

Original Paper

Direct Risk Comparison between Radiation and Smoking on Cancer Mortality among Nuclear Workers in Japan (J-EPISODE)

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The health effects of low-dose or low-dose rate of radiation are still controversial. There is little evidence to show if radiation risk is greater than other risks, such as lifestyle or socio-economic factors, including smoking. This study aimed to directly compare radiation and smoking risk on cancer mortality by deriving both risk factors simultaneously from one cohort. The study population was Japanese nuclear workers who were engaged until the end of March, 1999. A lifestyle questionnaire was distributed in 1997 and 2003 and smoking information was obtained. Radiation dose was supplied by Radiation Dose Registration Center in Radiation Effects Association. Poisson regression was used to derive radiation excess relative risk (ERR) per 100 mSv and smoking (ERR) per 20 pack-years. Radiation doses were lagged by 10 years. There were 71,733 subjects. The total person-years was 591,000, and the number of deaths for all cancers excluding leukemia was 1,326. For all cancers excluding leukemia, the ERR of radiation per 100 mSv was 0.08 (90% CI: -0.08, 0.28), and the ERR of smoking per 20 pack-years was 0.57 (90% CI: 0.44, 0.73). In addition to all cancers excluding leukemia, stomach cancer, lung cancer, smoking-related cancers showed significantly smaller radiation ERRs than smoking ERRs. These results suggest that, even if a low-dose radiation risk existed, it was much smaller than smoking risk.

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

I INTRODUCTION

Although health effects of high-dose or high-dose rate of radiation based on the studies of atomic bomb survivors¹⁻³⁾ has been demonstrated, the health effects of low-dose or low-dose rate of radiation are still controversial. There is little evidence to show if radiation risk is greater than other risks, such as lifestyle or socio-economic factors, including smoking.

Some studies have compared the risk between radiation and smoking,⁴⁻⁶⁾ however, comparison between cumulative radiation dose and total amount of smoking among nuclear workers are limited.

The Institute of Radiation Epidemiology (IRE) of Japan's Radiation Effects Association (REA) commenced an epidemiological study on low-dose radiation effects (J-EPISODE) among radiation workers in Japan in 1990. To examine non-radiation factors among radiation workers, the IRE conducted lifestyle questionnaire surveys among a sample of workers in 1997⁷⁾ and 2003.

The present study aimed to quantify the excess relative risk (ERR) of both radiation and smoking that were derived simultaneously from one cohort, and to directly compare the two risk factors.

II MATERIALS AND METHODS

1. Ethics statement

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects established jointly by Japan's Ministry of Health, Labour, and Welfare, and Ministry of Education, Culture, Sports, Science, and Technology. This work was reviewed and approved by the Research Ethics Committee of the REA.

2. Cohort definition and follow-up of vital status

We conducted a follow-up of Japanese workers who registered in the Radiation Dose Registration Center (RADREC), which manages workers' radiation dose records from nuclear facilities as of the end of March 1999. Copies of the workers' residence registration cards (RRCs) were acquired from local government offices to ascertain their vital statuses. Copies of RRCs were issued when subjects were alive, and copies of deleted residence records, including death dates or new addresses, were issued when subjects were deceased or had moved.

For those whose deaths could be ascertained through RRCs, causes of death were obtained by record linkage with the death

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records approved for use and provided by Japan's Ministry of Health, Labour and Welfare. Indices used for record linkage were date of birth, date of death, sex, and municipality code of residence.⁸⁾ A process to obtain individual informed consent through an opt-out method was performed from 2007–2009. The opt-out rate was approximately 7%. For those whose data we obtained but who later refused participation, we stopped all follow-up efforts, but included them among their cohort until the last day on which their vital statuses were known. The primary framework of the study population and follow-up methods of the J-EPISODE have been described in detail in previous papers.^{9–13)}

3. Dosimetry

For this study, the individual recorded doses, including photon, internal, and neutron doses, were used. The photon doses were the external exposure records of equivalent doses at a tissue depth of 10 mm [$H_p(10)$ (mSv)] for all workers in nuclear facilities who are registered in the RADREC dose database. Neutron doses and internal doses were monitored, but cases above the level to be recorded were rare. If they were detected, they were added to external doses. The dose records used in the analysis included the individual's amount that consisted of external, internal, and neutron doses by fiscal year. In the present study, exposures below the detectable level were set as zero mSv.

The use of nuclear energy in Japan commenced in 1957. Therefore, the dosimetry records of workers from 1957 to the time 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.

