

Original Paper

Occupational Radiation Exposure and Leukemia Mortality among Nuclear Workers in Japan: J-EPISODE, 1991–2010

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Whether exposure to radiation at low dose and at low dose rate is related to leukemia mortality and morbidity remains controversial. Cohort studies of nuclear workers chronically exposed to radiation at low dose and at low dose rate in their workplaces provide an opportunity to directly evaluate the risks of leukemia in the lower dose ranges. Previous findings have come mostly from Western countries, with few from Asian countries. The present study aimed to examine radiation's effects on mortality from leukemia, in a cohort of Japanese nuclear workers. The cohort consisted of 204,103 workers, who were followed from 1991 to 2010, with a total of 2.89 million person-years. The mean age and mean cumulative dose at the age at the end of follow-up were 55.6 years and 13.8 mSv. During the study, 209 leukemia deaths were observed. The linear excess relative risk (ERR) for all types of leukemia was negative, but not significant (ERR/Sv = -0.54; 90% confidence interval; -4.04, 2.96). Specific types of leukemia also showed no significant risks. A significant radiation-leukemia association for mortality was not observed in this study of Japanese nuclear workers. The cohort, however, is still young. Further follow-up is needed to obtain more reliable estimates of leukemia risks for Japanese workers exposed to low dose and low-dose rate radiation.

KEY WORDS: low dose radiation, radiation risk, leukemia, cohort study, epidemiological study.

I INTRODUCTION

Leukemia is well known as the earliest manifestation of the late effects of high-dose and high-dose-rate radiation exposure among the survivors of the atomic bombs dropped on Hiroshima and Nagasaki, Japan.¹⁻³⁾ However, whether radiation exposure at low dose and at low dose rate is related to leukemia mortality and morbidity remains controversial. Studying cohorts of nuclear workers who have been chronically exposed to radiation at low dose and at low dose rate in their workplaces can provide direct evidence for evaluating the risks of leukemia in the lower dose ranges, rather than evaluating them by extrapolating from dose-response findings in the higher dose range observed in the atomic bomb survivor studies.

Many studies on the risk of leukemia among nuclear workers exposed to low dose rate of radiation have been published in North America and Europe. Some have shown a

positive association between radiation exposure and leukemia mortality,⁴⁻¹⁴⁾ and others have demonstrated no association, partially because of the small number of leukemia cases observed.¹⁵⁻²¹⁾ The recent International Nuclear Workers Study (INWORKS) from France, the UK, and the USA showed a significantly high risk of leukemia excluding chronic lymphocytic leukemia and chronic myeloid leukemia similar to that seen in atomic bomb survivors.^{1, 3, 4)}

These findings were primarily based on nuclear workers in Western countries. Few findings on radiation risk have been obtained from Asian countries. Asian nuclear workers may have different mortality and morbidity rates of leukemia than do workers in the West,²²⁾ due to different characteristics in their lifestyle²³⁾ or varying susceptibility to radiation exposure.

A Japanese EPIdemiological Study Of low-Dose radiation Exposure among nuclear worker cohort (J-EPISODE) has been conducted since 1990 by the Radiation Effects Association (REA), with mortality follow-up. The study results have already been published.²⁴⁻²⁹⁾

The aims of the present study were to obtain larger statistical power by extension of follow-up period comparing previous study and to provide excess relative risks (ERRs) by subtype of leukemia for mortality among Japanese nuclear workers exposed to low dose and low dose rate of radiation.

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II MATERIALS AND METHODS

The study protocol was based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by Japan's Ministry of Health, Labour and Welfare and Ministry of Education, Culture, Sports, Science and Technology. It was reviewed and approved by the Research Ethics Committee of the REA. This work was fully funded by Japan's Nuclear Regulation Authority. The funder had no role in the study's design, data analysis, or data interpretation or in the writing of this report. The authors indicated no conflicts of interest.

