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Comparisons of Survival Time Estimates for Niigata Prefecture (Japan) Residents Exposed to Ingested Arsenic

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Survival analysis was used to analyze follow-up data on an arsenic-poisoned area, identified in 1959, in order to assess the effect of arsenic on survival time. The subjects were 443 residents of Namiki-cho, Nakajo-machi, Niigata Prefecture, Japan, who ingested well water contaminated with arsenic between 1955 and 1959. Their exposure to arsenic was only by ingestion of well water. We observed this historical cohort from October 1959 to February 1992. Survival time was calculated in two ways: from 1959 (the end of exposure) until death or until 1992 (the termination of follow-up); or from birth until death or until 1992. The entire cohort was divided into two groups according to the arsenic concentration measured in the wells in 1959. Different survival curves of the two were drawn using the Kaplan–Meier method. The lifetime survival curves indicate that the lifetimes of arsenic-exposed residents were significantly shorter than that of the low-dose exposure group or of unexposed residents. From the differences in the estimated lifetime survival curves, the effect of arsenic on the mortality of the residents can be inferred.

Keywords: Arsenic, environmental exposure, Kaplan–Meier method, lifetime survival, life test analysis, logrank test, survival analysis, survival time

INTRODUCTION

Inorganic arsenic compounds have been used for medicine since the dawn of history and have been claimed to be effective in treating many diseases. Furthermore, they have been indicated as a tonic.[1] It is estimated that more than 32 000 arsenic compounds have been synthesized since the introduction of Salvarsan.[1] On the other hand, arsenicals which were preferred homicidal and suicidal drugs during the Middle Ages have long been well known as poisonous agents.[1] Numerous reports have indicated that arsenic has toxicity, including carcinogenicity.[1,2] However, there is no estimate of the effect of arsenic on overall lifetime (survival time) in several epidemiological studies on arsenic exposure. These studies mainly focused on arsenic carcinogenicity, especially the relationship between ingested arsenic and skin cancer[3] or between occupationally inhaled arsenic and lung cancer.[4–6] In recent years, the relationship between ingested arsenic and internal cancer has been demonstrated in Taiwan,[7,8] and risk assessment on the relationship has been attempted in the USA.[9,10]

In Japan, there have been many cases of arsenic poisoning. In particular, poisonings from powdered milk, soy sauce and well water are well known.[11,12] We conducted an epidemiologic investigation in an area of well-water poisoning.[13] This investigation was characterized by its long follow-up period of 28 years. Analysis with standardised mortality ratios (SMRs) was presented in a previous paper.[13,14] Here, in order to estimate the magnitude of the effect of ingested arsenic on survival time, we have applied survival analyses to the data from the investigation.

Recently, survival analysis has often been employed to evaluate the effects of medical treat-

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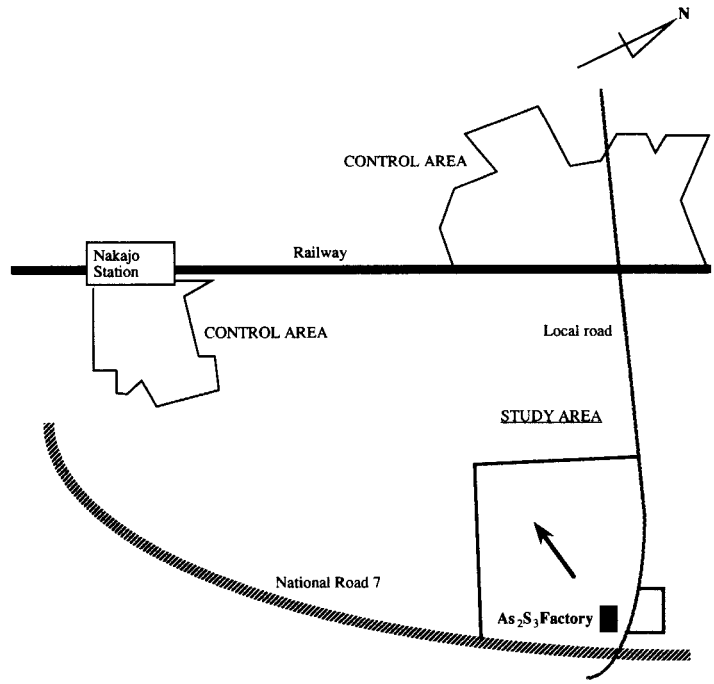