4. Lifestyle questionnaire survey

To examine factors potentially confounding the risk assessment of nuclear workers, lifestyle questionnaire surveys were performed twice (1997 and 2003) to a sample of workers. The questionnaire was self-administered and included questions on smoking, alcohol intake, and history of engaging in work involving hazardous materials, such as asbestos, benzene, etc. The first survey's questionnaire (1997–1999) was distributed to 55,271 workers in nuclear facilities; and almost all respondents were working at the time of the survey. The second survey's questionnaire (2003–2004) was distributed to 73,542 workers by postal mail to those who were 40 years old or more on July 1, 2003. Based on cumulative doses as of March 31, 2002, all workers exposed to 10 mSv or more were surveyed, while 40% of workers with less than 10 mSv were sampled. The questions in the second survey were almost identical to those of the first survey, with questions on socio-economic status such as years of education added. For those who answered both surveys, the first survey's answers were analyzed in this study. Female workers were also distributed to but were not included in the analysis because number of the responses from female workers was too small (387 workers). Those whose smoking status or pack-years were unknown were excluded.

5. Risk comparison strategy

To compare radiation and smoking risks, we had to set some assumptions on model and unit. In this study, a linear model was assumed to apply to both radiation and smoking. In radiation epidemiology field, a linear model is broadly used, although a linear no threshold (LNT) model is still controversial. The consensus is that determining low-level radiation risk is difficult due to a huge cohort that is needed to increase statistical power and adjustment for confounding factors such as lifestyle or socio-economic status is generally limited. LNT can be considered as a possible model under such situations. Therefore, a linear model was used for radiation risk estimate. To facilitate a comparison, linear model was also used for smoking.

For risk estimate units, both radiation risk estimate and smoking risk estimate vary by their unit. Workers who were exposed to over 100 mSv comprised approximately 5% of the whole cohort. Therefore, radiation risk estimate was based on 100 mSv to avoid underestimation of radiation risk. Smoking risk estimate was based on 20 pack-years to allow comparison with other studies.

6. Statistical analysis

All individuals contributed person-years from two years after the response date of the questionnaire¹⁴⁾ until the earliest of (a) the date of final confirmation of vital status, (b) the date of death, or (c) December 31, 2010. Poisson regression models were applied to analyze radiation risks and smoking risks.^{12, 13, 15–18)} Each individual's last residence was used to stratify respondents into eight regions within Japan. Given the differences between the characteristics of respondents to the first and second lifestyle surveys, as described above in the "lifestyle questionnaire survey" section, a binary indicator was used to show whether the first or the second survey was used for analysis.

Radiation cumulative doses were categorized into 14 groups by mSv levels: 0, > 0, 1–, 2–, 3–, 5–, 7.5–, 10–, 15–, 20–, 25–, 50–, 100–, 200+. Cumulative radiation doses were updated monthly, with the assumption that annual doses were distributed uniformly over the year. Cumulative doses were lagged by ten years.^{12, 13, 15–18)} The pack-years was defined as follows: the number of cigarettes per day \times (1 pack/20 cigarettes) \times duration of smoking (the number of years since the age at which an individual started to smoke, through the age on the survey date for current smokers). Pack-years were categorized into eight groups: 0, > 0, 10–, 15–, 20–, 25–, 30–, 50+. We used only pack-years for current smokers and added former smoker indicator as an adjusted variable. Adjustment variables were attained age, calendar year, birth year, residence, binary indicator of lifestyle questionnaire survey, and binary indicator of former smoker. Cumulative dose, attained age, and calendar period were treated as time-dependent variables. The model used to estimate radiation and smoking risks was a linear additive model (1):

$$\lambda = \lambda_0(a, c, y, r, s) \exp(\alpha z) (1 + \beta_1 z_1 + \beta_2 z_2) \quad (1)$$

We also fitted the data to a linear multiplicative model (2) and a log-linear model (3).

