SUMMARY OF THE FIFTH STUDY REPORT ON LOW-DOSE RADIATION EFFECTS ON HUMAN HEALTH

Abstract

This is a summary of the fifth study report on low-dose radiation effects on human health conducted by the Radiation Effects Association (REA), Japan.

Methods

A cohort of 204,103 radiation-monitored workers employed in Japanese nuclear energy industries was followed during 1991–2010, for a total of 2.89 million person-years. The underlying cause of death was ascertained based on ICD9/ICD10, and the Poisson regression was applied to quantify the association between cumulative dose and mortality (Table 1 and Table 2).

Findings

From lifestyle surveys for a subset of the cohort consisting of 75,442 respondents, the effects of adjusting confounding factors of smoking in the association between radiation and mortality from malignant neoplasms, excluding leukaemia, hereafter called simply “all cancers,” were first quantified among the large cohort radiation studies; the excess relative risk (ERR) decreased about 60% from 0.92 %/10 mSv to 0.36 %/10 mSv (Table 4).

For all 204,103 participants, a significant ERR of 1.20%/10 mSv for all cancers largely decreased to an insignificant ERR of 0.66 by the removal of lung cancer from among all cancers (Table 5).

Interpretation

The above findings suggest that smoking might be a strong confounding factor in the association between radiation and mortality from all cancers; the above association, before removing lung cancer, was apparently significant.

Funding

Nuclear Regulation Authority, Japan

KEYWORDS: Radiation workers, radiation epidemiology, excess relative risk (ERR), confounding factor, smoking, lung cancer, leukaemia

INTRODUCTION

In Japan, the operation and maintenance of nuclear power plants is carried out not only by employees of electric power companies but also by employees of many nuclear energy-related companies including subcontractors. In order to centrally manage the dose records of workers who might move from company to company, the Radiation Dose Registry Center was established by the Radiation Effects Association (REA) in 1977.

Mission of the REA

The REA has two missions related to the radiation exposure of nuclear workers; one is managing the abovementioned dose registry, and the other is radiation epidemiology study.

Research and the results up to the fourth study report

We have studied a cohort of radiation workers since 1991 and have compiled a study report every five years. The fourth study report discussed a significant association between all cancers and radiation exposure, which was found in the cohort of 204,103 participants during the study period 1991–2007. On the other hand, the result of lifestyle surveys for a subset of 75,442 respondents revealed a positive strong correlation between cumulative doses and smoking, which suggested a possible confounding factor in the association between all cancers and radiation exposure observed in the 204,103 participants.

METHODS

Study period

The study period for the fifth study report is 1991 to 2010.

Study design and participants

The cohort consists of radiation-monitored male workers employed in all Japanese nuclear energy-related industries for peaceful purposes. It excludes workers working only for radio isotope facilities and medical workers. The cohort started with the number of participants being 114,900 in 1991 and was enlarged to 204,103 participants as of the end of March 1999 (Table 1).

A process of obtaining informed consent by mail via an opt-out method was used since 2003, and in total, 6% of participants had not consented, as of the end of March 2014. We stopped following these participants after their requests.

Underlying causes of death

The cohort was followed from 1991 to 2010, and the number of deaths was 20,519.

We ascertained the underlying cause of death based on ICD9/ICD10, as follows.

We took the following data from the respective sources (Figure 1).

1) Name and birth date of all participants, from the Radiation Dose Registry Center, REA.

2) Participants' addresses from nuclear energy-related companies.

3) Participants' vital status and death date, if dead, from the Family Registers of city offices where their addresses were located. In Japan, the Family Registration System covers all Japanese people.

We ascertained the underlying causes of the above deaths by matching with participants' death forms from Vital Statistics, produced by the Ministry of Health, Labour and Welfare (WHLW), where the underlying cause of death was coded in ICD9 before 1994 and in ICD10 after 1995.

Data for monitoring exposure to ionizing radiation

Data for monitoring personal exposure to ionizing radiation, requested by regulation laws, were available from the Radiation Dose Registry Center, REA, providing individual yearly aggregates of external and internal effective doses from 1957 to 2010. It is noted that internal exposure is quite rare in Japan, except in accidents.

