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Historical cohort studies in three arsenic poisoning areas in Japan

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The results of historical cohort studies of three arsenic poisoning incidents in Japan are presented. The first episode was in a small mountainous community near an arsenic mine and refinery, at Toroku, where patients with chronic arsenism were certified by application of the Pollution Health Damage Compensation Law. The second area was in a small town, Namiki-cho, near Nakajo-machi, where wells were poisoned by arsenic produced in an arsenic(III) sulfide factory. As to the third cohort, eight residents of Nishikawa-machi who ingested well-water suffered arsenic poisoning about 35 years ago. The standardized mortality ratios were used in analyzing these data. Excesses of cancer mortality, especially lung cancer, were observed among the subjects in these areas. In Japan, there are many arsenic poisoning episodes, involving for example soy-sauce poisoning, powdered-milk poisoning and other incidents associated with arsenic mines. Thus it is necessary to clarify the chronic effects of arsenic in these areas.

Keywords: Arsenic, exposure cancer, standardized mortality rate ratio, epidemiology

INTRODUCTION

Arsenic and certain arsenic compounds have been used in homicidal and suicidal drugs, medical drugs, pesticides and industrial materials. Their toxicity has been well investigated during many incidents of arsenic poisoning. There also have been many reports on the carcinogenicity of arsenic. According to the evaluations of the International Agency for Research on Cancer (IARC), there is sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans.[1]

In Japan, many arsenic poisoning incidents have been reported, involving for example, soy-sauce poisoning, powdered-milk poisoning, well-water poisoning, pollution around arsenic mines and occupational exposure.[2] Several follow-up studies of these incidents[3–6] have been performed. We have conducted three follow-up studies on arsenic poisoning, focusing on carcinogenicity. The sites of each study area are the Toroku mine in Miyazaki Prefecture ('Toroku' hereinafter), a small town called Naniki-cho, near Nakajo-machi in Niigata Prefecture ('Nakajo'), and Nishikawa-machi in Niigata Prefecture ('Nishikawa') (Fig. 1). The types of exposure were different in these areas: one was ingestion and inhalation of arsenic, the other two cases were only ingestion.

We introduce and summarize here the features of cancer development in these arsenic poisoning areas, and the process of epidemiological inference.

TOROKU MINE INCIDENT

Toroku is a small village on the island of Kyushu with a total population of less than 300. During 28 of the years from 1920 to 1962, a mining company intermittently produced arsenic(III) oxide (As_2O_3) while refining ores. Not only the workers at the refinery but also the residents living near the mine–refinery were affected by the arsenic and sulfur oxides discharged by the refinery into the environment, mainly by arsenic pollution in the air and by arsenic water contamination downstream from the refinery.[7]

Roasters used at the arsenic refinery were primitive ones without desulfurization or dust-collection systems. Accordingly, effluent gases containing As_2O_3 and sulfur dioxide (SO_2) were discharged from the stack, so that the entire