1. Study population and mortality follow-up

Nuclear facilities in Japan include institutes of nuclear energy research and development, nuclear fuel processing plants, and nuclear power plants. Radiation workers at nuclear facilities in Japan are registered at the Radiation Dose Registration Center (RADREC) at the REA. The primary framework of the study population and follow-up methods of the J-EPISODE were described in detail in the previous papers.²⁴⁻²⁹ The present study started in 1990 and was based on records of approximately 204,000 workers who were registered in the RADREC as of the end of March 1999 with Japanese nationality. A follow-up with female workers was also undertaken, but they were not included in the analysis because they were too few in number (1,396 workers).

A mortality follow-up was carried out through the subjects' residence registration cards (RRCs) issued from the municipality offices administering their home addresses. Any deaths based on the record of obtaining a residential registry were confirmed. The cause of death was determined by record linkage with vital statistics death records approved for use and provided by the Ministry of Health, Labour, and Welfare. The causes of death could be identified in more than 99% of the deceased by a record linkage with their date of birth, date of death, sex, and municipality.³⁰ A process to guarantee an opportunity of refuse to be included to the cohort through an opt-out method was performed from 2007 to 2009. The opt-out rate was approximately 7%. For those whose data we obtained but who later refused participation, we stopped all follow-up efforts and they were censored at the last day at which their vital statuses were known.

Data analysis was based on the underlying cause of death coded according to the International Classification of Diseases (ICD) (9th revision³¹) was used for those whose year of death was during 1991–1994, and 10th revision³²) was used for those whose year of death was from 1995 forward). Since only two deaths were attributed to chronic lymphatic leukemia (CLL), we did not calculate the risk estimation for CLL. The present study considered the following categories of causes of death: all types of leukemia (ICD9: 204–208, ICD10: C91–C95), acute lymphatic leukemia (ALL) (ICD9: 204.0, 204.2, ICD10: C91.0, C91.2), acute myeloid leukemia (AML) (ICD9: 205.0, 205.2, ICD10: C92.0, C92.2, C92.4, C92.5), chronic myeloid leukemia (CML) (ICD9: 205.1, ICD10: C92.1), and adult T-cell leukemia (ATL) (ICD10: C91.5).

2. Dosimetry

For this study, the individual recorded doses, including photon, internal, and neutron doses, were used. The photon doses were the exposure records of equivalent doses at a tissue depth of 10 mm [$H_p(10)$ (mSv)] for all workers in nuclear facilities who have been transferred to and registered in the dose database at the RADREC. The internal exposure was rare in Japan, but if they had been positively detected, they were added to external doses. Neutron doses were restricted among workers engaged in producing mixed oxide (MOX) fuel. The production of MOX fuel to operate the experimental fast breeder reactor was limited to a short term at one specific section in institutes of nuclear energy research and development. For individuals performing this work, there are no records of estimated neutron exposure, but only records of total amount of exposure due to nuclear work.

The annual radiation exposure for each worker was calculated by adding the total from all facilities where workers worked in a given year. Exposures below the detectable level were set as 0 mSv in the present study.

The use of nuclear energy in Japan commenced in 1957. Therefore, the dosimetry records of all workers back to 1957, before the RADREC launched the registration in 1978, were retrospectively provided to the RADREC by the respective nuclear facilities that had stored the data. The present study covers radiation dose records from 1957 to 2010.

3. Statistical analysis

Person-years of observation were calculated from the date of entry (the latest date of April 1 of the first year of engagement at radiation work, the date of 20 years of age, or the date confirmed as alive by the RRC) until the date of exit (the earliest date of the date of death, the date when the RRC was issued in the most recent follow-up, or December 31, 2010). Therefore, the observation period differs by individual, but they exist from 1991 to 2010. The mean follow-up period for individuals was 14.2 years.