$$\lambda = \lambda_0(a, c, y, r, s) \exp(\alpha z) (1 + \beta_1 z_1)(1 + \beta_2 z_2) \quad (2)$$

$$\lambda = \lambda_0(a, c, y, r, s) \exp(\alpha z + \beta_1 z_1 + \beta_2 z_2) \quad (3)$$

where λ is the death rate at dose z_1 and pack-years z_2 . λ_0 is the background death rate (stratified by a : attained age (20–, 25–, ..., 100+), c : calendar period (< 2000, 2000–2004, 2005–2010), y : year of birth (< 1920, 1920–, 1925–, ..., 1970+), r : region (divided into eight areas), and s : survey indicator (1st, 2nd)), z indicates former smokers (1 = former smoker, 0 = current smoker or never smoker); z_1 represents the person-year weighted cumulative dose, and z_2 represents the person-year weighted pack-years for current smokers. α represents the coefficient of z and denotes relative risk for former smokers, and β_1 and β_2 represent the coefficient of z_1 and z_2 , respectively. The unit of z_1 was 100 mSv, and the unit of z_2 was 20 pack-years. Therefore, β_1 denotes radiation ERR per 100 mSv, and β_2 denotes smoking ERR per 20 pack-years. ERR denotes an increase of risk by radiation or smoking, namely it is equivalent to relative risk minus one. We also calculated the 90% confidence interval (CI) based on likelihood. When CI based on likelihood was not converged, CI based on Wald was calculated. Doses were lagged by 10 years, and sensitivity analyses were examined under five- and 15-year lag assumptions, in addition to a 10-year lag. In addition, we verified an interaction between radiation and smoking by using the model as follows (4):

$$\lambda = \lambda_0(a, c, y, r, s) \exp(\alpha z) (1 + \beta_1 z_1 + \beta_2 z_2 + \beta_{12} z_1 z_2) \quad (4)$$

where $z_1 z_2$ denotes interaction term of z_1 (radiation) and z_2 (smoking) and β_{12} represent the coefficient of $z_1 z_2$.

The person-year table was created and the models were fitted using Epicure software.¹⁹⁾ Using this model, we compared the ERRs of both radiation and smoking.

III RESULTS

There were 75,442 male workers who responded to the questionnaire survey. There were 3,709 workers (5%) excluded due to unknown smoking status. As a result, 71,733 with smoking information were analyzed as the present study cohort. **Table 1** shows the cohort characteristics. There were approximately 591,400 person-years accumulated from 1999 to 2010 by 71,733 cohort members. The mean of cumulative radiation dose which were lagged by 10 years and pack-years at the end of follow-up was 21.0 mSv and 27.8 pack-years, respectively. The age at the end of follow-up was 56.2 years old.

Table 2 denotes the proportion of subjects by the pack-years and dose categories at the end of follow-up. Some dose categories are combined for clarification purposes. The table illustrates positive correlation between the pack-years and radiation dose (p -value of Pearson correlation²⁰⁾ < 0.001). Namely, the proportion of non-smokers decreases with increasing dose categories, while the proportion of current smokers with 30 or more pack-years increases with increasing dose categories. More than half of workers are classified in the < 5 mSv dose category, while 5% of workers are classified in the 100+ mSv dose category.

Table 3 shows the distribution of deaths, person-years and mean attained age by dose category, smoking status and pack-years. The mean attained age showed a positive trend with cumulative dose and pack-years.

The results derived by model (1, 2, 3) were almost identical. For all cancers excluding leukemia, the ERR of radiation per 100 mSv was 0.08 (90%CI: –0.08, 0.28) and the ERR of smoking per 20 pack-years was 0.57 (0.44, 0.73) by linear additive model. The ERR of radiation per 100 mSv was 0.03 (90%CI: –0.08, 0.16) and the ERR of smoking per 20 pack-years was 0.56 (0.43, 0.72) by linear multiplicative model. The ERR of radiation at 100 mSv was 0.04 (90%CI: –0.07, 0.15) and the ERR of smoking at 20 pack-years was 0.30 (0.25, 0.36)

Table 1 Characteristics of Japanese nuclear workers.

Follow-up period		1999–2010
Number of subjects		71,733
Person-years		591,400
Age at first radiation exposure	Mean	30.0
	Median (IQR)	27 (21–37)
Duration of radiation exposure (Years)	Mean	17.1
	Median (IQR)	17 (6–26)
Cumulative radiation dose at the end of follow-up (mSv, Lagged by 10 years)	Mean	21.0
	Median (IQR)	4.5 (0.1–22.7)
Age at start to smoke ^a	Mean	19.5
	Median (IQR)	20 (18–20)
Duration of smoking ^a (Years)	Mean	24.1
	Median (IQR)	24 (14–33)
Pack-years ^a	Mean	27.8
	Median (IQR)	25.0 (13.0–38.0)
Age at the end of follow-up	Mean	56.2
	Median (IQR)	56 (47–65)

^a: Calculated among current smoker ($N = 41,495$).

Table 2 Number of subjects by smoking status, pack-years, and dose categories at the end of follow-up among Japanese nuclear workers.

