal organs have been reported in persons exposed to medicinal arsenic as well as vintners and smelters (10–12); however, there were no consistent results with regard to arsenic-induced neoplasms of internal organs except the lung (13, 14). In a recent study in Taiwan (15), a dose-response relation between standardized mortality ratios of various cancers and the prevalence of blackfoot disease, a peripheral vascular disorder related to cumulative arsenic exposure, was observed among villages in a limited area along the southwest coast of Taiwan. It was implied that the high arsenic content in the artesian well water might be one of the important determinants of cancers in the endemic area (16).

Besides malignant neoplasms, vascular diseases have been noted to be associated with chronic arsenic intake among West German vinedressers (17) and inhabitants of Antofagasta, Chile (8). Peripheral vascular diseases had been related to the high-arsenic well water in Taiwan (18–21). Although some studies (4, 12, 22) have suggested significantly increased cardiovascular mortality among workers at smelters, the findings were not observed in other studies (23, 24). The associations of arsenic exposure with vascular diseases, especially cardiovascular diseases and cerebrovascular accidents, remain to be assessed.

The purpose of the present study was to elucidate the effect of arsenic on the development of cancers and vascular diseases, and particularly to examine their dose-response relations.

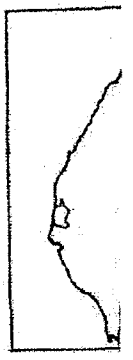
Materials and methods

Study area and demographic characteristics of population

The study area is confined to the southwestern coast of Taiwan Island, where the blackfoot disease has been endemic. In our previous report (15), all of the 84 villages in the townships of Peimen, Hsuechia, Putai, and Ichu were studied. However, because of the limited data on arsenic content in well water collected in 1964–1966 (25), only 27 villages in these four townships and an additional 15 villages in the townships of Yensui and Hsiaying were included in the present study (figure 1). Because the shallow well water in the study area had a high salinity, residents of the area started to use artesian well water in the second decade of this century (9). Artesian well water from the endemic area was found to have a high arsenic content, ranging from 0.35 to 1.10 parts per million (ppm) (26–28), while the shallow well water was almost free from arsenic, with levels between 0.00 and 0.30 ppm (mean value, 0.04 ppm) (27). During 1974–1976, a comprehensive survey of 83,565 wells in Taiwan showed that in the blackfoot disease endemic area, 29.1 percent of wells had water with an arsenic content 0.05 ppm or above and 5.2 percent had water with an arsenic content 0.35 ppm or above; the corresponding figures were only 5.7 percent and 0.3 percent in other areas surveyed (29). Because well water was the only drinking water source in the studied villages before the 1950s, all residents of a given village consumed well water from the same source in their daily home and working environment. It was noted in a recent survey (30) that even after 1956, when the piped water system was gradually implemented in the endemic area, some inhabitants still used artesian well water for drinking and washing, agriculture, aquaculture, and livestock husbandry, especially in the dry season when the water supply was insufficient. Agricultural products and fish were reported to contain high concentrations of arsenic in the endemic area (31, 32). It was estimated that the daily arsenic ingested by the local residents was as high as 1 mg in 1959 (33).

The living standard in the study area was below the average of that in Taiwan. Dried sweet potatoes with various amounts of rice were the staple food for local residents. A survey carried out in 1960 (34) indicated that residents in the blackfoot disease en-