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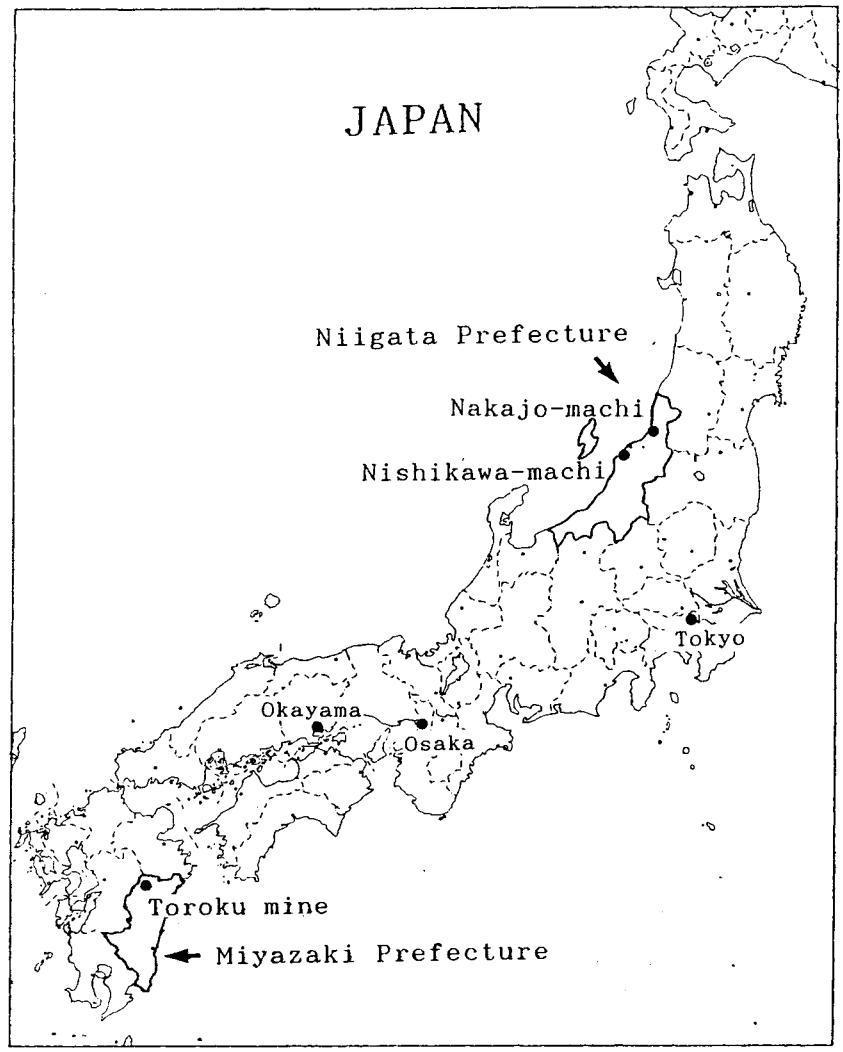

Figure 1 Location of each arsenic poisoning area.

valley of Toroku was covered by the smoke. Part of the slag was discharged into the stream, exposing the surroundings to contamination. Thus, the inhabitants living downstream drew water for daily life from the stream which was contaminated by arsenic. The concentration of arsenic and SO_2 in the workplace and the environment was never measured during the period of operation.[7]

In 1972 analysis near the mine and refinery revealed high arsenic contents in the dust from ceiling boards of residents' homes (200–8000 ppm), neighboring soils (2760 ppm on average) and percolated water from the slag (180 ppm).[7]

In 1972, certification of chronic arsenism began in the polluted area according to the Pollution Health Damage Compensation Law and, by 1991, 146 patients had been certified. Criteria for certification are the combinations of such clinical manifestations as skin lesions (hyperpigmentation and hyperkeratosis), scarring or perforation of the nasal septum, polyneuropathy and chronic bronchitis. Respiratory cancer and other cancers are not included in the criteria. We demonstrate here the results of the investigation until August 1988.

Method

Death certificates were obtained, with medical records as the occasion demanded. Causes of death were classified according to the *9th International Classification of Diseases* (ICD-9th).

The expected number of deaths and the standardized mortality ratios (SMRs) were based on the sex- and age-specific mortality of all Japanese in 1975, 1980, and 1985, calculating person-years divided into the three periods 1972–1977, 1978–1982 and 1983–1989. The number of person-years of the entire cohort was 1317 (male 599.75 and female 717.25), and of former workers 713.25 and unemployed residents 603.25. The mean age at the beginning of observation (±SD) was 60.8± 10.4 years and the average duration of follow-ups was 9.3 ± 4.0 years. The Poisson distribution was used for calculating 95% confidence intervals.

Result

Until August 1988, there were 55 deaths in the entire cohort compared with the expected number of 44.32, showing no significant difference. Among the specific causes of death, cancer of the trachea, bronchus and lung ('lung cancer' hereinafter) (ICD code 162), cancer of the respiratory and intrathoracic organs ('respiratory cancer') (ICD code 160–165), cancer of the bladder and kidney and other and unspecified urinary organs ('urinary tract cancer') (ICD code 188–189) and ischemic heart disease (ICD code 410–414) significantly exceeded the expected value based on the mortality rate in Japan (Table 1).

