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Long-term observational study on 6223 survivors of arsenic poisoning due to contaminated milk powder during infancy

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Abstract

In 1955, an outbreak of arsenic poisoning caused by the ingestion of arsenic-contaminated Morinaga Dry Milk occurred in western Japan. This study aimed to assess the mortality and cancer incidence risk among Japanese individuals who were poisoned during this time as infants. In total, 6223 survivors (mean age at enrollment, 27.5 y) who had ingested contaminated milk when they were aged ≤ 2 y participated in this study. Follow-up was conducted from 1982 to 2018 (mean follow-up duration, 30.3 y). Standardized mortality ratio (SMR) and standardized incidence ratio (SIR) were used to compare mortality and cancer incidence rates of subjects with the respective Japanese population rates, and 95% confidence intervals (95% CIs) of the SMR and SIR were also calculated. In total, 561 deaths and 524 new cancer cases were observed. A statistically significant increase in mortality rate was observed for all causes (SMR, 1.15; 1.01-1.19), nervous system disease (2.83, 1.62-4.19), respiratory disease (2.02, 1.37-2.62), genitourinary system disease (2.25, 1.10-3.73), and traffic accident (2.03, 1.14-3.04). In contrast, a significant decrease in cancer incidence rate was observed for all cancers (SIR, 0.96; 0.84-0.99), stomach cancer (0.77, 0.57-0.92), colon cancer (0.63, 0.41-0.85), rectum cancer (0.69, 0.43-0.95), and breast cancer (0.72, 0.52-0.89). Liver cancer showed a high mortality rate (SMR, 1.68; 1.06-2.31). In this study, after the long-term follow-up we revealed overall and cause-specific mortality and cancer incidence risk among survivors who ingested arsenic-contaminated dry milk as infants.

KEYWORDS
arsenic poisoning, epidemiology, observational study, standardized incidence ratio, standardized mortality ratio

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1 | INTRODUCTION

Arsenic is one of the most common sources of poisoning in the world.[1] Arsenic exposure can cause both chronic and acute toxicity in humans. Chronic arsenic poisoning has become a worldwide public health issue. The major source of arsenic exposure is drinking water containing high amounts of inorganic arsenic.[2] Previous studies have suggested that chronic arsenic exposure is related to skin, lung, bladder, kidney, and liver cancer,[3-13] hyperkeratosis, ischemic heart disease, cerebrovascular disease, type 2 diabetes, and peripheral neuropathy.[14-17] Acute arsenic poisoning in suicidal and homicidal attempts or by accidental ingestion is relatively rare. The clinical features manifest in virtually all body systems.[18]

In the early summer of 1955, an outbreak of acute arsenic poisoning from the ingestion of arsenic-contaminated milk powder occurred in western Japan. Infants who drank the arsenic-contaminated dry milk produced by the Morinaga Milk Company exhibited clinical symptoms of arsenic poisoning. In June 1956, in total, 12 131 infant victims, including 130 deaths, were reported,[19] and the incident was described in detail elsewhere.[20] In 1974, the Hikari Kyoukai Foundation, financially supported by the Morinaga Milk Company, was established to aid the victims by providing health checkups, health counseling, and financial support for their welfare. In 1995, the Foundation began to provide allowance for the victims in accordance with the severity of impairment caused by poisoning.

The health effects of this food poisoning incident have been reported previously in several studies.[21-24] In 1982, the Foundation sponsored a prospective registry to investigate the long-term adverse effects of arsenic exposure caused by the ingestion in infancy of Morinaga Dry Milk. In 2010, Tanaka and colleagues reported that a high mortality rate of nervous system diseases among the victims was observed from 1982 to 2006.[25] The current study aimed to update mortality and causes of death between 1982 and 2018 and additionally provide new findings on cancer incidence for the victims.

2 | MATERIALS AND METHODS

By the end of March 1982, in total, 13 397 individuals who had ingested arsenic-contaminated milk in 1955 were identified. Of these, 6400 (47.8%) established contact with the Foundation and agreed to be followed as part of the study. As we aimed to investigate the long-term adverse effects of arsenic exposure in infancy, in total, 6223 individuals who were aged ≤ 2 y at the time of the outbreak were enrolled in the present analysis.