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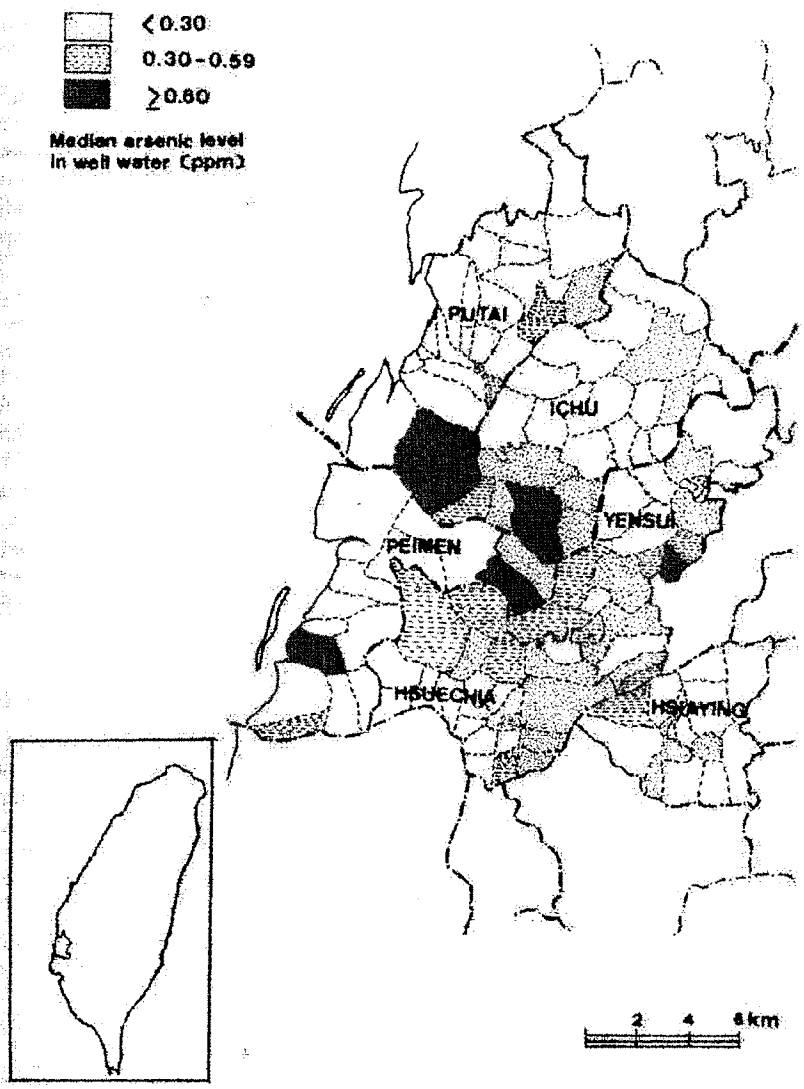

FIGURE 1. Geographic distribution of 42 studied villages in the endemic area of blackfoot disease in Taiwan, by median arsenic level of well water determined in 1964–1966.

demic area had an insufficient intake of fresh vegetables and animal protein. Most residents of the study area have been engaged in fishing or salt production or, in areas of less salinity, in farming. The population in the study area decreased from 203,344 in 1973 to 174,945 in 1986, and the average immigration rate and emigration rate were 3.81 percent and 6.76 percent, respectively. Both of these rates were lower than the average rates for rural areas in Taiwan (35). It was recently reported (30) that more than 90 percent of local residents lived in the study area all their lives. Because the study population lived in a small area, they shared similar dietary patterns, life-style, socioeconomic status, and even medical facilities.

Arsenic concentration in well water

Water samples were collected from a total of 155 wells of the 42 villages where shallow and/or deep well water was still being used in 1964–1966. The samples were examined by Natelson's method in 1964–1966, as reported in previous studies (9, 25). The arsenic content of well water samples ranged from 0.010 ppm to 1.752 ppm with two clusters at levels of 0.05–0.25 ppm and 0.45–0.65 ppm. Because the arsenic concentration of well water samples in the same village did not distribute normally, median arsenic levels of well water samples were used to classify the studied villages. In order to compare the present results with the results of previous studies (9, 20), the studied villages were categorized into three groups according to their median arsenic levels of well water, i.e., <0.30 ppm, 0.30–0.59 ppm, and ≥0.60 ppm. In all, there were 20 villages with median arsenic levels <0.30 ppm, 15 villages with levels 0.30–0.59 ppm, and seven villages with levels ≥0.60 ppm. The geographic distribution of villages by median arsenic levels of well water is depicted in figure 1.

Death certificates and population base

In Taiwan, it is mandatory to register any event of birth, death, marriage and divorce, migration, and employment in the household registration offices, so that the vital statistics and demographic data are therefore very complete. Death certificates of residents who died from cancers and vascular diseases during 1973–1986 were collected from local household registration offices of studied townships. All the death certificates were reviewed and coded for their underlying causes of death according to the Eighth Revision of the *International Classification of Diseases* (ICD-8) (36). Mid-year populations by age and sex of the studied villages were abstracted from demographic reports of the local household registration offices.

Person-years calculation and mortality analysis

The person-years observed during 1973–1986 were calculated first by the person-years method. In order to compare the difference in mortality among groups of varying arsenic exposure, the age-adjusted mortality rate for a given sex-exposure group was calculated using the direct method of standardization using a standard formula (37, chapter 2). Only a few or no deaths were observed among age groups under age 20 years, and standardized rates were calculated using specific rates for age groups of 20 years or more. To examine the exposure effect, an extension of Mantel-Haenszel χ^2 test (37, chapter 3) was used to test for the significance of the dose-response relation between the age-adjusted mortality rates from various cancers and vascular diseases and the arsenic exposure.