Lifestyle surveys

We conducted lifestyle surveys twice, in 1997–1999 and 2003–2004, covering items such as smoking, drinking, education, and so on. The total number of respondents for the first and the second surveys is 75,442.

Statistical analysis

We used a Poisson regression model to quantify the association between cumulative dose and mortality, as shown in Table 2. We estimated the excess relative risk (ERR) by a model of the form $\lambda = \lambda_0(1+\beta d)$, where λ is the mortality rate/person-year, d is the cumulative dose and β is an estimate of ERR/ mSv; we derived Wald-based CIs. All models were stratified according to age, calendar year and region. Cumulative doses were grouped by levels and lagged by 2 years for the analysis of leukaemia mortality and by 10 years for the analysis of other disease.

Adjustment for smoking

For 75,442 respondents to the lifestyle surveys, we estimated the ERR by a model including smoking as a confounding factor, as indicated in Table 2.

Funding source and conflict of interest

The Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan had entrusted this study to REA from 1990 to 2012. Then the Nuclear Regulation Authority of Japan has entrusted

since 2013. The funders indicated minimal specifications, and REA performed all processes from the study design to the writing of the report.

REA has no conflict of interest directly relevant to the contents of this article.

RESULTS

Characteristics of the study population (Table 1)

We assembled the cohort of 204,103 radiation-monitored workers. The total person-years was 2.89 million. Mean follow-up was 14.2 years (SD 4.1). The number of deaths during the follow-up was 20,519, nearly 10% of the cohort. The mean cumulative dose was 13.8 mSv. The median was 1.0 mSv (IQR 0.0–10.7). The mean age was 55.6 years (SD 13.0).

Estimated ERR for all 204,103 participants (Table 3)

The estimated ERR for leukaemia, other than for chronic lymphocytic leukaemia (CLL), hereafter simply called “leukaemia”, is negative at -0.27%/10 mSv and is not significant, even though it has been recognized that leukaemia has a strong association with radiation exposure. All cancers showed a significantly positive association with radiation exposure, with an ERR of 1.20.

Change of ERR by adjustment of smoking for 75,422 participants (Table 4)

For a subset of the cohort, consisting of 75,442 respondents from both the first and the second lifestyle surveys, we quantified the effects of confounding factors of smoking in association between radiation exposure and mortality from all cancers, and we found that the ERR decreased about 60%, from 0.92 to 0.36.

According to the type of cancer, the ERR for lung cancer decreased in the same way. However, the decrease in the ERR for liver cancer was not large.

Change of ERR by removing lung cancer for all 204,103 participants (Table 5)

We investigated the effects derived from smoking by comparing the ERRs before and after removing lung cancer from the causes of all cancers. The ERR for all cancers was 1.20 before removing lung cancer, and it was 0.66 after removing lung cancer, about a 45% decrease. Likewise, the ERR for smoking-related cancers decreased from 1.44 to 0.71.

DISCUSSION

The large decrease of ERR for all cancers for the 204,103 participants by removing lung cancer out from among all cancers suggests that smoking might be a strong confounding factor in the association between radiation and all cancers, while the above association before the removal of lung cancer showed an apparently statistically significant positive ERR of 1.20.

At the same time, the small decrease in ERR for liver cancer, after adjusting for the confounding factor of smoking, might suggest the existence of other confounding factors besides smoking.
Combining the results of a negative ERR for leukaemia, it is too early to draw conclusions about that low-dose radiation exposure affects cancer mortality. We need further study on confounding factors in the association between radiation exposure and mortality.

CHALLENGES

We intend to design a new prospective cohort to clarify the association between low dose-radiation and health, excluding biases caused by confounding factors such as smoking. For that, we are planning a workers' baseline survey, including possible confounding factors for all participants, as well as a process of obtaining informed consent through an opt-in method. The survey results will enable a more explicit internal comparison among several subgroups to be matched homogeneously according to the characteristics of the workers but heterogeneously according to dose level.
We will also make use of cancer incidence as a health index from the National Cancer Registry to be established in 2016.

