Corrigendum: Direct adjustment for confounding by smoking reduces radiation-related cancer risk estimates of mortality among male nuclear workers in Japan, 1999–2010 (2018 J. Radiol. Prot. 38 357)

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We found some trivial errors which might confuse the reader. The errors can be classified into the following two types.

1. One is the misuse of ‘ERR’ and ‘ERR/Sv’. We wrote ‘Table 4 shows ERRs/Sv and 90% CIs…’ in line 7 of page 366 while writing ‘ERR and 90% CI for all cancers, excluding leukaemia, by dose category…’ in the title of table 4. The values described in table 4 were ERR by dose category and not ERR/Sv. In addition, an explanation about the model that derived ERR by dose category should be added. Therefore, the description mentioned above should be changed as follows:

(misprinted)
Table 4 shows ERRs/Sv and 90% CIs for all cancers excluding leukaemia by dose category;
(corrected)
Table 4 shows the ERRs which were defined by the following equation and the 90% CIs for all cancers excluding leukaemia by dose category:

\[ \lambda = \lambda_0(a, c, y, r, s) e^{\alpha_1 t + \alpha_2 r + \alpha_3 y + \alpha_4 d} \]
where \( d_i \) is the dose category, and \( \beta_i \) is the ERR by dose category. The lowest dose category was set as the reference.

(2) The other comprises errors in the headings of several tables. We described ‘ERR without adjustment for smoking’ and ‘ERR with adjustment for smoking’ in table 4. These are the correct descriptions. However, ‘ERR with adjustment for smoking’ was described as ‘For smoking’ in table 2. In addition, ‘Without adjustment’ and ‘With adjustment’ in the headings of tables 5, 6, and 7 should be written as ‘Without adjustment for smoking’ and ‘With adjustment for smoking’.

The authors wish to apologise for the errors.
Direct adjustment for confounding by smoking reduces radiation-related cancer risk estimates of mortality among male nuclear workers in Japan, 1999–2010

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Abstract
A causal relationship between protracted exposure to low-dose rate radiation and health effects remains unclear despite extensive international studies of nuclear workers. One potential reason is that radiation epidemiological studies that adjust for tobacco smoking, which heavily influences mortality, have been limited. In the present study, we examined radiation-related cancer risk by directly assessing the possible confounding effect of smoking, using data from two questionnaire surveys performed among Japanese nuclear workers in 1997 and 2003. Mortality follow-up was carried out for 71 733 male respondents for an average of 8.2 years during the observation period of 1999–2010. The mean cumulative dose was 25.5 mSv at the end of the follow-up period. Estimates of excess relative risk per Sv (ERRs/Sv) were obtained by Poisson regression. By adjusting for smoking directly on the basis of a linear dose-response model, we quantified the confounding effects of smoking on radiation risks. Statistically significant ERRs/Sv were found for all causes, all diseases, all non-cancer diseases, and liver cancer: 0.97 (90% confidence interval: 0.23, 1.78), 1.32 (0.40, 2.34), 1.87 (0.47, 3.49), and 4.78 (0.09, 11.68), respectively, without adjustment for smoking. However, the ERRs/Sv were no longer statistically significant after adjustment for smoking: 0.45 (−0.22, 1.19), 0.77...
ERRs/Sv for all cancers excluding leukaemia and lung cancer were not significant before adjustment for smoking, but declined after adjustment for smoking. The present study demonstrates that in this cohort of workers, smoking heavily distorts radiation risk estimates of mortality. The possibility of confounding by smoking depends on how strongly smoking is correlated with radiation exposure. If a correlation between smoking and radiation dose is suggested, smoking is an important confounder when assessing the radiation and health risks.

Supplementary material for this article is available online

Keywords: cohort study, cancer, confounding factor, smoking, radiation

Introduction

Risk estimation of low-dose radiation exposure remains a controversial issue to this day. The uncertainty arises because radiation-related health effects at low doses are difficult to detect and are thus much more vulnerable to distortion by bias or by confounding factors such as smoking and socio-economic status, which are known to be important extrinsic factors that affect mortality.

To obtain an accurate risk estimate, some cohort studies of nuclear workers have used socio-economic status such as industrial classification or facility to identify or account for potential confounding [1–3]. However, there are few studies estimating radiation risks that have adjusted directly for smoking as a confounding factor [4, 5]. Wu et al reported that cancer risk was heavily influenced by extrinsic factors [6], and smoking is well known as a strong carcinogen [7, 8].