RESULTS

Age and sex distribution of study population

The age and sex distribution of person-years observed in villages of different median arsenic concentrations in well water is shown in table 1. In all, for males, there were 248,728 person-years in villages with median arsenic concentrations of <0.30 ppm, 138,562 person-years in villages with 0.30–0.59 ppm, and 79,883 person-years in villages with ≥0.60 ppm. For females, there were 230,048 person-years in villages with median arsenic concentrations of <0.30 ppm, 127,502 person-years in villages with 0.30–0.59 ppm, and 74,083 person-years in villages with ≥0.60 ppm.

Cancer and vascular deaths

The numbers of deaths from various cancers and vascular diseases among residents aged 20 years or more in villages of different median arsenic levels in well water are shown by sex in table 2. There were a total of 243, 244, and 150 male cancer deaths and 191, 180, and 144 female cancer deaths

Numbers of person-years

Age (years)	<0.30
0–9	47,12
10–19	61,87
20–29	53,21
30–39	24,27
40–49	25,20
50–59	19,17
60–69	11,47
70–79	5,25
80+	1,13
Total	248,72

Numbers of deaths from villages of the blackfoot

Cause of death (ICD-8)*
Cancers
All sites (140–209)
Bladder (188)
Kidney (189)
Skin (173)
Lung (162)
Liver (155)
Prostate (185)
Leukemia (204–208)
Nasopharynx (147)
Esophagus (150)
Stomach (151)
Colon (153)
Uterine cervix (180)
Vascular diseases
All vascular diseases (401–448)
Peripheral vascular dise (440–448)
Cardiovascular diseases (410–414, 420–429)
Cerebrovascular acciden (430–438)

* ICD-8, Eighth Revisio

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TABLE 1

Numbers of person-years observed in 42 villages of the blackfoot disease endemic area in Taiwan, by median arsenic levels in well water, age, and sex, 1973–1986

Age (years)	Median arsenic levels in well water (ppm)					
	Males			Females		
	<0.30	0.30–0.59	≥0.60	<0.30	0.30–0.59	≥0.60
0–9	47,124	26,334	16,879	44,277	25,223	15,731
10–19	61,875	36,045	20,981	58,296	33,945	19,642
20–29	53,219	29,246	16,529	40,721	20,715	12,950
30–39	24,271	12,894	8,116	22,027	11,401	7,397
40–49	25,200	13,664	7,607	24,743	13,986	8,073
50–59	19,175	10,472	5,572	19,353	10,995	6,062
60–69	11,475	6,375	2,973	12,763	7,079	2,973
70–79	5,250	2,851	1,073	6,104	3,323	1,022
80+	1,139	681	164	1,764	835	233
Total	248,728	138,562	79,883	230,048	127,503	74,083

TABLE 2

Numbers of deaths from various cancers and vascular diseases among residents aged 20 years or more in 42 villages of the blackfoot disease endemic area in Taiwan, by median arsenic levels in well water and sex, 1973–1986

Cause of death (ICD-8)*	Median arsenic levels in well water (ppm)					
	Males			Females		
	<0.30	0.30–0.59	≥0.60	<0.30	0.30–0.59	≥0.60
Cancers						
All sites (140–209)	243	244	150	191	180	144
Bladder (188)	23	36	26	30	36	30
Kidney (189)	9	11	6	4	13	16
Skin (173)	2	8	9	2	10	5
Lung (162)	53	62	32	43	40	38
Liver (155)	54	42	27	25	16	10
Prostate (185)	1	5	3			
Leukemia (204–208)	6	4	1	4	3	
Nasopharynx (147)	4	5	2	2	4	1
Esophagus (150)	8	5	2	2	2	
Stomach (151)	26	10	10	8	11	2
Colon (153)	8	6	3	11	5	5
Uterine cervix (180)				1	4	1
Vascular diseases						
All vascular diseases (401–448)	363	230	136	320	226	93
Peripheral vascular diseases (440–448)	21	29	14	21	29	8
Cardiovascular diseases (410–414, 420–429)	127	85	62	105	93	37
Cerebrovascular accidents (430–438)	137	81	44	106	60	30

* ICD-8, Eighth Revision, *International Classification of Diseases*.

in villages with median arsenic levels of well water <0.30 ppm, 0.30–0.59 ppm, and ≥0.60 ppm, respectively. There were 363, 230, and 136 male vascular deaths and 320, 226, and 93 female vascular deaths in villages with median arsenic levels of well water <0.30 ppm, 0.30–0.59 ppm, and ≥0.60 ppm, respectively.