Follow-up started on April 1, 1982. Investigators from the Foundation contacted the subjects by telephone, home visit, and/or post several times a year. The families of subjects who died could apply for condolence money using the copy of death certificate. Death information (name, sex, date of birth, date of death, and underlying cause of death) was collected from the certificate. Similarly, the cancer incidence information (name, sex, date of birth, date of

diagnosis, diagnostic method, diagnostic name) was abstracted when subjects who had cancer applied financial support for medical costs using copies of diagnostic certificates. The investigators anonymized the data and then transferred it to Osaka International Cancer Institute for analysis. Causes of death and diagnoses were coded in accordance with the International Classification of Diseases, 9th Revision.

Based on the severity of impairment caused by poisoning, and its impacts on the everyday lives and livelihoods of the subjects: no allowance, subjects with mild impairment after poisoning who had no or slight impacts on life and employment; partial allowance, subjects with moderate physical and mental impairment who had difficulties in life and employment; full allowance, subjects with serious physical and mental impairment who had extreme difficulties in life and employment.

Analyses on mortality and cancer incidence were conducted separately. For mortality, person-year accumulation began on April 1, 1982 and ended on the date of death, the date when subjects stopped contacting the Foundation, or December 31, 2018, whichever came first. The SMR was computed as the ratio of the observed number of deaths and the expected number, with 95% confidence intervals (95% CIs), assuming a Poisson distribution. The expected number of deaths was obtained by multiplying the number of person-years at risk with cause-specific mortality rates by sex, 5-y age band, and 5-y calendar period among the Japanese population and which are available from the Portal Site of Official Statistics of Japan (e-Stat).

In relation to cancer incidence, person-years at risk were calculated from April 1, 1982, to the date of first cancer diagnosis, date of death, date when subjects stopped contacting the Foundation, or December 31, 2018, whichever came first. We applied national site-specific cancer incidence rates by sex, 5-y age band, and 1-y calendar period to the person-years at risk to calculate the expected number of cancers. Japanese cancer incidence rates were obtained from the National Cancer Center Japan, with the rates of 2015 being used for the period of 2016-2018. Thereafter, we estimated the SIR as the ratio of observed numbers to expected numbers. The 95% CI was also calculated by Poisson distribution.

We performed analyses based on follow-up duration and conducted a stratified analysis for subjects with different types of allowance. Because the allowance was classified and granted from 1995-1996, we conducted the stratified analysis in 1997. All statistical analyses were performed using the SAS statistical package version 9.3 (SAS Institute Inc) with macro programming.[26]

This study protocol was approved by the Osaka International Cancer Institute (Epidemiological Research for Victims of Arsenic-contaminated Morinaga Dry Milk, No. 19203).

3 | RESULTS

Table 1 presents the characteristics of the subjects. The mean age of the subjects on April 1, 1982 was 27.5 y (age range 26-29). Subjects

TABLE 1 Characteristics of the subjects

Characteristics	n
Total eligible in 1982	6223
Men	3812
Women	2411
Deaths, 1982-1996	112
Cancer incidence, 1982-1996	52
Stopped contacting the Foundation, 1982-1996	918
Type of allowance in 1997[a]	5193
No allowance	4454
Partial allowance	324
Full allowance	415
Age on April 1, 1982[b]	27.5 (26-29)
Person-years (mortality)[c]	1 88 531
Person-years (cancer incidence)[d]	1 84 579

[a]Subjects for SMR calculation; subjects for SIR calculation: 5141, 4418, 314, and 409, respectively.

[b]Mean value (age range).

[c]Person-years for SMR calculation (see text).

[d]Person-years for SIR calculation (see text).

for SMR calculation were 5193 in 1997, of whom 5141 were eligible for SIR calculation. Most of them had no allowance.