Smoking status	Pack-years	Dose categories (mSv) ^a								Total
		0	>0	5–	10–	20–	50–	100–	200+	
Never	0	3,954 (25.2%)	5,085 (24.2%)	1,331 (21.5%)	1,759 (18.9%)	1,862 (17.8%)	833 (15.1%)	388 (13.6%)	78 (10.8%)	15,290 (21.3%)
	Former	3,716 (23.7%)	4,064 (19.4%)	1,114 (18.0%)	2,092 (22.4%)	2,154 (20.6%)	1,107 (20.1%)	564 (19.8%)	137 (18.9%)	14,948 (20.8%)
Current	>0	1,483 (9.5%)	2,966 (14.1%)	892 (14.4%)	902 (9.7%)	845 (8.1%)	322 (5.8%)	74 (2.6%)	10 (1.4%)	7,494 (10.4%)
	10–	1,472 (9.4%)	2,507 (11.9%)	848 (13.7%)	1,126 (12.1%)	1,387 (13.3%)	738 (13.4%)	333 (11.7%)	51 (7.0%)	8,462 (11.8%)
	20–	1,520 (9.7%)	2,169 (10.3%)	713 (11.5%)	1,141 (12.2%)	1,436 (13.7%)	914 (16.6%)	487 (17.1%)	133 (18.4%)	8,513 (11.9%)
	30+	3,545 (22.6%)	4,203 (20.0%)	1,283 (20.8%)	2,304 (24.7%)	2,778 (26.6%)	1,598 (29.0%)	1,000 (35.1%)	315 (43.5%)	17,026 (23.7%)
	Total	15,690 (100%)	20,994 (100%)	6,181 (100%)	9,324 (100%)	10,462 (100%)	5,512 (100%)	2,846 (100%)	724 (100%)	71,733 (100%)
Proportion by dose category		21.9%	29.3%	8.6%	13.0%	14.6%	7.7%	4.0%	1.0%	100%

Note: Parentheses indicate percentage of pack-years within each dose category. Some categories are combined for clarification purposes.

^a: Lagged by 10 years.

Table 3 Distribution of deaths, person-years and mean attained age by dose category, smoking status and pack-years among Japanese nuclear workers.

	Cause of death							Person-years/ 10 ⁴	Mean attained age
	All cancers excluding leukemia	Stomach cancer	Liver cancer	Lung cancer	Smoking- related cancers ^b	Nonsmoking- related cancers ^c			
Total	1,326	218	138	319	952	322	59.1	49.3	
Cumulative dose (mSv)									
0	313	58	31	68	223	79	19.3	44.9	
>0	312	44	33	65	206	92	16.5	48.8	
5–	107	16	8	33	82	22	4.5	50.0	
10–	181	31	14	45	128	44	6.1	53.2	
20–	214	37	25	54	166	42	6.9	53.6	
50–	132	24	17	33	97	31	3.6	54.7	
100–	47	5	9	17	38	7	1.8	56.2	
200+	20	3	1	4	12	5	0.4	58.7	
Smoking status Pack-years ^a									
Never	155	26	19	19	94	50	12.7	48.1	
Former	372	53	35	89	247	110	10.8	56.9	
>0	21	6	1	3	13	6	7.6	33.6	
Current	10–	52	9	5	37	11	8.2	42.0	
20–	386	59	45	102	283	91	10.7	53.5	
30+	340	65	33	99	278	54	9.2	56.6	

^a: Calculated among current smokers. (Zero for non-smokers.)

^b: Buccal and pharynx, esophagus, stomach, liver, pancreas, nasal cavity, larynx, lung, bladder, kidney, ureter. C00–C16, C22, C25, C30.0, C31–C34, C64–C67.

^c: All solid cancers other than smoking-related cancers.

C17–C21, C23–C24, C26–C29, C30.1–C30.9, C35–C63, C68–C80.

by log-linear model. These results showed lower radiation ERR compared with smoking ERR by all models and suggests that our results were robust. The linear additive model showed the best fit in all causes of death except non-smoking related cancers. AIC's of all cancers excluding leukemia were 9,540.680 for the linear additive model, 9,541.092 for the

linear multiplicative model and 9,554.756 for the log-linear model, respectively. Therefore, the results from the linear additive model were used for the rest of the analysis.

Table 4 shows the ERRs and 90% CIs of radiation and smoking. No significantly higher ERR per 100 mSv was shown, while significantly higher ERRs per 20 pack-years

Table 4 Excess relative risk and 90% confidence interval of radiation and smoking by cause of death among Japanese nuclear workers.