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2006 report [9] indicates that ‘[epidemiological studies of occupational exposure] could provide useful information in [the] future,’ adding that one limitation to such studies is the fact that ‘lifestyle factors (e.g., smoking histories)’ are ‘generally not available.’

The Institute of Radiation Epidemiology (IRE) of the Radiation Effects Association (REA) of Japan commenced an epidemiological study of Japanese nuclear workers in 1990. The study results through 1997 have already been published as the first, second, and most recent analyses [10–12], which reported the possibility of lifestyle factors confounding the relationship between radiation dose and cancer mortality among nuclear workers in Japan. To examine non-radiation factors among nuclear workers, the IRE conducted lifestyle questionnaire surveys among different samples of workers in 1997 and 2003, finding a positive correlation between radiation doses and smoking rates [13]. This correlation means that adjustment for smoking actually reduces radiation risk estimates.

Most of the findings to date about radiation risks among nuclear workers have been derived from studies on largely Western populations; the studies to date focusing on Asian nuclear workers are insufficient to draw reliable conclusions. The subjects in the present study are Japanese nuclear workers, who might have different characteristics from Western workers in terms of smoking rates, cancer mortality, circulatory disease mortality, etc [14–16].
In the present study, we examine the confounding effects of smoking on radiation risk estimates by utilizing smoking information obtained from individuals who completed questionnaire surveys distributed among Japanese nuclear workers.

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 have no conflicts of interest.

Cohort definition and follow-up of vital status

A registry system of workers at nuclear facilities was established in Japan in 1977, operated by the Radiation Dose Registration Center (RADREC) of the REA. There were two requirements to meet the cohort definition. The first was to be a worker who was registered in RADREC as of the end of March 1999. The second was to have Japanese nationality. The present follow-up study was based on those who satisfied the two requirements within around 200 000 nuclear workers.

For follow-up of the study subjects, personal identification information was first obtained from RADREC, including each individual’s registration number, name, sex, and date of birth. Next, residential address information was obtained from the nuclear facilities at which the individuals worked. Then, copies of their residence registration cards (RRCs) were acquired from local government offices to ascertain the vital status of each study subject. If any resident had died or moved to another municipality, the information on date of death or subsequent address, as appropriate, was maintained in the aforementioned municipality but was deleted from the registration files after precisely 5 years. Due to the limited period of maintenance of RRCs for those who died or moved away, inquiries with municipalities were carried out at intervals of less than 5 years.

Lifestyle questionnaire surveys (described below) were conducted in 1997 and 2003 among different samples of workers in order to examine potential factors confounding the radiation risk assessment of nuclear workers. In the first survey, the questionnaire was distributed in nuclear facilities, while the second survey questionnaire was distributed by mail to those who were 40 years old or above on July 1, 2003. In the second survey, based on the cumulative dose 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. When considering both surveys, the questionnaire was distributed to a total of 116 000 workers, of whom 80 596 replied (69.5% response rate). Thus, the response rate was comparatively high. The higher-dose group showed a higher response rate (68% <10 mSv, while 85% were in the over 100 mSv category): we obtained data from more than two-thirds of those to whom the questionnaire was distributed, and in particular gained more information from the higher-dose group. The data gathered from the higher-dose group were sufficient to make it unlikely that the validity of the data was compromised. Responses that were missing values of smoking status or pack-years (described in the Statistical Analysis section below) were excluded from analysis. Those who met the analysis criteria (71 733 male workers—89% of those who responded) were assembled as a cohort. Follow-up with female workers was also undertaken.
but they were not included in the analysis because they were too few in number (387 workers).

For those whose deaths could be ascertained through RRCs, causes of death were obtained by record linkage with the death records approved for use and provided by Japan’s Ministry of Health, Labour and Welfare. The indices used for record linkage were date of birth, date of death, sex, and municipality code of residence. Iwasaki et al reported a successful determination of cause of death by means of this record linkage approach in 99.4% of all subjects [17]. 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. Causes of death were coded according to the International Classification of Diseases (ICD) 10th revision.