Figure 1 Location of study area, Nakajo-machi, Niigata Prefecture, Japan. Two 'control areas' were investigated by the Niigata Prefectural Government in 1988: no excess cancer mortality was observed in these areas. The arrow indicates the direction of groundwater flow.

ment. Life test analysis and Cox's proportional hazards analysis are popular methods of survival analysis.[14–15] Life test analysis demonstrates the survival curve which is useful for evaluating the effect over a time sequence. Therefore, it is very meaningful to apply survival analyses to arsenic data.

MATERIALS AND METHODS

Source of poisoning

There was an incident of chronic arsenic poisoning in the small town of Namiki-cho, Nakajo-machi, Niigata Prefecture, Japan, in

Table 1 The age-, gender-, and arsenic concentration-specific distribution in 1959

	Male		Female	
Age	≥0.05 ppm As	<0.05 ppm As	≥0.05 ppm As	<0.05 ppm As
0–9	22	31	25	23
10–19	17	24	19	26
20–29	11	21	18	22
30–39	12	15	23	24
40–49	10	17	7	13
50–59	8	5	2	9
60–69	2	7	5	8
70–79	2	1	5	7
80	1	0	0	1
Total	85	121	104	133

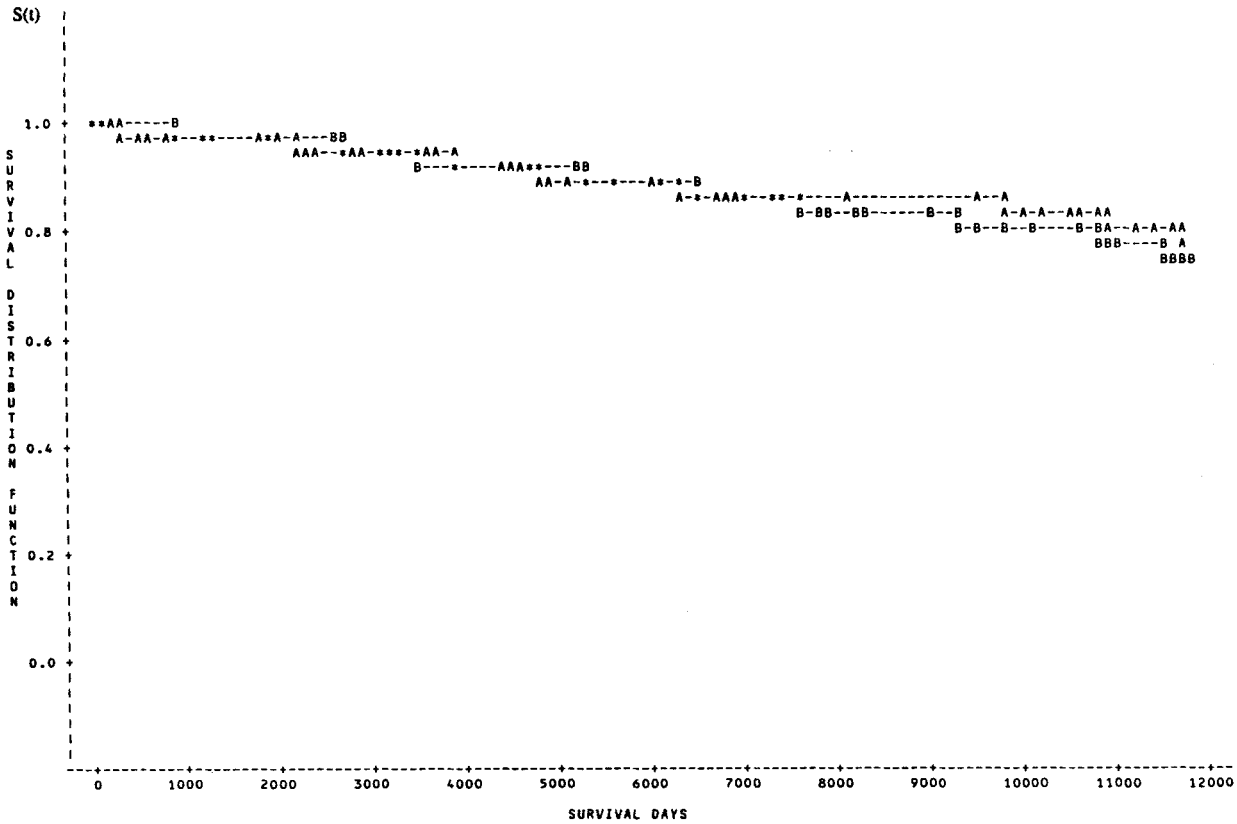

Figure 2 Survival curves on all deaths from 1959 to death or 1992. A, <0.05 ppm As (low-dose group); B, ≥0.05 ppm As (high-dose group). *P* (logrank test) = 0.3695.

September 1959.[11,16] The polluted area is displayed in Fig. 1. Near the affected houses there was a small factory where the pigment King's Yellow (As_2S_3) had been produced for more than 40 years. The factory disposed of waste water to the underground gravel by infiltration. As a result, wells near the factory had become contaminated. It was presumed that the waste water had mainly contained anhydrous arsenous oxide (As_2O_3) and micro-particles of As_2S_3 used in the production process. Though the factory had been producing King's yellow by the same process for 45 years, the arsenic concentration in the wells was assumed to have substantially increased from 1954, when the flow of underground water markedly decreased 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.