Causes of Death	ICD10 codes	Observed Deaths	Radiation ERR per 100 mSv 90%CI	Smoking ERR per 20 pack-years 90%CI
All cancers excluding leukemia	C00–C97 except C91–C95	1,326	0.08 (–0.08, 0.28)	0.57 (0.44, 0.73)
Stomach cancer	C16	218	–0.24 (–0.55, 0.05) ^c	0.71 (0.33, 1.09) ^c
Liver cancer	C22	138	0.71 (–0.004, 1.89)	0.61 (0.26, 1.25)
Lung cancer	C33–C34	319	0.19 (–0.21, 0.81)	2.14 (1.33, 3.49)
Smoking-related cancers ^a		952	0.09 (–0.13, 0.37)	0.87 (0.65, 1.13)
Nonsmoking-related cancers ^b		322	–0.04 (–0.30, 0.22) ^c	0.18 (0.03, 0.33) ^c

^a: Buccal and pharynx, esophagus, stomach, liver, pancreas, nasal cavity, larynx, lung, bladder, kidney, ureter.
C00–C16, C22, C25, C30.0, C31–C34, C64–C67.

^b: All solid cancers other than smoking-related cancers.
C17–C21, C23–C24, C26–C29, C30.1–C30.9, C35–C63, C68–C80.

^c: Wald based confidence interval.

were shown in all analyzed causes of death. For all cancers excluding leukemia, significantly smaller radiation ERRs (0.08 (90%CI: –0.08, 0.28)) compared with smoking ERRs (0.57 (0.44, 0.73)) were observed. Stomach cancer, lung cancer, and smoking-related cancers also showed significantly smaller radiation ERRs compared with smoking ERRs. The radiation ERR for liver cancer (0.71 (–0.004, 1.89)) was higher than for smoking ERR (0.61 (0.26, 1.25)) with regards to point estimate.

For all cancers excluding leukemia, the ERR of radiation was 0.08 (90%CI: –0.08, 0.26) and the ERR for smoking was 0.57 (0.44, 0.73) when a five-year lag was assumed, and the ERR of radiation was 0.09 (–0.09, 0.30) and the ERR for smoking was 0.57 (0.44, 0.72) when a 15-year lag was assumed. The lags were adapted only to radiation and were not adapted to smoking. Therefore, the ERRs of smoking were quite stable. We verified that all cancers excluding leukemia, stomach cancer, lung cancer and smoking-related cancers showed significantly smaller radiation RRs compared with smoking RRs when lag assumptions were five or 15-years (data not shown for stomach cancer, lung cancer and smoking-related cancers).

We found no interaction between radiation and smoking. The *p*-values of coefficient of the interaction term were 0.415 for all cancers excluding leukemia, and the *p*-values of other causes of death were all greater than 0.1.

IV DISCUSSION

1. Principal findings

In this study, direct comparison between radiation risk and smoking risk on cancer mortality was examined. Significantly smaller radiation ERRs per 100 mSv compared with smoking ERRs per 20 pack-years were shown for all cancers excluding leukemia, stomach cancer, lung cancer, and smoking-related cancers. For all cancers excluding leukemia, ERR of radiation

per 100 mSv was approximately one seventh of smoking ERR per 20 pack-years. Considering that the mean cumulative dose of this cohort was 21.0 mSv, the estimated risk of cancer mortality by smoking per 20 pack-years was over 30 times larger than that of radiation risk for ordinary nuclear workers.

2. Liver cancer radiation risk

The radiation ERR for liver cancer was higher than other causes of death and the point estimate was also higher than for smoking ERR. We have examined the adjustment for alcohol consumption status as follows:

$$\lambda = \lambda_0 (a, c, y, r, s) \exp(\alpha z + \gamma y)(1 + \beta_1 z_1 + \beta_2 z_2) \quad (5)$$

where *y* denotes alcohol consumption status (1 = current drinker, 2 = former drinker, 3 = never drinker, 4 = unknown) and *γ* denotes coefficient of *y*. Exp(*γ*) means relative risk by each alcohol category. After adjustment for alcohol consumption status, the results were almost stable. The ERR of radiation was 0.72 (0.006, 1.90) and smoking ERR was 0.56 (0.22, 1.17). This suggests the possible existence of other factors, such as hepatitis virus^{21, 22)} or that radiation itself may increase ERR. However, the results of other radiation epidemiology studies showed no significant increase in liver cancer.^{15, 16)} The high radiation ERR for liver cancer might be caused by chance, but this cannot be verified.