Dosimetry

Dose records for all workers in the cohort were comprised of individual doses monitored by nuclear facilities, based on Japanese law. Each nuclear facility reports to RADREC the amount of combined external and internal doses. Japanese workers with neutron exposure were limited to those engaged in producing mixed oxide (MOX), which usually consists of plutonium blended with uranium. The use of nuclear energy in Japan commenced in 1957 and the first commercial power plant went online in 1966; the shielding technique had already been established. The dose data that RADREC supplied to the IRE were annual individual effective doses of radiation exposure, including photon, neutron, and internal doses. Neutron doses and internal doses were recorded, but cases above the level to be recorded were so rare that those doses may be negligible under normal operational circumstances in Japan.

Film badge dosimeters, thermoluminescence dosimeters, electronic personal dosimeters, and, especially in recent years, fluoroglass dosimeters were used to determine external radiation doses. Detectable levels, ranging from 0.01–0.1 mSv [18], were dependent on dosimeter and time period. Doses below detectable levels were regarded to be 0 mSv for this study. Although RADREC began registration in 1978, earlier dosimetry records of workers maintained at specific nuclear facilities dating back to 1957 were provided to RADREC. Consequently, dose data are available for this study for the entire period from 1957–2010; they were used to calculate the cumulative radiation doses for individual workers. Personal dose equivalent Hp (10) values, which are used as external dose and internal doses were used in the analysis.

Lifestyle questionnaire survey

To examine factors potentially confounding the risk assessment of nuclear workers, lifestyle questionnaire surveys were performed twice.

First survey (1997–1999). This questionnaire was distributed in nuclear facilities, including electric power companies, research foundations, and fuel processing companies; almost all respondents were still working at the time of this survey. The questionnaire was self-completed and included questions about smoking status (current, former, never), age at starting to smoke, cigarettes smoked per day, and age of smoking cessation for former smokers, alcohol consumption, and history of engaging in work involving hazardous materials such as asbestos, benzene, etc.
Second survey (2003–2004). This questionnaire was distributed by mail to those who were 40 years old or above on July 1, 2003. Based on the cumulative dose 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 were almost identical to those in the first survey, but years of education and job status as a substitution for socio-economic status were added. For those who answered both surveys, the first survey’s answers were used for analysis in the present study.

Statistical analysis

The cohort for analysis consisted of respondents to the lifestyle surveys, excluding those whose smoking status or pack-years were unknown. All individuals contributed person-years at risk, excluding the first 2 years from the date of the reply to the questionnaire [19] until the earliest of (a) the date of last known vital status, (b) the date of death, or (c) December 31, 2010. Poisson regression models were applied to analyse radiation risks based on the number of deaths and person-years cross-classified by attained age (in 5-year intervals), calendar period (in 5-year intervals), birth year (in 5-year intervals), residence, an indicator of particular questionnaire survey, time-dependent radiation dose, pack-years, and years since the cessation of smoking. Each individual’s last residence was used to stratify respondents into eight regional categories within Japan. Given the differences between the characteristics of respondents to the first and second lifestyle surveys, as described in the Lifestyle questionnaire survey section, a binary indicator was also used to indicate either the first or the second survey. The pack-year was defined as follows: the number of cigarettes per day × (1 pack/20 cigarettes) × the number of years since the age at which at individual started to smoke through the age on the survey date for current smokers, or until the age of smoking cessation for former smokers. For former smokers, the years since the cessation of smoking were defined as the years from age at the cessation of smoking until the age on the survey date.

Time-dependent radiation cumulative doses were categorised into 14 groups by mSv levels: 0, >0, 1−, 2−, 3−, 5−, 7.5−, 10−, 15−, 20−, 25−, 50−, 100−, and 200+. Cumulative radiation doses were updated every month, on the assumption that annual doses were distributed uniformly over the year. Pack-years were categorised into eight groups: 0, >0, 10−, 15−, 20−, 25−, 30−, and 50+. The years since cessation of smoking were categorised into three groups: <5, 5−, and 10+. Each stratum of the cross-classification includes the number of deaths, the number of person-years, and person-weighted mean values of age attained, radiation dose, pack-years, and years since the cessation of smoking. The model used to estimate radiation risks is a linear excess relative risk (ERR) model:

\[
\lambda = \lambda_0(a, c, y, r, s)e^{a_1z_1+a_2z_2+a_3z_3(1 + \beta d)},
\]