There were 17 deaths caused by cancer; nine of these were lung carcinoma and the others were one case each of laryngeal carcinoma, carcinomatous pleuritis, ureteral carcinoma, urethral carcinoma, non-Hodgkins's lymphosarcoma, angiosarcoma of the skin, female breast cancer and rectum carcinoma. Twelve of them were histologically confirmed as follows: four lung cancers and a laryngeal cancer as squamous-cell carcinoma; one lung cancer, a carcinomatous pleuritis, a female breast cancer and a rectum cancer as adenocarcinoma; two urinary tract cancers as transitional-cell carcinoma; and one cancer as angiosarcoma of the skin (Table 2).

There were 26 cases of Bowen's disease observed, i.e. intra-epidermal squamous cell carcinoma, among the 55 dead certified patients. No other occupational histories in Toroku were related to the occurrence of lung cancer. Eleven cases had a smoking history, and the smoking index (cigarettes smoked per day × duration in years) of seven cases ranged from 200 to 1000.

WELL-WATER POISONING IN NAKAJO-MACHI

There was an incident of chronic arsenic poisoning in a small town called Namiki-cho, near Nakajo-machi in Niigata Prefecture, in September 1959.[2,8]

In that month, an 11-year-old boy living in Nakajo-machi was given a medical examinations for white spots, hyperpigmentation and hyperkeratosis of the skin. The diagnosis was chronic arsenism. Drinking water from the well in his house was suspected to be the source of arsenic. The polluted area is displayed in Fig. 1. Near the affected houses there was a small factory where King's Yellow (As_2S_3) had been produced for more than 40 years. The factory disposed of waste water into underground gravel by infiltration. As a result, wells near the factory had become contaminated. It was presumed that the waste water had chiefly contained anhydrous arsenic(III) oxide (As_2O_3) and micro-particles of As_2S_3 used in the production process. Although the factory had

Table 1 Observed and expected deaths and SMRs for selected causes of death for the entire cohort in Toroka, Japan

Cause of death	ICD code	Observed	Expected	SMR	95% confidence interval
All causes		55	44.32	124	95–161
All cancers	140–208	17	8.90	191	116–307
Stomach	151	0	2.72	0	0–138
Trachea, bronchus and lung	162	9	1.40	643	319–1236
Respiratory and intrathoracic organs	160–165	11	1.52	724	379–1304
Bladder, kidney and other and unspecified urinary organs	188–189	2	0.26	774	137–2822
Causes except cancer		38	35.42	107	78–147
Cerebrovascular disease	430–438	8	10.51	76	36–151
Ischemic heart disease	410–414	7	3.26	214	101–439
Respiratory system disease	460–519	5	4.80	104	41–246

Table 2 Employment history, smoking history, histological types of 18 cancer deaths among the Toroku certified patients

Case	Cancer site	Year of certification	Year of death	Age at death	Job	Smoking history	Histological type	Accompanying cancer
1M[a]	Lung	1974.2	1974.4	57	+(Refining)	+(700)	Unclear	Bo[h]
2M	Pleura	1976.3	1979.1	67	+(Refining)	+(900)	Adeno[d]	
3M	Lung	1977.12	1979.2	63	+(Other jobs)	+(350)	Squamous[e]	
4F[b]	Lung	1979.4	1979.10	72	–	+(500)	Unclear	
5M	Lung	1976.3	1979.11	69	+(Other jobs)	—	Unclear	
6M	Lung	1974.2	1981.9	71	+(Mining)	+(?)	Adeno	Prostate cancer (adeno) Bo
7M	Larynx	1974.2	1982.8	68	+(Mining)	+(400)	Squamous	Skin cancer (basal[i])
8M	Lung	1974.2	1983.8	83	+(Refining)	+(600)	Unclear	Bo
9M	Lung	1979.4	1986.4	75	+(Refining)	+(1000)	Squamous	Stomach cancer (adeno)
10M	Lung	1982.6	1987.11	78	+(Refining)	+(?)	Squamous	Bo
11M	Lung	1977.5	1988.8	68	+(Mining)	+(700)	Squamous	Bo
12M	Luing	1980.1	1989.1	73	+(Other jobs)	+(200)	Squamous	Bo
1M	Ureter	1972.8	1978.10	55	+(Refining)	+	TCC[f]	Bo
2F	Urethra	1973.7	1980.8	67	+(Refining)	+	TCC	Bo
3M	Lymph node	1976.3	1986.8	76	+(Mining)	+	Non-Hodgkin[g]	Bo
4F	Skin	1976.3	1984.2	74	—	—	Angisarcoma	
5F	Breast	1972.8	1982.12	81	+(Refining)	—	Unclear	Bo
6M	Rectum	1974.2	1987.10	81	—	—	Unclear	