3. Comparison with other studies

Table 5 shows the comparison of ERRs of radiation for all cancers excluding leukemia and lung cancer with other studies. An atomic bomb survivor's life span study (LSS),^{3, 4)} 15-country study¹⁵⁾ (Pooled analysis include Australia, Belgium, Canada, Finland, France, Hungary, Japan, Korea, Lithuania, Slovakia, Spain, Sweden, Switzerland, UK and USA), National Registry for Radiation Workers' study¹⁶⁾ (NRRW: Cohort study performed by UK), International

Table 5 Comparison of excess relative risk and 90% confidence interval of mortality by radiation with other studies.

Study	All cancers excluding leukemia	Lung cancer
	Observed deaths ERR per 100 mSv 90% CI	Observed deaths ERR per 100 mSv 90% CI
J-EPISODE	1,326	319
	0.08 ^a (-0.08, 0.28)	0.19 ^a (-0.21, 0.81)
LSS	5,235	1,445
	0.03 ^{bc} (0.02, 0.04) ^d	0.08 ^{ac} (0.02, 0.15) ^d
15-country	5,024	1,457
	0.10 ^c (0.03, 0.18)	0.19 ^c (0.05, 0.36)
NRRW-3	7,455	2,230
	0.03 ^c (0.002, 0.06)	0.01 ^{cf} (-0.04, 0.07)
INWORKS	19,064	5,802
	0.05 ^c (0.02, 0.08)	0.05 ^c (0.00, 0.11)
Mayak		446
		0.01 ^g (-0.004, 0.04) ^d

^a: Derived by linear additive model.

^b: All solid cancers.

^c: Derived by linear model.

^d: 95% confidence interval.

^e: Incidence.

^f: Trachea, bronchus and lung cancer.

^g: Derived by linear multiplicative model.

Nuclear Workers Study^{17,18)} (INWORKS: Pooled analysis include UK, US, France) and study of Russia's Mayak nuclear facility⁶⁾ were chosen for comparison of radiation risk. The ERR for all cancers excluding leukemia of present study per 100 mSv was comparable with other studies. The ERR for lung cancers of the present study was also comparable, although the point estimate of the present study was slightly higher than other studies.

Japan Collaborative Cohort Study for Evaluation on Cancer (JACC),²³⁾ Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases (JPHC),^{24,25)} Three-Prefecture Cohort study,²⁶⁾ LSS³⁾ and Mayak⁶⁾ were chosen for comparison of smoking risk (Table 6). The ERR for all cancers excluding leukemia of present study per 20 pack-years was compatible with JPHC. However, the point estimate was lower than JACC, although the confidence interval overlapped. The ERR for lung cancer of the present study was compatible with JACC, JPHC and Three-Prefecture study, but was significantly lower than LSS or Mayak. This may be caused by the difference in pack-years unit. While, 20 pack-years was used in our study, 50 pack-years was used in the LSS study. The smoking category (current, former, never) was used in the Mayak study, and it showed exceptionally high

Table 6 Comparison of excess relative risk and 90% confidence interval of mortality by smoking with other studies.

Study	All cancers excluding leukemia	Lung cancer
	Observed deaths Smoking ERR 90% CI	Observed deaths Smoking ERR 90% CI
J-EPISODE	1,326	319
	0.57 ^{ab} (0.44, 0.73)	2.14 ^{ab} (1.33, 3.49)
JACC	2,513	645
	0.93 ^{cde} (0.72, 1.19) ^f	2.97 ^{ce} (1.96, 4.32) ^f
JPHC	342	1,354
	0.41 ^{edg} (-0.06, 1.10) ^f	3.69 ^{ch} (2.32, 5.62) ^e
Three-Prefecture		339
		1.10 ^{ce} (0.62, 1.71) ^f
LSS		1,445
		5.70 ^{aij} (4.10, 8.07) ^f
Mayak		446
		9 ^{ch} (5.4, 17) ^f

^a: Derived by linear additive model.

^b: Smoking excess relative risk at 20 pack-years vs 0 pack-years.

^c: Denoted as relative risk or hazard ratio in original paper.

They are denoted as excess relative risk in this table by extracting one.

^d: All cancers.

^e: Smoking relative risk at 20–39 pack-years vs 0 pack-years.

^f: 95% confidence interval.

^g: Smoking relative risk at 20–29 pack-years vs 0 pack-years.