Mortality rates of various cancers

Table 3 shows the age-adjusted mortality rates of various cancers by sex in villages of different median arsenic levels in well water. A significant dose-response relation was observed for cancers of the bladder, kidney, skin, and lung in both males and females, and for cancers of the prostate and liver in males. Mortality rates for cancers of the nasopharynx, esophagus, stomach, colon, and uterine cervix, and for leukemia were not associated with the arsenic concentration in well water.

Mortality rates of various vascular diseases

As shown in table 4, a significant trend of mortality rates from peripheral vascular diseases and cardiovascular diseases was observed in villages of different arsenic concentrations in well water. However, there was no significant association for cerebrovascular accidents.

Discussion

Mortality data have been widely used to generate epidemiologic hypotheses, despite their inherent limitations. The completeness and accuracy of the death registration system should be evaluated before any conclusion based on mortality analysis is made. Because, in Taiwan, it is mandatory to register all deaths at local household registration offices, death certificate registration is quite complete. Although causes of deaths may be misdiagnosed and/or misclassified, cancer has been reported to be one of the most complete and unequivocal causes of death in the registration system (38). While there might be some problems in the diagnosis and classification of vascular diseases, it was believed that the misdiagnosis and/or misclassification were not made differentially among the comparison groups. The group differences in mortality might thus be underestimated rather than overestimated under this conservative circumstance. Because the 42 studied villages are clustered in a limited area, local residents have received the same medical care services. The discrepancy in the quality of mortality registration among comparison villages was further lessened. The completeness and accuracy of death certificate registration are thus believed to be comparable.

Table 3

Age-adjusted mortality rates (per 100,000†) from various cancers among residents aged 20 years or more in the blackfoot disease endemic area in Taiwan, by sex and concentration of arsenic in well water, 1973–1986

Cause of death (ICD-8)‡	Median arsenic levels in well water (ppm) and significance levels							
	Males				Females			
	<0.30	0.30–0.59	≥0.60	*p* value	<0.30	0.30–0.59	≥0.60	*p* value
All sites (140–209)	224.56	405.12	534.81	**	162.22	277.20	487.20	**
Bladder (188)	22.64	61.02	93.71	**	25.60	57.92	111.30	**
Kidney (189)	8.42	18.90	25.26	*	3.42	19.42	57.98	**
Skin (173)	2.03	14.01	32.41	**	1.73	14.75	18.66	**
Lung (162)	49.16	100.67	164.08	**	36.71	60.82	122.16	**
Liver (155)	47.78	67.62	86.73	*	21.40	24.18	31.75	NS
Prostate (185)	0.95	9.00	9.18	*				
Leukemia (204–208)	4.87	6.52	2.69	NS§	3.08	4.35	0.00	NS
Nasopharynx (147)	3.58	8.16	8.58	NS	1.59	5.81	4.89	NS
Esophagus (150)	7.62	9.37	6.55	NS	1.83	3.64	0.00	NS
Stomach (151)	25.66	17.82	56.42	NS	6.71	18.72	5.98	NS
Colon (153)	7.94	8.30	12.51	NS	9.05	8.16	17.21	NS
Uterine cervix (180)					0.91	5.46	3.92	NS

* $p < 0.05$; ** $p < 0.001$, based on the trend test of the extension of the Mantel-Haenszel χ^2 test.
† Using the 1976 world population as the standard population.
‡ ICD-8, Eighth Revision, *International Classification of Diseases*.
§ NS, nonsignificant.

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Cause of death (ICD-8)‡
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Peripheral vascular diseases (440–448)
Cardiovascular diseases (410–414, 420–429)
Cerebrovascular accidents (430–438)

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TABLE 4

Age-adjusted mortality rates (per 100,000†) from various vascular diseases among residents aged 20 years or more in the blackfoot disease endemic area in Taiwan, by sex and concentration of arsenic in well water, 1973–1986

Cause of death (ICD-8)‡	Median arsenic levels in well water (ppm) and significance levels							
	Males				Females			
	<0.30	0.30–0.59	≥0.60	*p* value	<0.30	0.30–0.59	≥0.60	*p* value
All vascular diseases (401–448)	364.10	421.47	572.68	**	277.50	370.79	386.41	**
Peripheral vascular diseases (440–448)	22.54	57.80	60.40	**	18.20	48.00	35.82	*
Cardiovascular diseases (410–414, 420–429)	125.87	153.98	259.51	**	91.14	153.07	144.74	**
Cerebrovascular accidents (430–438)	137.80	145.36	175.72	NS§	92.42	98.11	120.68	NS

* $p < 0.05$; ** $p < 0.001$, based on the trend test of the extension of the Mantel-Haenszel χ^2 test.
† Using the 1976 world population as the standard population.
‡ ICD-8, Eighth Revision, *International Classification of Diseases*.
§ NS, nonsignificant.