Poisson regression models were used to determine the relationship between exposure dose and leukemia mortality, based on stratified data cross-tabulated by calendar period (four categories with cut points at 1995, 2000, and 2005), birth year (12 generally five-year categories), attained age (14 five-year categories for ages 20 through 99, and one category for ages 100 or greater), residence location (eight areas in Japan, from north to south), and cumulative dose (14 categories by mSv levels: 0, > 0, 1–, 2–, 3–, 5–, 7.5–, 10–, 15–, 20–, 25–, 50–, 100–, and 200+).

A minimum latent period of two years for any radiation effects on leukemia was considered in the present analyses. Cumulative exposures at risk were time-dependent, calculated by adding two year-lagged exposures from the first year of engagement in radiation work.

The risk of leukemia due to radiation exposure was evaluated using the excess relative risk (ERR) model:

$$\lambda_0(c, b, a, r) (1 + \beta d) \quad (1)$$

where βd is a linear dose response with cumulative dose

d , and $\lambda_0(c, b, a, r)$ represents the background death rate of leukemia stratified by calendar period (c), birth year (b), attained age (a), and residence location (r). Since many cases showed no convergence for the likelihood confidence interval (CI), we unified CI to Wald based. We also evaluated ERRs by each dose category by using the model as follows:

$$\lambda_0(c, b, a, r) (1 + \beta d_i) \tag{2}$$

where i is a dose category (the lowest dose category is set as reference). Stratification by duration of employment was examined for sensitivity analysis as follows:

$$\lambda_0(c, b, a, r, du) (1 + \beta d) \tag{3}$$

where du is a category of duration of employment (8 categories: < 2, 2-, 3-, 5-, 7.5-, 10-, 15-, 20+).

Cross-tabulation and model fitting were performed using the Epicure statistical package.³³⁾

III RESULTS

The characteristics of Japanese nuclear workers' cohort are shown in **Table 1**. The mean age was 55.6 years and the mean cumulative dose was 13.8 mSv at the end of follow-up.

Figure 1 shows the distribution of the cumulative dose at the end of follow-up. Two thirds of the workers had < 5 mSv of cumulative dose. Only 3% of the workers had a cumulative dose of ≥ 100 mSv.

Table 2 describes the distribution of deaths due to leukemia, mean dose and person-years by dose category, birth year, attained age, calendar period, and geographic regions among Japanese nuclear workers. There were more than 100 deceased for all types of leukemia and AML, but for ALL, CML, and ATL, there were around 20 deceased. Two thirds of person-years were accounted for under 5 mSv. The mean dose and person-years varied among geographic regions.

Table 3 shows the ERRs/Sv and 90% CIs based on Wald

Table 1 Characteristics of Japanese nuclear workers.

Follow-up period		1991–2010
Number of subjects		204,103
Person-years (million)		2.89
Year of first radiation exposure	Mean	1985.4
	Median (IQR)	1985 (1980–1992)
Age at first radiation exposure	Mean	31.7
	Median (IQR)	29 (22–40)
Age at the end of follow-up	Mean	55.6
	Median (IQR)	56 (45–65)
Duration of employment (years)	Mean	8.1
	Median (IQR)	4 (1–12)
Cumulative dose at the end of follow-up (mSv)	Mean	13.8
	Median (IQR)	1.0 (0–10.7)