Table 2 shows the number of deaths and SMRs among subjects. During the follow-up period, 403 men and 158 women died. The all-cause death risk of all subjects (1.15, 1.01-1.19) was significantly higher than that of the general population, and women presented a higher SMR than men. The SMRs of nervous system and respiratory diseases were significantly increased, that is 2.53 and 1.83 in men, 3.54 and 2.82 in women, and 2.83 and 2.02 in all subjects, respectively. Furthermore, the risks of genitourinary system disease were also higher than those in the general population, although the SMR in women was not statistically significant (men, 2.48, 1.13-4.33; women, 1.53, 0.18-5.26; all subjects, 2.25, 1.10-3.73). Of the deaths due to external causes, a high mortality rate due to traffic accident was observed (SMR in all subjects, 2.03, 1.14-3.04).

Table 3 presents the number of subjects, person-years, number of deaths, and SMRs of all-cause death by follow-up duration. A high mortality rate was noted among all subjects with follow-up duration of 0-4 y (SMR, 1.54, 1.03-2.03), 5-9 y (SMR, 1.51, 1.02-1.96), and 15-19 y (SMR, 1.44, 1.07-1.73). However, the mortality risk of all subjects with follow-up duration > 20 y was close to unit. Furthermore, the SMR of subjects who had no allowance with 15-19 y of follow-up was not significantly different from that of the general population. However, subsequently, the SMRs significantly decreased. The results for subjects who had partial or full allowance showed increased SMRs, representing two-fold to four-fold higher death risks than that of the general population. Moreover, we did not observe decreasing SMRs by increasing the follow-up duration among subjects with full allowance.

Table 4 shows the SIRs and SMRs of main cancer sites among subjects. In total, 524 patients with cancer (308 men and 216 women) were analyzed. The SIRs of all cancer sites were 0.90 (0.76-0.96) in men, 1.06 (0.87-1.15) in women, and 0.96 (0.84-0.99) in all subjects. Furthermore, the SIRs of stomach (0.77, 0.57-0.92), colon (0.63, 0.41-0.85), rectal (0.69, 0.43-0.95), and breast cancers (0.72, 0.52-0.89) in all subjects were significantly low. In contrast, the incidence risks of liver and bladder cancer were increased although not significantly. In relation to the risk of cancer mortality, there were 208 deaths (136 in men and 72 in women). The SMRs of most cancers were not significantly different from that of the general population. However, the results for liver cancer showed increased mortality risk among men (SMR, 1.74, 1.08-2.42) and all subjects (SMR, 1.68, 1.06-2.31). The SMRs of bladder cancer were also higher, especially in women.

Table 5 displays the risks of all cancer incidence and mortality by follow-up duration. The SIRs of all subjects initially increased and then decreased across the follow-up period. The total cancer incidence of subjects who had no allowance with 15-30 y of follow-up was not different from that of the general population. However, after > 30 y of follow-up, the cancer incidence was lower than expected. For subjects who had partial and full allowance, we observed some evidence of decreasing incidence ratios by increasing the follow-up duration. Regarding mortality risk, high cancer mortality rates were not observed among the subjects. The SMRs of subjects with no allowance were close to unity. The cancer mortality rate of subjects with partial allowance was high, especially in the 15-19 y of follow-up. Moreover, the mortality ratios for subjects with full allowance showed a decreasing trend during the follow-up period.

4 | DISCUSSION

This long-term observational study showed that, compared with the general population, subjects who had ingested arsenic-contaminated Morinaga Dry Milk when they were aged ≤ 2 y had an increased mortality risk. The current study also demonstrated that subjects had significantly higher SMR from nervous, respiratory, and genitourinary system diseases and traffic accidents. Compared with subjects who had no allowance, subjects who had an allowance had higher mortality risk. In contrast, the SIR of all cancers was significantly lower, while the SMR of all cancers was close to unity. In addition, the incidence risk of stomach, colon, rectal, and breast cancers was significantly decreased. The death risk of liver cancer was significantly increased. Subjects who had a partial allowance had higher SIRs and SMRs of cancers during the study period.