^h: Smoking relative risk of current smoker vs non-smoker.

ⁱ: Incidence.

^j: Smoking excess relative risk at 50 pack-years vs 0 pack-years.

ERR (9, 95%CI (5.4, 17)). The most likely possibility was that many of the Russian workers smoked strong cigarettes, usually without filters and in large quantities, as stated by the authors.⁵⁾

Risk estimates of radiation in the present study were comparable with other studies (Table 5), while risk estimates of smoking were slightly smaller than in other studies (Table 6). Nevertheless, our study's results showed that radiation risks were smaller than smoking risks (Table 4). Therefore, it was likely that, if a low-dose radiation risk existed, it was much smaller than smoking risk.

4. Limitations and strengths of this study

Our study includes some limitations, one of which was deficiency of statistical power. Wide confidence intervals for radiation ERR comparing with other studies were caused by short person-years (591,400) and observed deaths (1,326 for all cancers excluding leukemia). Another limitation was

that smoking information was outdated to some extent, since the original questionnaires were performed in 1997 and 2003, while the follow-up period closed at the end of 2010. Significantly higher ERR per 20 pack-years was shown for nonsmoking-related cancer, although the point estimate was slightly smaller compared with other causes of deaths. This may be caused by confounding factors other than smoking. To overcome these limitations, a new lifestyle questionnaire survey is currently underway. The results of this new survey may lead to more conclusive results for future research.

V CONCLUSION

The present study provided the evidence suggesting that, even if a low-dose radiation risk for cancer mortality existed, it was much smaller than smoking risk. This study was important in deriving the risks of radiation and smoking simultaneously from one cohort.

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CONFLICTS OF INTEREST

The authors indicated no conflicts of interest.

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REFERENCES

- 1) DA. PIERCE, Y. SHIMIZU, DL. PRESTON, M. VAETH and K. MABUCHI; Studies of the mortality of atomic bomb survivors. report 12, part I. cancer: 1950–1990, *Radiat. Res.*, **146**, 1–27 (1996).
- 2) DL. PRESTON, Y. SHIMIZU, DA. PIERCE, A. SUYAMA and K. MABUCHI; Studies of mortality of atomic bomb survivors. report 13: solid cancer and noncancer disease mortality: 1950–1997, *Radiat. Res.*, **160**, 381–407 (2003).
- 3) K. OZASA, Y. SHIMIZU, A. SUYAMA, F. KASAGI, M. SODA, et al.; Studies of the mortality of atomic bomb survivors, report 14: an overview of cancer and noncancer diseases, *Radiat. Res.*, **177**, 229–243 (2012).
- 4) EK. CAHOON, DL. PRESTON, DA. PIERCE, E. GRANT, AV. BRENNER, et al.; Lung, laryngeal and other respiratory cancer incidence among Japanese atomic bomb survivors: an updated analysis from 1958 through 2009, *Radiat. Res.*, **187**, 538–548 (2017).
- 5) M. KREISHEIMER, ME. SOKOLNIKOV, NA. KOSHURNIKOVA, VF. KHOKHRYAKOV, SA. ROMANOW, et al.; Lung cancer mortality among nuclear workers of the Mayak facilities in the former Soviet Union, *Radiat. Environ. Bioph.* **42**, 129–135 (2003).
- 6) ES. GILBERT, ME. SOKOLNIKOV, DL. PRESTON, SJ. SCHONFELD, AE. SCHADILOV, et al.; Lung cancer risks from plutonium: an updated analysis of data from the Mayak worker cohort, *Radiat. Res.*, **179**, 332–342 (2013).
- 7) M. MURATA, T. MIYAKE, Y. INOUE, S. OHSHIMA, S. KUDO, et al.; Life-style and other characteristics of radiation workers at nuclear facilities in Japan: base-line data of a questionnaire survey, *J. Epidemiol.*, **12**, 310–319 (2002).
- 8) T. IWASAKI, T. MIYAKE, S. OHSHIMA, S. KUDO and T. YOSHIMURA; A method for identifying underlying causes of death in epidemiological study, *J. Epidemiol.*, **10**, 362–365 (2000).
- 9) Y. HOSODA, M. KUBA, T. MIYAKE, S. KUDO, H. MATSUDAIRA, et al.; First analysis of mortality of nuclear industry workers in Japan, 1986–1992, *J. Health Phys.*, **32**, 173–184 (1997).
- 10) T. IWASAKI, M. MURATA, S. OHSHIMA, T. MIYAKE, S. KUDO et al.; Second analysis of mortality of nuclear industry workers in Japan, 1986–1997, *Radiat. Res.*, **159**, 228–238 (2003).
- 11) S. AKIBA and S. MIZUNO; The third analysis of cancer mortality among Japanese nuclear workers, 1991–2002: estimation of excess relative risk per radiation dose, *J. Radiol. Prot.*, **32**, 73–83 (2012).
- 12) S. KUDO, J. ISHIDA, K. YOSHIMOTO, S. MIZUNO, S. OHSHIMA, et al.; Fifth analysis of mortality of nuclear industry workers in Japan, 1991–2010, *Jpn. J. Health Phys.*, **51**, 12–18 (2016) (in Japanese).
- 13) S. KUDO, J. ISHIDA, K. YOSHIMOTO, S. MIZUNO, S. OHSHIMA, et al.; Direct adjustment for confounding by smoking reduces radiation-related cancer risk estimates of mortality among male nuclear workers in Japan, 1999–2010, *J. Radiol. Prot.*, **38**, 357–371 (2018).
- 14) MT. GOODMAN, H. MORIWAKI, M. VAETH, S. AKIBA, H. HAYABUCHI, et al.; Prospective cohort study of risk factors for primary liver cancer in Hiroshima and Nagasaki, Japan, *Epidemiology*, **6**, 36–41 (1995).
- 15) E. CARDIS, M. VRIJHELD, M. BLETNER, E. GILBERT, M. HAKAMA, et al.; The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks, *Radiat. Res.*, **167**, 396–416 (2007).
- 16) CR. MUIRHEAD, JA. O'HAGAN, RG. HAYLOCK, MA. PHILLIPSON, T. WILCOCK, et al.; Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers, *Br. J. Cancer*, **100**, 206–212 (2009).
- 17) DB. RICHARDSON, E. CARDIS, RD. DANIELS, M. GILLIES, JA. O'HAGAN et al.; Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS), *BMJ*, **351**, h5359 doi:10.1136/bmj.h5359 (2015).
- 18) DB. RICHARDSON, E. CARDIS, RD. DANIELS, M. GILLIES, R. HAYLOCK, et al.; Site-specific solid cancer mortality after exposure to ionizing radiation: a cohort study of workers (INWORKS), *Epidemiology*, **29**, 31–40