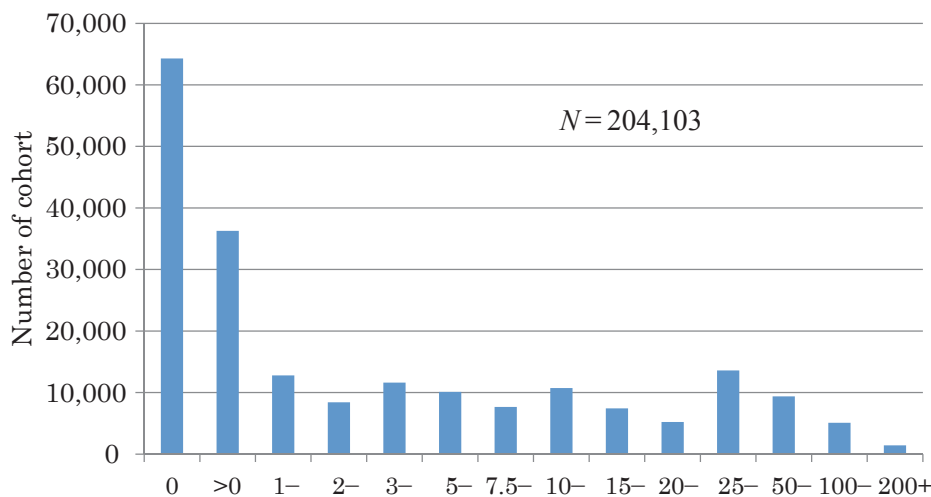


Fig. 1 Cumulative dose at the end of follow-up (mSv).

Table 2 Distribution of deaths due to leukemia, mean dose and person-years by dose category, birth year, attained age, calendar period, and geographic regions among Japanese nuclear workers.

	Leukemia					Mean dose (mSv)	Person-years (10 ⁴ years)
	All types	ALL	AML	CML	ATL		
Total	209	19	119	21	21		288.9
Dose category (mSv)							
0	71	8	38	11	5	0.0	89.2
>0	58	5	36	3	6	1.4	100.2
5–	26	2	16	1	2	7.2	25.7
10–	15	2	9	0	3	14.4	26.5
20–	26	2	12	3	4	31.7	27.0
50–	8	0	6	0	1	70.0	12.8
100+	5	0	2	3	0	157.3	7.5
Birth year							
<1930	30	3	15	6	1	10.8	11.8
1930–	71	2	39	6	9	13.0	37.4
1940–	53	7	29	5	6	14.4	68.9
1950–	34	3	20	3	5	15.4	78.0
1960+	21	4	16	1	0	9.0	92.7
Attained age							
20–29	4	0	4	0	0	5.1	16.3
30–39	10	3	7	0	0	9.6	59.7
40–49	28	5	15	2	4	14.1	75.4
50–59	50	6	27	6	3	14.8	72.2
60–69	60	2	33	6	11	13.6	46.0
70+	57	3	33	7	3	11.5	19.2
Calendar period							
<2000	53	10	21	7	6	13.2	92.8
2000–	60	4	37	5	8	11.4	93.3
2005+	96	5	61	9	7	13.2	102.8
Geographic regions							
Hokkaido, Tohoku	40	3	26	6	1	20.8	51.7
Kanto	71	7	43	11	5	8.0	100.6
Hokuriku	16	2	5	2	0	17.0	28.0
Chubu	16	2	10	1	1	11.4	19.4
Kinki	26	3	15	0	3	14.2	38.2
Chugoku	11	0	8	1	2	9.4	17.8
Shikoku	6	0	1	0	3	8.1	8.0
Kyushu	23	2	11	0	6	11.5	25.1

Some categories are combined for clarification purpose.

Table 3 ERRs/Sv and 90% CIs based on Wald by the type of leukemia among Japanese nuclear workers.

Type of leukemia	Observed deaths	ERR/Sv	90%CI ^a
All types	209	-0.54	(-4.04, 2.96)
Acute lymphatic leukemia	19	-2.08 ^b	(-11.92, 7.76) ^b
Acute myeloid leukemia	119	-0.83	(-5.28, 3.61)
Chronic myeloid leukemia	21	9.70	(-10.49, 29.89)
Adult T-cell leukemia	21	5.20	(-13.05, 23.45)

a: Wald-based CI.

b: Last estimate is denoted because the ERR did not converge.

by the type of leukemia. All types of leukemia ALL, AML, CML, and ATL did not show significantly high ERRs/Sv. The ERR/Sv for all types of leukemia was -0.54 (-4.04, 2.96)¹. Since only two deaths were attributed to CLL, the ERR/Sv for leukemia excluding CLL was completely identical to ERR/Sv for all types of leukemia. The ERR/Sv for ALL did not converge, and the ERR/Sv which described in **Table 3** was the last estimate. Thus, this value includes some uncertainty. **Figure 2** shows the ERRs/Sv and 90% CIs for the dose-response and ERRs with 90% CIs by each dose category. No monotonous increasing trend of ERRs were not seen in all causes of death which were analyzed in present study. Wide CIs were shown in ALL, CML, and ATL due to small number of death.