Human exposure to arsenic was mainly through ingestion, followed by inhalation and skin absorption. Chronic exposure to arsenic from drinking water has been extensively studied in Taiwan,[27] Chile,[28] India,[29] Bangladesh,[30] and Argentina.[31] Acute arsenic poisoning happened once in Wakayama, Japan, in 1998 due to the deliberate poisoning of curry soup with arsenic at a local festival.[32]

This Morinaga Dry Milk arsenic poisoning happened in 1955. There were a few physicians and researchers collecting data on arsenic

TABLE 2 SMRs for major causes of death among the subjects, 1982-2018

	Men			Women			All		
	n = 3812			n = 2411			n = 6223		
	115 709 Person-years			72 822 Person-years			188 531 Person-years		
Causes of death (ICD-9 code)	Observed	SMR	95% CI	Observed	SMR	95% CI	Observed	SMR	95% CI
All causes (001-999)	403	1.08	(0.93-1.13)	158	1.39	(1.12-1.54)	561	1.15	(1.01-1.19)
All cancers (140-208)	136	1.06	(0.85-1.19)	72	1.21	(0.90-1.45)	208	1.11	(0.92-1.21)
Endocrine and metabolic disease (240-279)	7	1.03	(0.39-2.01)	3	1.84	(0.36-5.11)	10	1.18	(0.54-2.07)
Disease of the blood and blood-forming organs (280-289)	1	1.07	(0.03-5.64)	1	2.20	(0.05-11.63)	2	1.44	(0.17-4.93)
Mental disorders (290-319)	2	1.30	(0.15-4.45)	0	0.00	(–)	2	1.04	(0.12-3.58)
Nervous system (320-389)	12	2.53	(1.24-4.19)	7	3.54	(1.35-6.93)	19	2.83	(1.62-4.19)
Circulatory system (390-459)	90	1.04	(0.79-1.21)	25	1.33	(0.82-1.87)	115	1.09	(0.86-1.25)
Cerebrovascular disease (430-438)	24	0.79	(0.48-1.12)	8	0.96	(0.39-1.80)	32	0.83	(0.54-1.11)
Respiratory system (460-519)	29	1.83	(1.16-2.50)	11	2.82	(1.34-4.79)	40	2.02	(1.37-2.62)
Pneumonia (480-486)	19	2.19	(1.25-3.25)	9	4.45	(1.93-8.02)	28	2.62	(1.65-3.59)
Digestive system (520-579)	21	0.90	(0.53-1.31)	4	1.12	(0.29-2.73)	25	0.93	(0.57-1.31)
Chronic liver disease and cirrhosis (571)	11	1.32	(0.63-2.24)	2	1.49	(0.17-5.11)	13	1.34	(0.68-2.18)
Genitourinary system (580-629)	10	2.48	(1.13-4.33)	2	1.53	(0.18-5.26)	12	2.25	(1.10-3.73)
Disease of the skin and subcutaneous tissue (680-709)	0	0.00	(–)	1	37.04	(0.89-196.04)	1	4.67	(0.11-24.73)
Diseases of the musculoskeletal system and connective tissue (710-739)	1	0.98	(0.02-5.18)	2	1.88	(0.22-6.44)	3	1.44	(0.28-3.99)
Congenital anomalies (740-759)	2	2.65	(0.31-9.10)	0	0.00	(–)	2	1.74	(0.20-5.98)
External causes (E800-E999)	62	0.83	(0.60-1.01)	19	1.34	(0.76-1.98)	81	0.91	(0.69-1.08)
Traffic accident (E810-E819)	14	1.86	(0.97-2.96)	4	2.96	(0.77-7.20)	18	2.03	(1.14-3.04)
Suicide (E950-E959)	29	0.70	(0.45-1.03)	11	1.33	(0.63-2.26)	40	0.81	(0.55-1.04)