[a] M, Male. [b] F, Female. [c] Brinkmann's smoking index. [d] Adeno, adenocarcinoma. [e] Squamous, Squamous-cell carcinoma. [f] TCC, transitional-cell carcinoma. [g] Non-Hodgkin, non-Hodgkin lymphosarcoma. [h] Bo, Bowen's disease. [i] Basal, basal-cell carcinoma.

been producing King's Yellow by the same process for 45 years, the arsenic concentration in the wells was assumed to have increased substantially in 1954, when the flow of underground water decreased markedly due to the improvement of a nearby river by the Local Government. The operation of the factory was stopped as soon as the incident was reported. Simultaneously, the use of all the wells was banned in September 1959. At that time, waterworks were constructed by the Government.

As the Prefectural Government demonstrated that the arsenic concentration exceeded 0.1 ppm within a distance of 500 m from the factory, the area was designated a contaminated area. Well-to-well measurements of arsenic concentration were taken in all 54 wells within that area in September 1959. The results of measurements of 34 wells were available. Their arsenic concentration ranged from non-detectable to 3.0 ppm, with 11 wells exceeding 1.0 ppm. The records concerning the remaining 20 wells could not be obtained. However, interviews were held with the owners of these 20 wells in 1987. They stated that the Prefectural Government notified them in 1959 that the water of these wells did not contain arsenic. In addition, from the Government document issued on the incident, all wells in which arsenic concentration exceeded 0.05 ppm seemed to be listed. Therefore, we considered the arsenic concentration of these 20 wells was undetectable or at a very low level. The Prefectural Government concluded from their investigation that exposure to arsenic from the area was limited to ingestion only, there being no sign of inhalation effects.[2,8]

An attempt was made to conduct medical examinations on all 467 residents of the town in 1959. Not all of them worked at the factory. Three hundred and ninety-three residents were examined by Niigata University Medical School, and 88 residents had signs of arsenism.[8]

Method

From the 1959 list we identified 467 residents, of whom we were able to follow 454: 443 residents were confirmed to have drunk well-water. We calculated the standardized mortality ratios (SMRs) according to the arsenic concentration of the well-water on these 443 residents. Then we divided the 454 residents into five categories

Table 3 Standardized mortality rate ratios for all causes of death, all cancer deaths, lung cancer deaths and smoking rates according to arsenic concentration of well-water in 1959 in Nakajo, Japan

	Cohort (number of residents)		
Cause of death	Entire cohort (443)	0.05 ppm As and more (189)	Less than 0.05 ppm As (254)
All deaths (*O/E*)[a]	102 (77/75.69)	120 (37/30.85)	89 (40/44.84)
All cancers (*O/E*)	129 (23/17.78)	235 (17/7.22)	57 (6/10.56)
All lung cancers (*O/E*)	404 (7/1.73)	1002 (7/0.70)	0 (0/1.30)
No. of smokers (Rate %)	180 (40.6)	79 (41.8)	101 (39.8)

[a] *O/E* = Observed deaths/expected deaths.

according to the degree of the main diagnostic signs in 1959, such as hyperpigmentation, pancytopenia and hepatomegaly. These 454 residents had been examined by the Medical School in 1959; 88 residents had signs of chronic arsenism and 294 residents had none. The remaining 72 residents did not undergo the examination.

The causes of death were classified according to the *International Classification of Disease* (ICD-9th). The expected number of deaths was based on the sex, age and cause-specific mortality of Niigata Prefecture from 1961 to 1989. The Poisson distribution was used for calculating 95% confidence intervals.

Results

As shown in Table 3, the SMRs of the residents who ingested well-water of more than 0.05 ppm arsenic concentration were 120 (95% confidence interval 87–165) in all causes of death, 235 (143–378) in deaths from all cancers, and 1002 (470–2052) in lung cancer deaths. Liver cancer and uterine cancer had also increased statistically significantly, although only two cases of each occurred. Then, we analyzed 88 patients who had signs of chronic arsenism in 1959. SMRs of the sub-cohorts of the residents who had signs and of those with no sign in 1959 are shown in Table 4 The histological types of seven lung cancer deaths were two small-cell carcinoma, one large-cell carcinoma, one squamous-cell carcinoma, one small-cell carcinoma accompanied by squamous-cell carcinoma, and two histologically unknown cases.