Sensitivity analyses were performed under zero-year, five-year, and 10-year lag assumptions for all types of leukemia.

¹ Numbers in parenthesis represent the 90% CI.

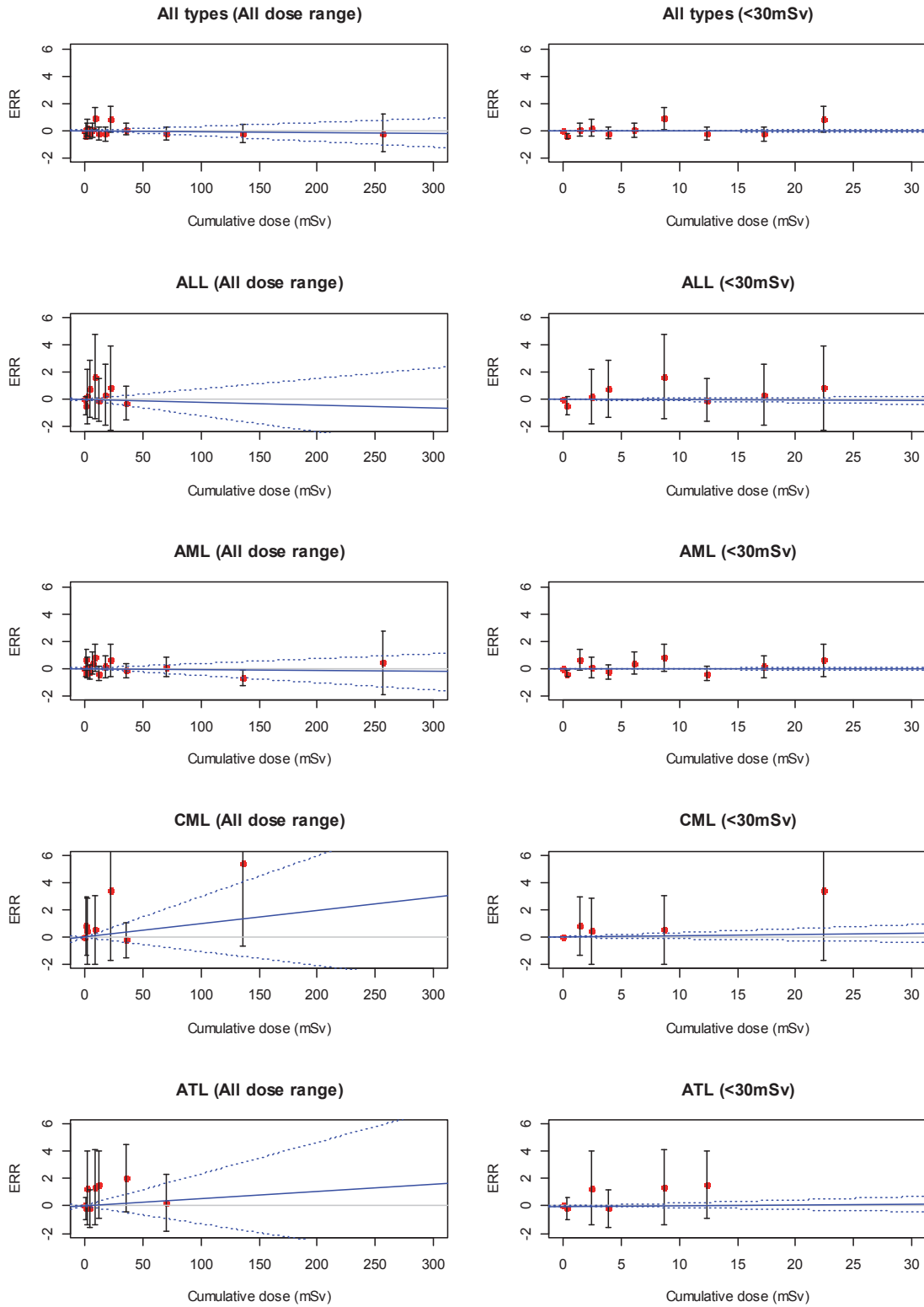


Fig. 2 The ERRs/Sv and 90% CIs for the dose-response and ERRs with 90% CIs by each dose category by type of leukemia. The lowest dose category was set as reference. The left panel shows the results based on all dose ranges and the right panel shows the results based on under 30 mSv.

The ERRs/Sv were -0.66 ($-4.01, 2.69$), -0.08 ($-3.96, 3.80$), and 0.73 ($-3.92, 5.37$) for zero-year, five-year, and 10-year lag years, respectively. The ERRs were higher for longer lag years. However, these values were not significant. Some radiation epidemiology studies have used stratification by the duration of employment to allow for a possible healthy worker survivor effect (HWSE).^{8, 11, 15, 19, 20} When the duration of employment was added as an adjustment variable, it showed little impact on the ERRs/Sv for all types of leukemia, ALL, and AML. The ERRs/Sv were from -0.54 ($-4.04, 2.96$) to -0.56 ($-4.45, 3.33$), from -2.08 ($-11.92, 7.76$) to -2.04 ($-10.06, 5.99$) (both of them were last estimates), and from -0.83 ($-5.28, 3.61$) to -1.03 ($-5.63, 3.58$) for all types of leukemia, ALL, and AML, respectively. However, the ERRs/Sv for CML and ATL were changed largely. The ERRs/Sv were from 9.70 ($-10.49, 29.89$) to 32.61 ($-27.95, 93.17$) and from 5.20 ($-13.05, 23.45$) to -2.09 ($-11.49, 7.30$), respectively. To restrict routine nuclear workers, we excluded workers who had only one-year dose record. Among 150,830 workers, there were 146 leukemia deaths, resulting in an ERR/Sv -0.42 ($-4.05, 3.20$) for all types of leukemia.