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

exposure levels or tissue concentrations after the outbreak. However, based on the average volume of milk consumption, it was estimated that daily arsenic intake would be approximately 2.5 mg for a 1-mo-old infant, 3.2 mg for a 2-mo-old infant, and 4.6 mg for a 6-mo-old infant.[19]

Acute exposure to arsenic in humans is related to problems of memory, difficulties in concentration, mental confusion, and anxiety.[33] In our study, the high mortality rate of nervous system disease was notable. Epilepsy and cerebral palsy mainly contributed to this increased mortality risk. In 1970, 47 victims of arsenic-contaminated milk with symptoms underwent physical examination. Of these, 11 showed central nervous system disorders.[34] This report, together with our results, indicates that arsenic poisoning in infancy can permanently damage the central nervous system.

TABLE 3 SMRs for all causes of death by follow-up duration, 1982-2018

	Follow-up duration (years)	No. of subjects	Person-years	Observed	SMR	95% CI
All subjects	0-4	6223	30 394	36	1.54	(1.03-2.03)
	5-9	5944	28 898	39	1.51	(1.02-1.96)
	10-14	5631	26 807	37	1.10	(0.74-1.45)
	15-19	5193	25 045	70	1.44	(1.07-1.73)
	20-24	5011	24 136	71	1.00	(0.74-1.19)
	25-29	4856	23 242	111	1.13	(0.88-1.30)
	>30	4679	30 010	197	1.06	(0.87-1.16)
Type of allowance						
Subjects with no allowance	15-19	4454	21 453	46	1.11	(0.77-1.41)
	20-24	4296	20 678	45	0.74	(0.51-0.94)
	25-29	4167	19 939	69	0.82	(0.61-0.99)
	>30	4032	25 965	119	0.74	(0.58-0.84)
Subjects with partial allowance	15-19	324	1588	11	3.58	(1.70-6.08)
	20-24	313	1525	10	2.22	(1.01-3.88)
	25-29	303	1466	15	2.43	(1.29-3.81)
	>30	288	1824	30	2.67	(1.71-3.61)
Subjects with full allowance	15-19	415	2003	13	3.33	(1.69-5.41)
	20-24	402	1933	16	2.79	(1.51-4.30)
	25-29	386	1838	27	3.46	(2.17-4.78)
	>30	359	2221	48	3.49	(2.45-4.40)

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

The subjects had twice the mortality risk of a traffic accident as the general population. In 1971, a community-based survey for victims of Morinaga Dry Milk arsenic poisoning was conducted in Hiroshima.[35] It was found that the victims had a higher prevalence of visual field narrowing due to macular degeneration than control children. Additionally, motor or sensory dysfunction caused by the after-effects of arsenic poisoning might lead to a traffic accident.

Inorganic arsenic is clearly a human carcinogen causing tumors of the skin, lung, urinary bladder, and possibly the liver.[36] In this study, we observed 35 new cases and 28 deaths of liver cancer. The SMR of liver cancer was significantly higher (1.68; 1.06-2.31). Between 1950s and 1980s, Japan had one of the highest endemic rates of hepatitis C virus (HCV) infection, especially in the western region.[37] Most victims of arsenic-contaminated milk were living in western Japan. Individuals with impairment after poisoning might frequently visit the hospital and subsequently be infected with HCV or become HCV carriers. It is well known that HCV is a major cause of liver cancer in the Japanese population.[37] Furthermore, there were 15 new cases and 5 deaths of bladder cancer. The mortality risk of bladder cancer was high but not significant (SMR, 2.88; 0.89-6.39).

Compared with SMRs during the 0-19 y of follow-up, the mortality ratios were lower and not different from those of the general population after > 20 y of follow-up. From 1982, the Foundation continuously provided financial support, medical advice, and daily activity support for individuals who needed it. There are indications that with the assistance of the Foundation, the health status of subjects has improved. Moreover, our results presented the significantly decreased SIR of all cancer sites. The incidence risk of stomach, colon, rectal, and breast cancers was also significantly lower than unity. Furthermore, the SIRs of subjects with 0-9 y of follow-up were obviously lower than those in other periods. Cancer registration in this study was based on self-reporting, that is cancer incidence data were collected when the victims who had cancer applied for financial support for treatment using diagnosis certificates. Therefore, cancer incidence risk might be underestimated, especially in the early years of the study. In contrast, the SMRs of cancer were not significantly different from those of the general population, except at 15-19 y of follow-up.