WELL-WATER POISONING IN NISHIKAWA-MACHI

On August 5, 1950, a glass factory was burnt in a fire. In the ruins of the fire, anhydrous arsenic(III) oxide (As_2O_3) was piled up, which the fireman buried there. The arsenic-contaminated well-water was used by two families, composed of eight persons: three males and five females (Fig. 2). Several signs of chronic arsenism began to appear after 1954. The use of well-water was prohibited in June 1956. The signs and symptoms were anorexia, cough, numbness, loss of hair, a feeling of warmth in the legs, and hyperpigmentation and hyperkeratosis of the skin. Seven of these were diagnosed as chronic arsenism.

Table 4 Standardized mortality rate ratios for all causes of death, all cancer deaths, lung cancer deaths and smoking rates according to severity of chronic arsenism in 1959 in Nakajo

	Cohort (number of residents)	
Cause of death	Patients (88)	Non-patients (294)
All deaths (*O/E*)[a]	133 (26/19.58)	101 (44/43.78)
All cancers (*O/E*)	305 (14/4.58)	93 (10/10.78)
All lung cancers (*O/E*)	1490 (7/0.47)	0 (0/1.03)
No. of smokers (Rate, %)	44 (50.0)	96 (32.7)

[a] *O/E*, Observed deaths/expected deaths.

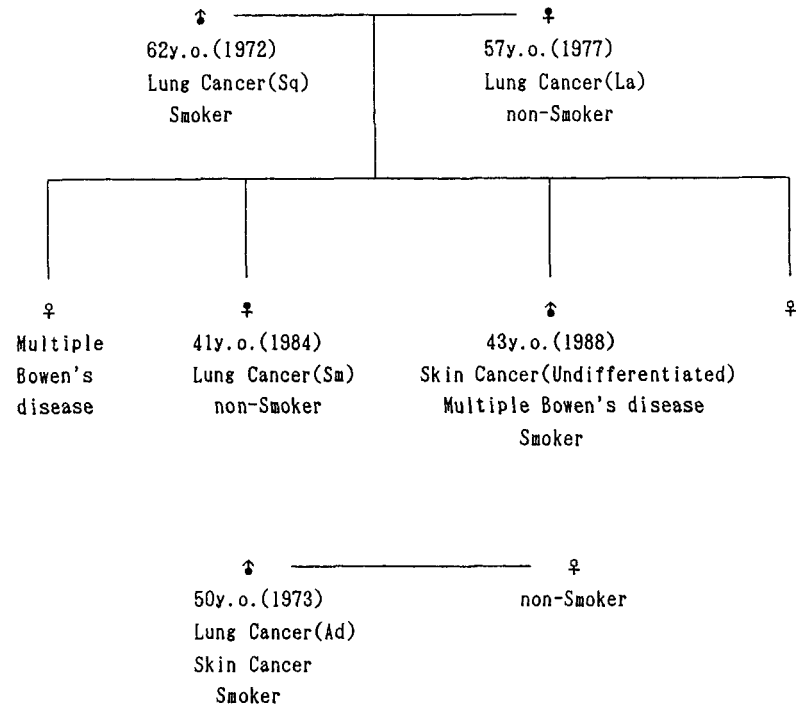

Figure 2 Eight chronic arsenic-poisoning patients (two families) in Nishikawa-machi, Niigata Prefecture. Key: y.o., years old; Sq, squamous-cell carcinoma; La, large-cell carcinoma; Sm, small-cell carcinoma; Ad, adenocarcinoma; Undifferentiated, undifferentiated carcinoma.

In 1987, one of them visited the Prefectural Cancer Center, Niigata Hospital, with hyperplasia of his feet. The hyperplasia was undifferentiated skin carcinoma (Fig. 2). In his body, multiple lesions of Bowen's disease were observed. Then we studied his family members. The result of this observational study is displayed in Fig. 2. Smoking history, histological types of cancer, and accompanied cancers are also displayed.