We attempted to fit pure quadratic model and linear quadratic model; however, only the pure quadratic model for CML could converge (data not shown) and remaining cases could not converge.

IV DISCUSSION

1. All types of leukemia

Many studies have reported significantly high ERRs for all types of leukemia or leukemia excluding CLL,¹⁻¹⁴ while some studies have reported non-significant ERRs.¹⁵⁻²¹ The ERR/Sv for all types of leukemia of the present study was negative and not significant (ERR/Sv = -0.54 ($-4.04, 2.96$)). Our previous studies also described non-significant ERRs.^{25-27, 29} IWASAKI et al. reported that the ERR/Sv for leukemia was 0.01 ($-10.0, 10.0$),²⁵ AKIBA and MIZUNO have reported that the ERR/Sv for leukemia was -1.93 ($-6.12, 8.57$),²⁶ and KUDO et al. found that the ERRs/Sv for leukemia excluding CLL were -0.27 ($-4.07, 3.52$)²⁷ and -1.95 ($-5.80, 1.89$).²⁹ Present study showed narrower CI.

Leukemia is a rare disease. Therefore, almost all studies suffered from an insufficient statistical power. To solve this problem, DANIELS et al. conducted a meta-analysis of leukemia and estimated significantly high integrated ERR at 100 mGy of 0.19 (95% CI: $0.07, 0.32$).³⁴ However, the adjustment for confounding factors is generally restricted in meta-analyses of observational studies, and the study is not an exceptional case, as the authors stated smoking and concomitant leukemogen exposures were not accounted for.