The division standards of the allowance were not fixed until 1995. Therefore, we were unable to estimate the risk of cancer incidence and mortality by types of allowance before 1995. For subjects with no allowance, poisoning in infancy did not have a great influence on their health, and thus cancer incidence and mortality were not different from the general population. The total cancer deaths of subjects with partial and full allowance was 26 and 16, with SMR 2.60 (1.74-3.76) and 1.23 (0.73-1.96), respectively (data not shown). As previously mentioned, subjects with full allowance had the most serious physical impairment. However, their cancer mortality risk was

TABLE 4 SIRs and SMRs of main cancer sites among the subjects, 1982-2018

(ICD-9 code)	Person-years	Observed	SIR	95% CI	Person-years	Observed	SMR	95% CI
Men (n = 3812)	1 13 913				1 15 709			
Stomach (151)		55	0.78	(0.55-0.96)		23	1.07	(0.64-1.52)
Colon (153)		25	0.73	(0.45-1.02)		9	1.02	(0.44-1.84)
Rectum (154)		16	0.54	(0.29-0.83)		4	0.50	(0.13-1.22)
Liver (155)		30	1.32	(0.85-1.80)		26	1.74	(1.08-2.42)
Pancreas (157)		12	0.94	(0.46-1.57)		13	1.26	(0.64-2.04)
Lung (162)		40	0.93	(0.63-1.21)		28	1.14	(0.72-1.57)
Bladder (188)		12	1.32	(0.65-2.19)		3	1.98	(0.39-5.51)
All sites (140-208)		308	0.90	(0.76-0.96)		136	1.06	(0.85-1.19)
Women (n = 2411)	70 666				72 822			
Stomach (151)		16	0.74	(0.40-1.15)		8	0.97	(0.40-1.81)
Colon (153)		7	0.43	(0.16-0.84)		2	0.45	(0.05-1.54)
Rectum (154)		11	1.16	(0.55-1.97)		2	0.80	(0.09-2.76)
Liver (155)		5	1.64	(0.51-3.64)		2	1.18	(0.14-4.06)
Pancreas (157)		7	1.50	(0.57-2.94)		4	1.11	(0.29-2.70)
Lung (162)		10	0.74	(0.34-1.30)		7	1.29	(0.49-2.52)
Breast (174)		56	0.72	(0.52-0.89)		9	0.69	(0.30-1.25)
Bladder (188)		3	2.42	(0.47-6.72)		2	8.96	(1.03-30.75)
All sites (140-208)		216	1.06	(0.87-1.15)		72	1.21	(0.90-1.45)
All (n = 6,223)	1,84,579				1,88,531			
Stomach (151)		71	0.77	(0.57-0.92)		31	1.04	(0.67-1.40)
Colon (153)		32	0.63	(0.41-0.85)		11	0.83	(0.39-1.41)
Rectum (154)		27	0.69	(0.43-0.95)		6	0.57	(0.20-1.18)
Liver (155)		35	1.36	(0.90-1.80)		28	1.68	(1.06-2.31)
Pancreas (157)		19	1.09	(0.63-1.62)		17	1.22	(0.67-1.85)
Lung (162)		50	0.89	(0.63-1.11)		35	1.17	(0.77-1.54)
Breast (174)		56	0.72	(0.52-0.89)		9	0.69	(0.30-1.25)
Bladder (188)		15	1.45	(0.77-2.28)		5	2.88	(0.89-6.39)
All sites (140-208)		524	0.96	(0.84-0.99)		208	1.11	(0.92-1.21)

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

lower than that of subjects with partial allowance during the study period. The reason for this difference was unclear. Those unable to function properly due to serious physical impairment had difficulty not only in attending regular cancer screening but also in visiting the hospital for examination when they had cancer symptoms. This might explain the lower cancer incidence risk among subjects with full allowance than among subjects with partial allowance.