Comparison of age-adjusted mortality rates was made under circumstances of similar life-style, medical accessibility, and socioeconomic status among the studied groups. The results showed that the mortality rates from several internal organ cancers and from vascular diseases were significantly related to increasing arsenic exposure. The association observed at the village level may not hold at the individual level. This ecologic fallacy should be considered in this study. According to our previous retrospective studies (16), the arsenic consumption in terms of the years of use of artesian well water was significantly associated with cancers of the bladder, lung, and liver at the individual level. The use of high-arsenic well water was not associated with cigarette smoking, alcohol drinking, consumption of fermented beans, or other cancer risk factors. In other words, these potential risk factors might not confound the association between the arsenic exposure and cancer. In the residents of the blackfoot disease endemic area, serum cholesterol levels and blood pressures were found to be even lower than those found in the general population of Taiwan (39). Arsenic content is thus strongly suspected to be the main cause of the cancers and vascular diseases among the local residents.

The associations of inorganic arsenic with skin cancer and lung cancer have been well documented in previous studies (40). 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 (1, 41). Among residents of the study area, besides the expected excess in mortality from skin cancer and lung cancer, we also found increased mortality from cancers of the bladder and kidney in both males and females, and prostate and liver cancers in males. The associations between arsenic concentration in well water and mortality from these five cancers were in a dose-response pattern. However, no association of arsenic concentration with cancers of the nasopharynx, esophagus, stomach, colon, and uterine cervix, and leukemia was observed. The results of this study are in accordance with the results of our previous report (15) except for those concerning colon cancer and liver cancer in females. Colon cancer was found to have a positive, but less remarkable, association with high-arsenic artesian well water (15). Although statistically nonsignificant, liver cancer mortality for females still followed a striking dose-response trend. These discrepancies may result from the different coverage of the

study population and/or the small numbers of deaths observed in this study. The differential associations between arsenic and various cancers deserve further exploration. Because chemical carcinogenesis results from the very specific interaction of the target cell and the carcinogen, most carcinogens are regarded as organotropic (42). Arsenic, however, seems to be associated with a wide range of cancers. Although the mechanism of deoxyribonucleic acid (DNA) damage induced by arsenic is still unclear, in vitro studies (43–45) have shown that arsenic affects the enzymes involved in the DNA repair system or interferes with DNA synthesis by the interaction between arsenite ion and thiol groups. This effect has been supported by a recent study (46) that indicates that posttreatment with sodium arsenite synergistically increases the clastogenicity of S-dependent agents. These results suggest that arsenic may act as a potentiator of the carcinogenic process rather than as a direct carcinogen (47, 48).

Arsenic has been regarded as the most important determinant of blackfoot disease in Taiwan (18, 20). According to the theory advanced by Hueper (49), arsenic is thought to have a vasodilating effect on the walls of blood vessels. Generalized arteriosclerosis has also been found in autopsied patients of blackfoot disease (39). Higher, but not significantly higher, mortality from cardiovascular diseases has been observed among workers at smelters in some Western countries (12, 22, 24). Because cardiovascular mortality is usually much higher in Western countries than in Oriental countries, a large sample size is required to examine the effect of arsenic on the excess cardiovascular mortality in Western countries. Unfortunately, the smelter populations under observation in previous studies seem too small to detect significant effects of arsenic on the cardiovascular system.

In this study, excess mortality from peripheral vascular diseases and cardiovascular diseases was observed for residents in the study area. However, no trend was found for cerebrovascular mortality among the study population. The discrepancy between cerebrovascular accidents and other vascular diseases may be partly explained by the fact that much less arsenic is distributed in the brain (50).

Besides arsenic, several compounds are found in the high-arsenic well water, including ergotamine, organic chlorides, and fluorescent substances (51). In addition, trace elements, such as molybdenum, mercury, copper, and cadmium, were reported to be higher in the serum and/or urine of blackfoot disease patients and in the ground water they used (52, 53). Even so, arsenic is the only element that has been extensively measured from thousands of wells in Taiwan. Arsenic thus remains one of the most important determinants of cancers and vascular diseases observed in the blackfoot disease endemic area. Further examination of the effects of arsenic on carcinogenesis, atherogenesis, and their interrelation by means of experimental studies and an extensive epidemiologic follow-up study are recommended.

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