Because the Prefectural Government took prompt measures to cope with the incident in 1959, spread of the contamination was prevented. Arsenic concentration in the well water was measured at the end of the exposure period, and disposal of the waste water was immediately banned. Repeated measurements showed the concentration to have diminished in the following two months. As the results of the first measurements are considered to reflect the exposure, we used them as an indication of arsenic exposure concentration.

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 as a contaminated area. Well-to-well measurements of arsenic concentration were taken in all 54 wells within the area in September 1959. 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.

None of the local inhabitants had worked at the factory.

We identified 467 residents from the list which was made in 1959. We could obtain information on 455 residents out of 467 (97.4%). Of these 455 residents, 12 residents drank water from a nearby stream. Therefore, we examined information from 443 residents (94.9%).

Analysis

The Kaplan–Meier method[15] was employed for estimating survival curves. In estimating the survival curves, two definitions can be made of survival time. It may be defined either from 1959 (the end of arsenic exposure) until death or until 1992 (the termination of follow-up); or from birth until death or until 1992. In the former definition, it means that persons of various ages who were exposed to arsenic from 1955 to 1959 were followed. In the latter definition, it means that persons who had been exposed to arsenic for five years during some stage of their lives were followed.

The entire cohort was divided into two groups according to the concentration of arsenic in 1959. One was the high-dose group (0.05 ppm and over); the other was the low-dose group (less than 0.05 ppm). In Japan, the environmental water quality standard of arsenic was 0.05 ppm until 1992. There were 189 residents in the high-dose group, and 254 residents in the low-dose group. The survival curve of each group was estimated by the Kaplan–Meier method. The survivors at the end of the observation period (29 February 1992) were analyzed as censored cases (i.e. those alive at the end of this study). The difference between these two survival curves was tested by the logrank test.

We calculated these data with the package Statistical Analysis System (SAS) installed in a FACOM M-380 computer at the Information Processing Center, Okayama University of Science.