There were several limitations in this study. First, the dose-response relationship between the level of exposure and risk of death and cancer incidence could not be analyzed because there were no quantitative data on individual levels of arsenic ingestion. Therefore, we used the type of allowance as an indicator of different levels of poisoning and then estimated the risk of each group. Second, among 13 397 victims, there were 622 who died during 1955-1981. In addition to the 6400 victims who enrolled, 1581 had contact with the Foundation but refused to participate the study. In addition, 577 refused any contact, 4217 had no contact with the Foundation. Therefore, we were unable to evaluate the mortality and cancer incidence risk of all victims comprehensively. Those who suffered no or slight impact on life/employment might not have contacted the Foundation. In contrast, those with serious physical and mental impairment were more likely to contact the Foundation for assistance. Lastly, some unmeasured confounders, such as environmental risk factors and socioeconomic factors, might affect our results.

Therefore, this long-term observational study revealed overall and cause-specific mortality and cancer incidence risk among survivors who ingested arsenic-contaminated dry milk in infancy. Further follow-up is needed as the survivors are at this time in their 60s, and evaluation of their health could help to improve health aid programs for them.

TABLE 5 SIRs and SMRs of all cancers among the subjects, 1982-2018

Follow-up duration (years)	Incidence					Mortality				
	No. of subjects	Person-years	Observed	SIR	95% CI	No. of subjects	Person-years	Observed	SMR	95% CI
All subjects										
0-4	6223	30 362	5	0.50	(0.15-1.11)	6223	30 394	5	1.20	(0.37-2.66)
5-9	5939	28 827	15	0.81	(0.43-1.27)	5944	28 898	5	0.78	(0.24-1.73)
10-14	5611	26 637	32	1.12	(0.73-1.50)	5631	26 807	12	1.19	(0.58-1.98)
15-19	5141	24 724	51	1.17	(0.82-1.46)	5193	25 045	31	1.90	(1.22-2.56)
20-24	4908	23 596	94	1.29	(0.99-1.50)	5011	24 136	25	0.94	(0.58-1.32)
25-29	4659	22 331	122	1.02	(0.80-1.15)	4856	23 242	47	1.16	(0.81-1.46)
>30	4360	28 102	205	0.81	(0.67-0.89)	4679	30 010	83	1.00	(0.75-1.17)
Type of allowance										
Subjects with no allowance										
15-19	4418	21 209	38	1.01	(0.68-1.32)	4454	21 453	23	1.23	(0.99-2.34)
20-24	4222	20 258	78	1.25	(0.94-1.48)	4296	20 678	20	0.88	(0.51-1.29)
25-29	4015	19 183	104	1.01	(0.78-1.16)	4167	19 939	34	0.98	(0.64-1.30)
>30	3776	24 308	172	0.79	(0.64-0.87)	4032	25 965	67	0.93	(0.68-1.12)
									1.00	
Subjects with partial allowance										
15-19	314	1540	8	2.94	(1.20-5.50)	324	1588	5	4.81	(1.48-10.67)
20-24	295	1460	9	2.00	(0.87-3.61)	313	1525	2	1.19	(0.14-4.10)
25-29	276	1364	11	1.50	(0.71-2.55)	303	1466	7	2.74	(1.05-5.36)
>30	250	1668	19	1.28	(0.73-1.89)	288	1824	12	2.37	(1.17-3.94)
Subjects with full allowance										
15-19	409	1975	5	1.42	(0.44-3.15)	415	2003	3	2.28	(0.45-6.32)
20-24	391	1878	7	1.20	(0.46-2.36)	402	1933	3	1.40	(0.27-3.90)
25-29	368	1783	7	0.73	(0.28-1.42)	386	1838	6	1.86	(0.65-3.84)
>30	334	2126	14	0.73	(0.38-1.17)	359	2221	4	0.65	(0.17-1.58)

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

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