DISCUSSION

There are two major objectives in this report. One is to introduce long-term follow-up studies of victims affected by arsenic in Japan to emphasize the importance of such follow-up work. Another is to offer suggestions to researchers in different fields, from an epidemiological point of view, in order to elevate the plausibility of a causal relationship between arsenic and cancer.

This report includes two epidemiological investigations (Toroku and Nakajo) and a smaller investigation. Because the Nishikawa study is too small to analyze the data, it should more properly be called a case report. Therefore, we should first discuss the strong and weak points of the epidemioligical studies in inferring causal relationships between possible causes and diseases. It is, needless to say the case that epidemiological studies involve searching and analyzing one population with a higher incidence rate than another spatially and/or temporally by using statistical methods. Usually, we cannot clarify direct relationships.[9] We can only estimate or infer these by using epidemiology. Other scientific methodologies will be necessary for further clarification of causality. The strongest approach to epidemiology, however, is to deal directly with human data. The results of such epidemiological studies are then directly combined with public health policy. We should consider these limitations and the advantages of epidemiology in conducting these studies.

In inferring the relationship between arsenic exposure and development of cancer, however, epidemiology can be very useful, because cancer development takes much time and because it is very difficult to make models of cancer development after exposure to arsenic. Therefore, we

Table 5 Cases of disease and number of person-years in an exposed population and a reference population[10]

	Exposed population			Reference population		
	Person-years	No. of cases	Incidence rate	Person-years	No. of cases	Incidence rate
Young	3000	?	?	1000	5	0.005
Old	1000	?	?	9000	225	0.025
All	4000	60	0.015	10 000	230	0.023

In this example, the observed number of cases in the exposed population (O) is 60. The corresponding 'expected' number (E) is:

$$E = 3000 \times 0.005 + 1.000 \times 0.025 = 40$$

Therefore,

$$\text{SMR} = (O/E) \times 100 = (60/40) \times 100 = 150$$

should recognize the carcinogenicity of arsenic before clarifying the causality in detail.

In the two present epidemiological studies, the two indicators of gender and tobacco smoking combine with each other. We should control these possible confounders. However, a remarkable increase of SMRs of lung cancer is enough to infer a causal relationship.

The standardized morbidity (or mortality) rate ratio (SMR) is the ratio of the observed number of deaths to the expected number. The expected number is the number of cases that would have occurred in the exposed population had all the age-specific incidence rates in the exposed population been the same as in the reference population. For both the observed and the expected numbers of cases the underlying age distribution is the same as that in the exposed population. The underlying incidence rates are, for the observed number, those in the exposed population, and for the expected number, those in the reference population. The ratio of the observed number of cases to that expected is therefore equivalent to a standard relative comparison of the incidence rates in the exposed population and the reference population, with the exposed population as standard population. This method for controlling differences in age distribution is called 'indirect standardization'.[10] These explanations are demonstrated in Table 5. We calculated the expected number of deaths by using the sex- and age-specific mortality of all Japanese in the Toroku investigation, and using the sex and age specific mortality Niigata Prefecture in the Nakajo investigation as the mortality of the standard population.

Several Agencies on toxic substances have documented carcinogenicity of arsenic and certain arsenic compounds. The International Agency for Research on Cancer (IARC) evaluates the evidence as sufficient that inorganic arsenic compounds are skin and lung carcinogens in humans.[1] The Occupational Safety and Health Administration (OSHA) lists arsenic and arsenic compounds as regulated carcinogens.[11] The National Institute for Occupational Safety and Health (NIOSH) recommends they be treated as potential human carcinogens.[11] The National Toxicology Program (NTP) also classifies them as known human carcinogens.[12]

These evaluations are based, however, on overall arsenic exposure. Actually, the toxicity of substances depends on the route of exposure. Most of the evaluations are based on arsenic inhaled in the workplace. On ingested inorganic arsenic, the Risk Assessment Forum of the US Environmental Protection Agency proposed that ingested inorganic arsenic is a class A carcinogen resulting in an increased incidence of skin cancers, and that arsenic may cause cancer in internal organs.[13]

In the Toroku village, there are three small communities in the designated area. Two of them were affected by only inhaled arsenic which was discharged from the primitive refinery. Another one was affected by both inhaled and ingested arsenic which was digested by the residents through stream water. But we could not quantify the carcinogenic effect of ingested arsenic in the cohort.