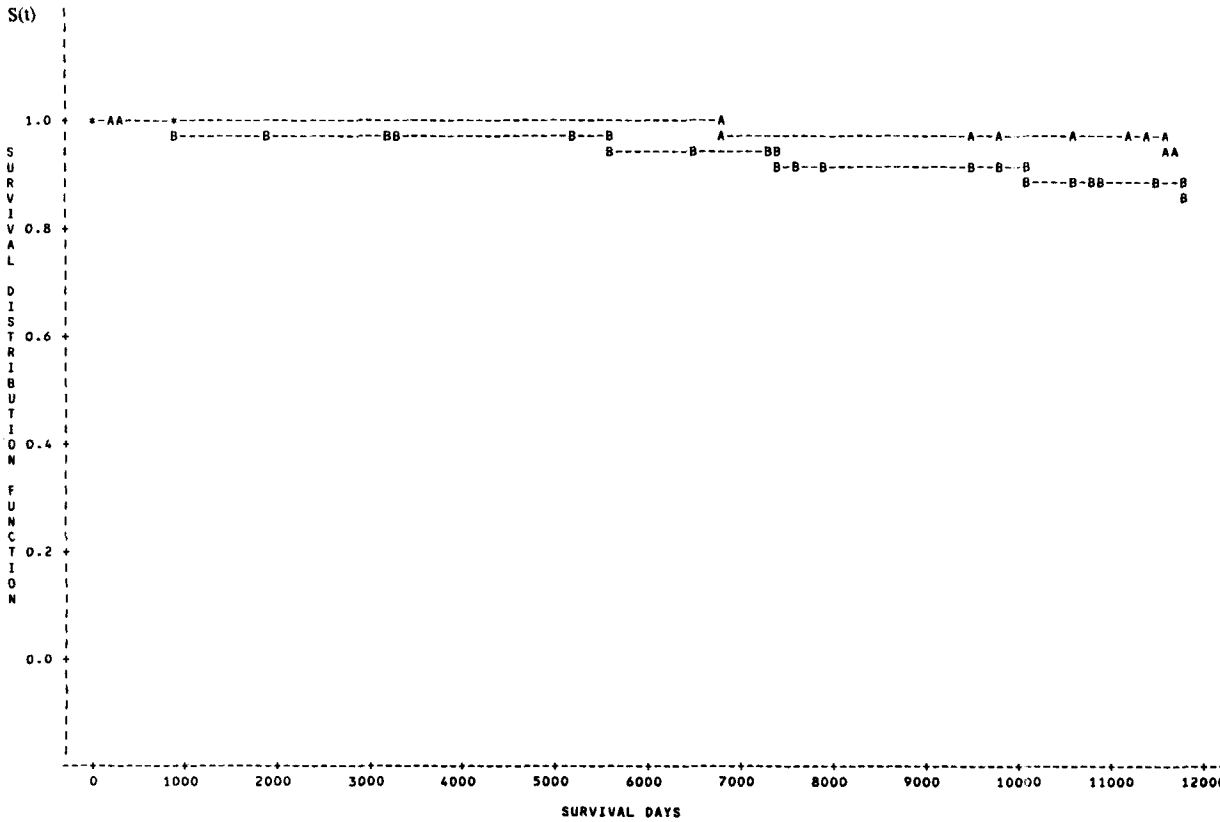

Figure 3 Survival curves on cancer deaths from 1959 to death or 1992. A, <0.05 ppm As (low-dose group); B, ≥0.05 ppm As (high-dose group). *P* (logrank test) = 0.0027.