- doi:10.1097/ede.0000000000000761, (2018).
- 19) EPICURE [EpiWin]: [computer program], Version 1.81, Seattle HiroSoft International Corporation, (2008).
- 20) J. ADLER and I. PARMRYD; Quantifying colocalization by correlation: the Pearson correlation coefficient is superior to the Mander's overlap coefficient, *Cytometry Part A*, **77**, 733–742 (2010).
- 21) M. MORI, M. HARA, I. WADA, T. HARA, K. YAMAMOTO, et al; Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors associated with hepatocellular carcinoma risk in Japan, *Am. J. Epidemiol.*, **151**, 131–139 (2000).
- 22) S. ISHIGURO, M. INOUE, Y. TANAKA, M. MIZOKAMI, M. IWASAKI, et al; Impact of viral load of hepatitis C on the incidence of hepatocellular carcinoma: a population-based cohort study (JPHC Study), *Cancer Lett.*, **300**, 173–179 (2011).
- 23) K. OZASA; Smoking and mortality in the Japan collaborative cohort study for evaluation of cancer (JACC), *Asian Pac. J. Cancer Prev.*, **8**, Suppl: 89–96 (2007).
- 24) M. HARA, T. SOBUE T, S. SASAKI, and S. TSUGANE; Smoking and risk of premature death among middle-aged Japanese: Ten-year follow-up of the Japan public health center-based prospective study on cancer and cardiovascular diseases (JPHC Study) Cohort I, *Jpn. J. Cancer Res.*, **93**, 6–14 (2002).
- 25) L. ZHA, T. SOBUE, T. KITAMURA, Y. KITAMURA, N. SAWADA, et al.; Changes in smoking status and mortality from all causes and lung cancer: a longitudinal analysis of a population-based study in Japan, *J. Epidemiol.*, **29**, 11–17 (2019).
- 26) T. MARUGAME, T. SOBUE, H. SATOH, S. KOMATSU, Y. NISHINO, et al.; Lung cancer death rates by smoking status: comparison of the three-prefecture cohort study in Japan to the cancer prevention study II in the USA, *Cancer Sci.*, **96**, 120–126 (2005).



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