Table 1: Characteristics of individuals included in the study

Study period 1)	1991 - 2010
Number of male participants 2)	204,103
Person-years (millions)	2.89
Duration of follow-up (years)	
Mean (SD)	14.2 (4.1)
Median (IQR)	13.9 (11.4-17.9)
Age at the end of follow-up (years)	
Mean (SD)	55.6 (13.0)
Median (IQR)	56 (45-65)
Cumulative dose (mSv)	
Mean (SD)	13.8 (34.4)
Median (IQR)	1.0 (0.0-10.7)
Vital status at the end of 2010	
Alive	183,584 (89.9%)
Dead	20,519 (10.1%)
Underlying cause of death	
Leukaemia 3)	207
All cancers 4)	7,929
Lung cancer	1,756
Liver cancer	1,219

Note: 1) The study period was prior to the 2011 Japan earthquake & tsunami and the Fukushima Daiichi nuclear disaster. Therefore, the cumulative dose does not include this unconventional radiation exposure of emergency workers.

2) Female radiation workers are excluded from the cohort because the number of female workers compatible with male workers is 1,329, and the number of deaths is only 49, of which leukaemia constitutes 0, malignant neoplasms excluding leukaemia 13, and lung cancer and liver cancer 1.

3) Leukaemia, other than chronic lymphocytic leukaemia (CLL), is hereafter simply called “leukaemia” in Tables 3 and 4.

4) Malignant neoplasms, excluding leukaemia, are hereafter simply called “all cancers” in Tables 3 to 5.

Table 2. Outline of statistical analysis

Procedure	We estimated ERR(%/10 mSv) by a Poisson regression model and derived Wald-based CIs.
Model	$\lambda = \lambda_0$ (a, c, r) (1+βd) where, λ: mortality rate λ_0: background mortality rate d: cumulative dose (mSv) β: ERR/ mSv
Adjustment of confounding factors	$\lambda = \lambda_0$ (a, c, r) (1+βd) for no adjustment of smoking, $\lambda = \lambda_0$ (a, c, r) $\exp(\alpha_2 s_2+\alpha_3 s_3+\alpha_4 s_4)$ (1+βd) for adjustment of smoking, where, a: age c: calendar year r: region s_i: dummy variables of smoking; s_1: current smoker (as reference), s_2: quit smoker, s_3: never smoker, s_4: unknown
Application software	EPICURE
Stratification	
Age	Five-year age groups from 20-24 years old to 95-99, and 100 and over
Calendar year	1991-1994, 1995-1999, 2000-2004 and 2005-2010
Region	8 regions
Cumulative dose	Less than 5 mSv, 5-10, 10-20, 20-50, 50-100, and 100 and over
Lag assumptions for cumulative dose	0 year for all causes of death 2 years for Leukaemia 10 years for other diseases

Table 3. Estimated ERR for all 204,103 participants

Cause of death	ERR%/10 mSv and 90%CI	Number of death
All causes of death	0.29 [-0.09: 0.68]	20,519
Leukaemia	-0.27 [-4.07: 3.52]	207
All cancers	1.20 [0.43: 1.96]	7,929
Lung cancer	3.15 [1.34: 4.96]	1,756
Liver cancer	2.52 [0.33: 4.72]	1,219

Table 4. Effects on ERR of adjusting confounding factor of smoking
(75,442 participants who answered both the first and second lifestyle surveys)

Cause of death	Change of ERR%/10 mSv and 90%CI		Number of death
	Before adjustment	After adjustment of smoking	
All causes of death	1.05 [0.31: 1.80]	0.45 [-0.24: 1.13]	3,281
Leukaemia	-3.12 [-6.50: 0.25]	Not determined	47
All cancers	0.92 [-0.30: 2.16]	0.36 [-0.79: 1.50]	1,421
Lung cancer	2.18 [-0.51: 4.88]	1.20 [-1.20: 3.61]	340
Liver cancer	6.32 [0.70: 11.95]	5.54 [0.21: 10.86]	148

Table 5. Changes to ERR by removing lung cancer from cause of death
(All 204,103 participants)

Cause of death	Changes of ERR%/10 mSv and 90%CI	
	Before removing lung cancer	After removing lung cancer
All cancers	1.20 [0.43: 1.96] (Number of death 7,929)	0.66 [-0.18: 1.50] (6,173)
Smoking-related cancers	1.44 [0.52: 2.34] (5,850)	0.71 [-0.32: 1.74] (4,094)

Figure 1: Study Method