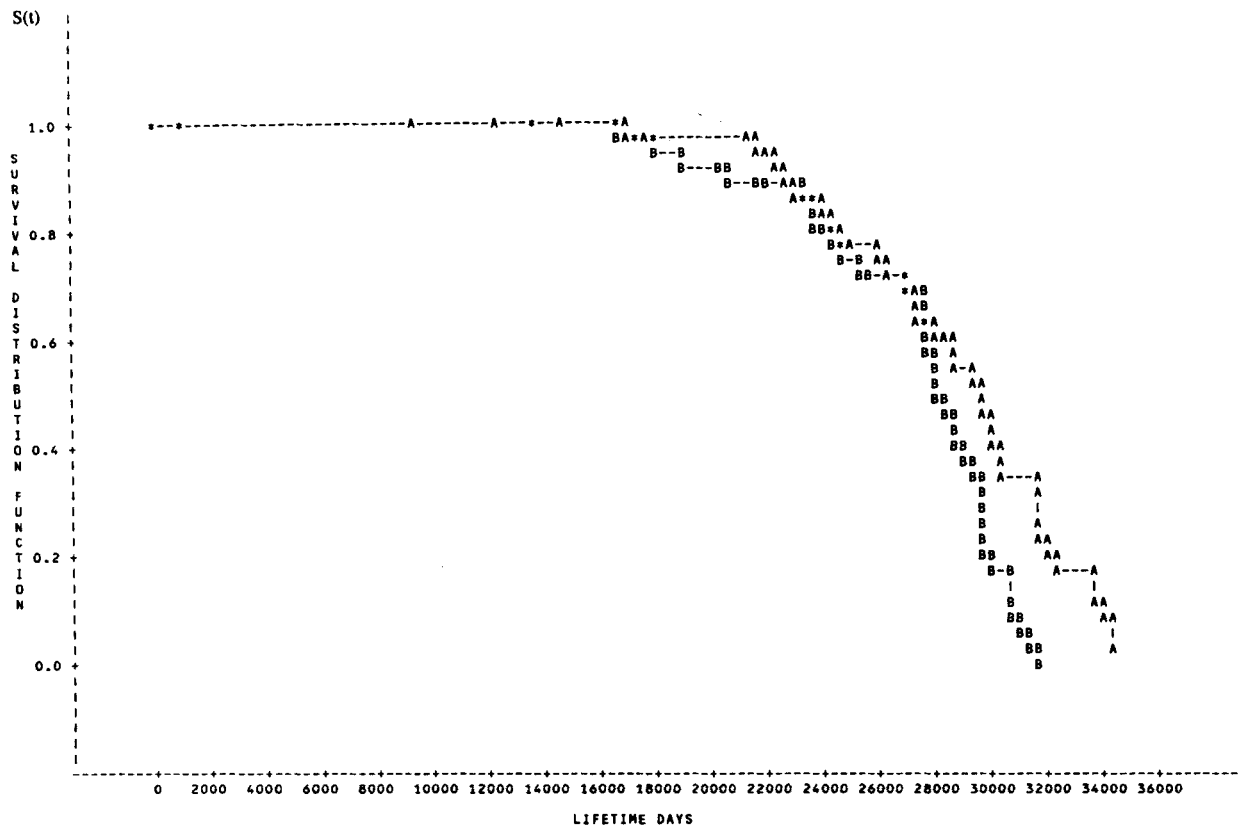

Figure 4 Survival curves on all deaths from birth to death or 1992. A, <0.05 ppm As (low-dose group); B, ≥0.05 ppm As (high-dose group). P (logrank test) = 0.0076.

RESULTS

Table 1 shows the age distributions of the two different dose groups on 1 October 1959. The number of smokers including ex-smokers was 81 (42.9%) in the high-dose group and 106 (41.7%) in the low dose-group. There were no statistically significant differences in characteristics among the two dose groups. Forty-nine deaths were observed in the high-dose group, 56 deaths in the low-dose group between 1959 and 1992.