In Japan, a well-known investigation on the relationship between inhaled arsenic and lung

cancer was reported in 1974.[14] High lung cancer mortality among males was discovered accidentally in a small town in the course of a routine vital-statistical investigation by the local health department. A case-control study revealed that these men had been employees at the copper smelters. Later, a historical cohort study indicated that the SMR of lung cancer death was 1189 (observed 29, expected 2.44). The dose was estimated from the length of employment and the time of exposure. A dose–response relationship was observed in the cohort.[15]

On the other hand, in the cohort of Nakajo and Nishikawa, there was no effect of inhaled arsenic. The residents of these cohorts had no occupational history in arsenic factories. Therefore, we can estimate the carcinogenic effects of ingested arsenic.

We discuss now several incidents of ingested arsenic poisoning elsewhere in the world. The most famous and largest arsenic poisoning case occurred on the south-west coast of Taiwan. This incident is well known as 'Blackfoot disease', of which a typical sign is necrosis of the extremities. In 1985, Chen *et al.*[16] demonstrated an ecological correlation between the arsenic poisoning area and cancer mortality. The standardized mortality ratios for cancers of the bladder, kidney, skin, lung, liver and colon were 1100, 772, 534, 320, 170 and 160 respectively for males, and 2009, 1119, 652, 413, 229 and 168 respectively for females. All were statistically significant ($P<0.05$). There was a dose–response relationship according to the type of well used (artesian, shallow, or both) for bladder, kidney, skin, lung and liver cancer SMRs. However, chemicals other than arsenic were found in the drinking water, which may have confounded the observed association between cancer and arsenic ingestion, and this is an important uncertainty in the study.[13]

In 1964, a proportional mortality study was performed using 137 702 deaths between 1949 and 1959, in the province of Cordoba, Argentina, which was known to be an arsenic-contaminated area.[17] Concentrations in drinking water were reported to be 0.9–3.4 mg dm^{-3}.[18] The proportion of deaths attributed to cancer and malignant tumors (23.8%) was higher in a specific region with high arsenic levels in water compared with cancer deaths (15.3%) in the entire province. Increased proportions of mortality ratios were noted for respiratory and skin cancer in the high-arsenic region. This study lacked data for arsenic exposure in individuals.

These reports indicate the carcinogenicity of ingested arsenic for internal organs. In Nakajo, excesses of internal cancers were observed among those who ingested well-water with a high concentration of arsenic. As indicated in Table 3, these excesses could not be explained by smoking history.

As mentioned above, the concentrations in drinking water in Cordoba were reported to be 0.9–3.4 mg As dm^{-3}.[18] Fierz discussed the relationship between skin cancer and the total dose of Fowler's solution (1% As_2O_3) ingested as medication. The percentage of cancer among persons who ingested a total dose of 1.32 g arsenic was about 5%, and from 7.92 g arsenic about 35%.[19] On the assumption that mean water intake was 2 dm^3 day^{-1} and that mean arsenical concentration of well-water was 1.0 ppm in Nakajo, the total arsenic dose during five years is presumed to be about 3.5 g, which seems to be sufficient to cause cancer, according to other studies.

We present here several recommendations in our conclusions.

CONCLUSIONS AND RECOMMENDATIONS

Our recommendations for research on carcinogenicity of arsenic are as follows:

(1) There is a need to clarify the mechanism of developing cancer from arsenic. Especially, a study of the interaction between arsenic and other carcinogenic substances should be carried out. These findings should give a lead to other cancer researches.

(2) There is a need to investigate epidemiologically the causal relationship between arsenic and cancers other than lung cancer. Because the size of an arsenic-polluted area is often small, its reproducibility of rare cancer is very low. However, the features of the cancers will be similar to those in the Blackfoot disease endemic area in Taiwan.

(3) There is a need to analyze specific histological types of lung cancer. Undifferentiated or poorly differentiated types seem to be dominant in our cohort.

(4) There is, finally, a need to collect information on the victims of other arsenic poisoning incidents in Japan, such as those from soy-sauce poisoning, powdered-milk poisoning and other arsenic mines.

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