2. Acute lymphatic leukemia (ALL)

A cause of ALL is unknown. LSS studies^{1, 3} showed significantly high ERR/Sv for ALL, while INWORKS⁴ showed no significance. The ERR/Sv for ALL did not converge in the present study. The last estimate was -2.08 ($-11.92, 7.76$), but it includes some uncertainty.

3. Acute myeloid leukemia (AML)

It is reported that secondary AML was caused by prior exposure to cytotoxic therapy and/or radiotherapy for a malignancy.³⁵ Therefore, it is possible that radiation is a leukemogen of AML. LSS^{1, 3} studies showed significantly high ERR/Sv for AML, while INWORKS,⁴ the study among French worker cohort,¹² Canadian worker cohort,¹³ and the 15-country study¹⁵ showed no significance. The ERR/Sv for AML of the present study was negative and not significant (ERR/Sv = -0.83 ($-5.28, 3.61$)). Benzene is an established myeloid leukemogen.^{36, 37} We administered a lifestyle questionnaire survey from 1997³⁸ and 2003 to a sample of worker and obtained information on the occupational history of benzene. However, there were no deceased with an occupational history of benzene, so we could not discuss benzene's effect.

4. Chronic myeloid leukemia (CML)

CML is a stem cell disorder characterized by the occurrence of the Philadelphia chromosome, which is due to reciprocal translocation between q arm 34 region of 9th chromosome and q arm 11 region of 22nd chromosome.^{39, 40} LSS studies^{1, 3} and INWORKS⁴ showed significantly high ERR/Sv for CML, while the study among French worker cohort¹² and the 15-country study¹⁵ showed no significance. The ERR/Sv for CML of the present study was positive but not significant with a wide CI due to the small number of deaths (21 observed deaths; ERR/Sv = 9.70 ($-10.49, 29.89$)).

5. Adult T-cell leukemia (ATL)

ATL is caused by human T-cell leukemia virus type I (HTLV-1) infection and often occurs in HTLV-1-endemic areas, such as the Caribbean islands, Central and South America, Intertropical Africa, Middle East, and southwestern Japan.⁴¹ Therefore, the analyses of ATL are quite limited. LSS study have reported non-significant ERR/Sv for ATL both mortality (ERR/Sv = -0.2 (Not determined, 1.78))¹ and incidence (ERR/Sv = 0.05 ($-0.51, 1.54$)).³ The ERR/Sv for ATL of the present study was positive but not significant with a wide CI due to the small number of deaths (21 observed deaths; ERR/Sv = 5.20 ($-13.05, 23.45$)).

6. Limitation

The main limitation of the present study was the limited statistical power. The total number of observed deaths by all types of leukemia was 209. This is less than LSS¹ (310) or INWORKS⁴ (531). In particular, the numbers of deaths caused by CML, ALL, and ATL were very small. One reason was that this cohort was young: the mean age at the end of follow-up was 55.6. The fitting failure of quadratic terms might be caused by the small number of observed deaths. For this reason, we could not discuss dose-response linearity.

Another limitation was that adjusting for confounding factors might be insufficient. In our previous studies, we demonstrated that smoking was a considerable confounding factor to evaluate radiation risk.²⁷⁻²⁹ However, the workers who have smoking information were a sample of the present

cohort, and when we adjusted for smoking among the sample of workers, the ERR/Sv for leukemia excluding CLL did not converge.²⁹⁾

V CONCLUSION

We estimated the ERRs/Sv for leukemia by subtype and found no statistically significant ERRs/Sv. Sensitivity analyses also showed no risk. However, we realize the present study had insufficient statistical power. Adjusting for leukemogen also might have been inadequate. To solve these problem, a new lifestyle questionnaire survey is now underway and has collected more than 60,000 replies so far.

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