Survival time from the end of exposure

The survival time is defined from 1959, the end of arsenic exposure, until death or until 1992. This means that persons of various ages who were exposed to arsenic in 1959 were followed. Figure 2 shows the survival curves of the two groups under this definition. Statistically significant differences were not observed between the two survival curves by the logrank test. On the other hand, survival curves on cancer deaths are shown in Fig. 3, where deaths from causes other than cancers are treated as censored cases. A statistically significant difference was observed between the two survival curves ($P = 0.0027$) by the logrank test.

Lifetime survival

According to the second definition, persons who were exposed to arsenic for five years were followed. The survival time of the high-dose group was statistically significantly shorter than that of the lower group ($P = 0.0076$) by the logrank test (Fig. 4). In the survival curves on cancer deaths, the difference of the two survival curves was statistically significant ($P = 0.0007$) by the logrank test (Fig. 5).

DISCUSSION

In several reports on arsenic, especially on occupational exposure by inhalation, exposure levels of arsenic have been studied by various

methods.[17,18] This study has an advantage because the information concerning the concentration of arsenic was obtained from the report made in 1959.[17] We have performed a historical cohort study with a long observation period. Arsenic concentration in the well water was measured only once, but this measurement was considered to be good enough to use as an exposure indicator. Of the residents listed in 1959, we could follow up 97.4%. Arsenic concentration of the lost cases was considered to be undetectable. We judged this follow-up rate as satsifactory. Selection bias is unlikely to exist because these data are based on the list made in 1959, the beginning of observation. The existence of confounding factors is also unlikely because arsenic exposure does not seem to be related to other potential factors.

As mentioned above, we have demonstrated mortality using the data of this area by SMRs (Table 2)[13,14] We reanalyzed these data by survival analysis. There are two definitions of survival time in the life test analysis, i.e. survival time from the end of exposure, and also from the birth of each resident. We analyzed the data under both definitions. Using the former definition, there was no statistically significant difference on all deaths. However, in the analysis on cancer deaths, a statistically significant difference is observed. From Fig. 1 we can observe the trend that the exposed population may die earlier than the unexposed population. When 1 ppm was chosen as the cut-off point, a statistically significant difference is not observed (Fig. 6) ($P=0.1627$). The observed difference between the two curves, however, seems to be clearer.

On the contrary, analysis with the latter definition showed statistically significant differences both on all deaths and on cancer deaths, shown in Figs 4 and 5. This phenomenon can be explained by the fact that the difference between the distributions of the survival time according to the former definition in the two populations exists on the whole range of the survival time, while this

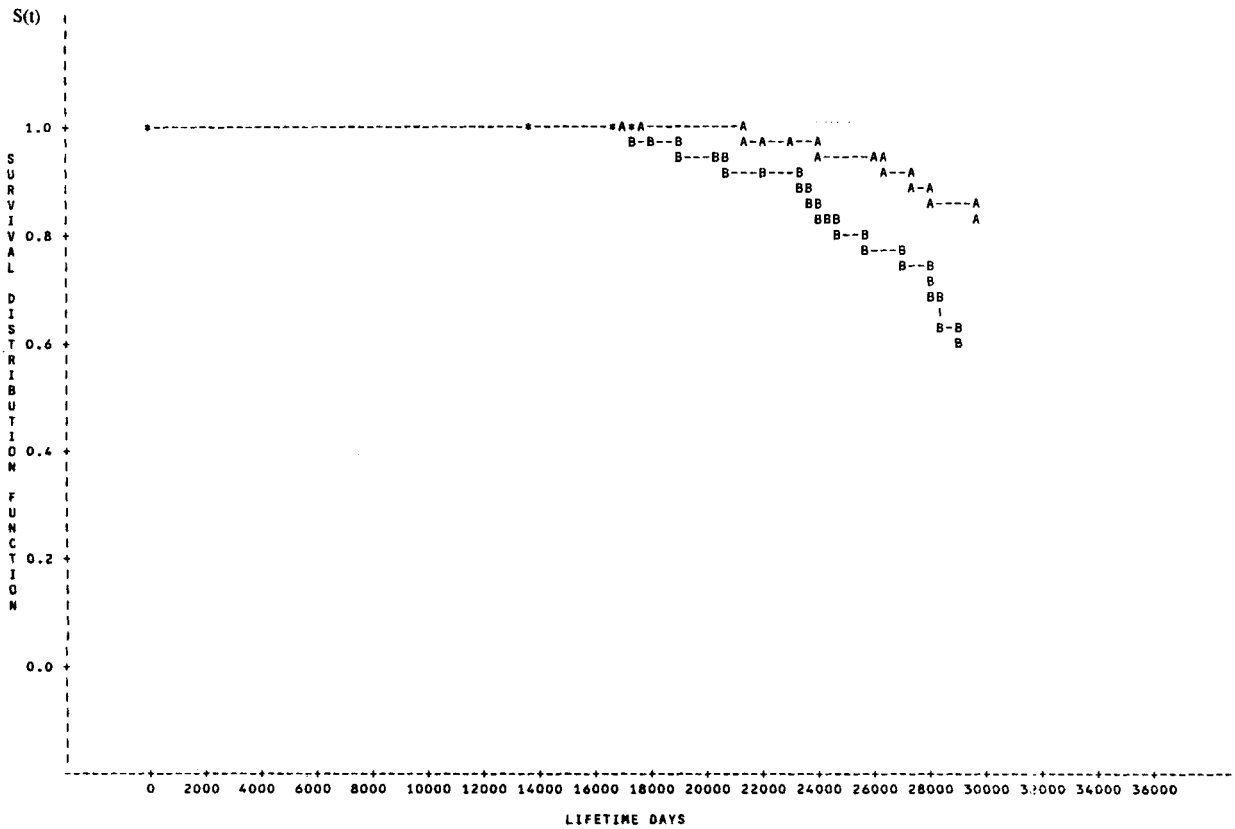

Figure 5 Survival curves on cancer deaths from birth to death or 1992. A, <0.05 ppm As (low-dose group), B, ≥0.05 ppm As (high-dose group). P (logrank test) = 0.0007.

Table 2 The observed and expected numbers of deaths, standardized mortality ratios and their 95% confidence intervals according to the arsenic concentration of well water in September 1959 (modified from Ref. 13)

SMR[a]	≥1 ppm As (107)[b]	<1 ppm As, ≥0.05 ppm As (79)[b]	<0.05 ppm As (95)[b]
All Death (95% C.I.)*	1.57 (1.08–2.27)	0.93 (0.52–1.61)	0.74 (0.43–1.23)
Observed/Expected**	27/17.25	12/12.95	14/18.94
All Cancer	3.70 (2.14–6.17)	0.98 (0.27–2.87)	0.26 (0.01–1.52)
	14/3.78	3/3.07	1/3.78
Smoking[d] (proportion)	50 (0.44)	31 (0.41)	106 (0.42)

[a] SMR, standardized mortality ratio.
[b] No. of subjects, in parentheses.
[c] Observed number of deaths/expected number of deaths.
[d] No. of subjects.

difference using the latter definition concentrates on the right tails of the distributions. Since the logrank test is powerful against right tail differnces to the distribution,[16] it was sensitive to the survival time according to the latter definition. Moreover, cancer deaths were the main cause of excess deaths in the exposed area (Table 2). Therefore, it is preferable to choose the lifetime survival definition because cancer deaths are closely related to age. Therefore, we conclude

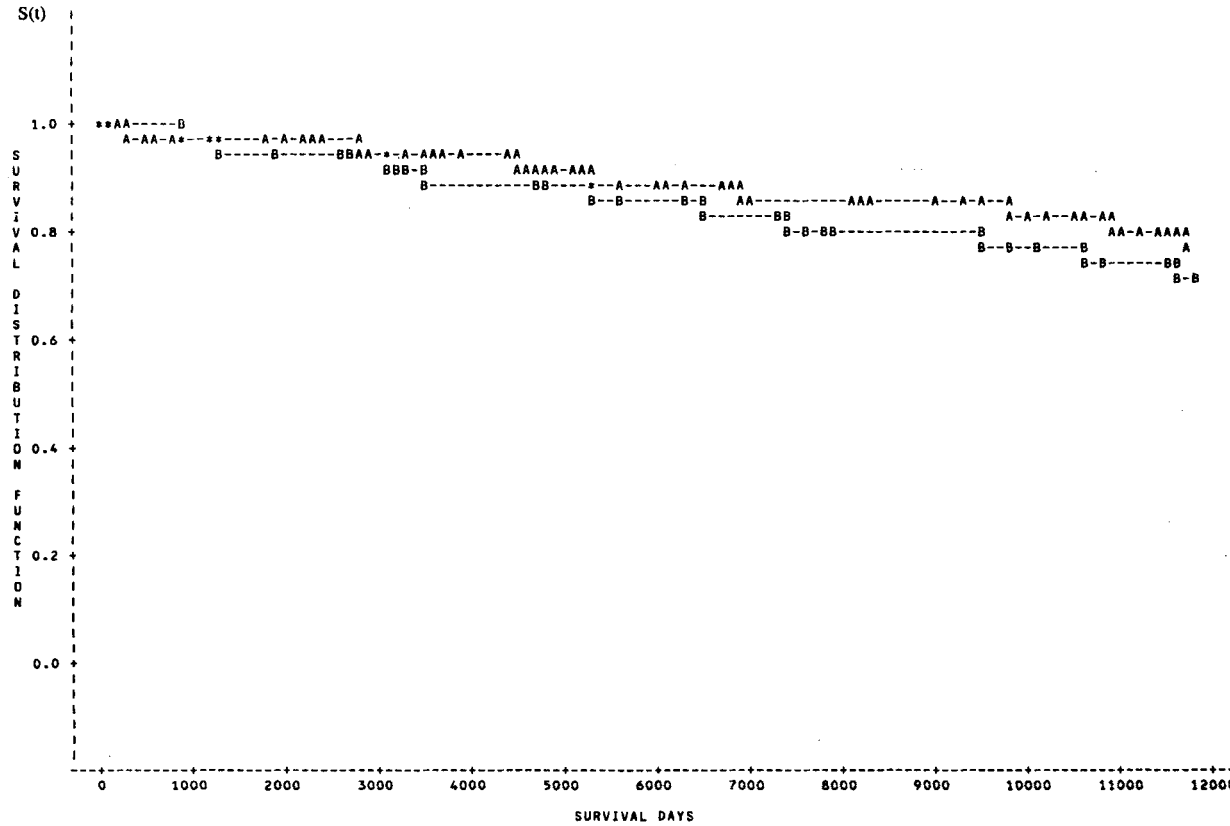

Figure 6 Survival curves with cut-off point 1 ppm, on all deaths from 1959 to death or 1992. A, <1 ppm As (low-dose group); B, >1 ppm As (high-dose group). P (logrank test) = 0.1627.

that the latter definition was superior to the former in the test to check chronic arsenic ingestion effects appearing in the latter stage of life. When considering these results, we can conclude that arsenic ingestion shortens human lifetimes. The main reason for the reduction can be inferred from Figs 3 and 5 and Table 2 to be excessive cancer deaths.

Several reports on metabolism of inorganic arsenic suggest that the majority of absorbed arsenic is eliminated within a few days after ingestion.[1,12] The difference between the two survival curves, however, was able to be demonstrated after a long survival time in the present study. The result of this study indicates the importance of the later effects of arsenic over a long period.

In conclusion, we have observed the effect of ingested arsenic on lifetime survival. The difference in the survival curves indicates that arsenic exposure shortens the lifetimes of the exposed residents. We recommend a long follow-up system for all arsenic-exposed residents. We also suggest further investigation concerning the effect of ingested arsenic on humans.

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