where \(\lambda\) is the death rate at dose \(d\), \(\lambda_0\) is the background death rate stratified by \(a\) (attained age: 20−, 25−, ..., 100+), \(c\) (calendar period: <2000, 2000–2004, and 2005–2010), \(y\) (year of birth: <1920, 1920−, 1925−, ..., and 1970+), \(r\) (residence, divided into eight areas), \(s\) (survey indicator: first or second), and \(d\) (person-year weighted cumulative dose in sieverts in each stratum). \(\beta\) is the ERR per Sv (ERR/Sv), \(z_1\) represents pack-years for current smokers, \(z_2\) represents pack-years for former smokers, and \(z_3\) represents years since cessation of smoking for former smokers. Finally, \(a_1\)–\(a_3\) represent the respective coefficients of \(z_1\)–\(z_3\). In this model, \(\lambda_0\) is regarded as the death rate of persons whose cumulative dose was 0 and pack-years were 0 (never smoked). We calculated 90% confidence intervals (CIs) based on the
Table 1. Number of subjects by smoking status, pack-year, and dose categories at the time of the survey among Japanese nuclear workers.

| Smoking status | Pack-year | Dose categories (mSv)\(^a\) | Total |
|----------------|-----------|------------------------------|-------|
|                | 0         | >0                          |       |
| Never          |           |                              |       |
| Current        |           |                              |       |
|                | 0         | 4097 (25.4%)                | 15290 |
|                | >0        | 2434 (15.1%)                | 10722 |
|                | 10−       | 2426 (15.0%)                | 12120 |
|                | 20−       | 2252 (13.9%)                | 11269 |
|                | 30+       | 4939 (30.6%)                | 22332 |
|                |           | 16148 (100%)                | 71733 |
| Total          |           | 16148 (100%)                | 71733 |
| Proportion by dose category | 22.5% (100%) | 31.1% (100%) | 8.6% (100%) | 12.6% (100%) | 13.9% (100%) | 7.0% (100%) | 3.5% (100%) | 0.8% (100%) | 100% |

\(a\) Note: Parentheses indicate percentage of pack-years within each dose category.
Some categories are combined for clarification purposes.
likelihood method. We also used Wald-based CIs in cases in which we could not calculate likelihood-based CIs.

Cross-tabulation and model fitting were performed using the Epicure statistical package [20]. Using this model to examine the confounding effects of smoking, we compared the ERRs of radiation risks with and without adjusting for smoking. Cumulative doses were lagged by 2 years for leukaemia and by 10 years for other diseases [1–3] but not lagged for the category of all causes and external causes.

Results

Approximately 591 000 person-years were accumulated from 1999–2010 by 71 733 members of the cohort. The arithmetic mean and standard deviation of age at the date of the survey response were 45.1 and 14.1 years, respectively: the mean follow-up period was 8.2 years.

Table 1 shows the number of subjects by pack-year and dose categories at the time of survey response; it shows a significantly positive correlation between pack-years and radiation dose ($p < 0.0001$, Mantel–Haenszel non-zero correlation [21]: degree of freedom = 1). More than half the workers were in the $<10$ mSv dose class, while 4% were in the $>100$ mSv dose class. The mean cumulative doses were 19.1 mSv at the time of the survey response and 25.5 mSv at the end of the follow-up period.

Table 2 shows the results of ERRs/Sv of radiation risks with and without adjustment for smoking. All causes, all diseases, all non-cancer diseases, and liver cancer each showed significantly high ERRs/Sv of 0.97 (90% CI 0.23, 1.78), 1.32 (0.40, 2.34), 1.87 (0.47, 3.49), and 4.78 (0.09, 11.68), respectively, but their ERRs/Sv declined and did not show significance after adjusting for smoking: 0.45 (−0.22, 1.19), 0.77 (−0.08, 1.72), 1.28 (−0.03, 2.79), and 3.89 (−0.46, 10.34), respectively. This study did not include 37 deaths caused by in situ neoplasms, benign neoplasms, or neoplasms of uncertain or unknown behaviour for both all cancers and all non-cancer diseases. The ERR/Sv for leukaemia excluding chronic lymphocytic leukaemia could not be converged due to the small number of such deaths, but the last estimate was negative. The ERR/Sv for all cancers excluding leukaemia decreased after adjusting for smoking from 0.80 (−0.39, 2.19) to 0.29 (−0.81, 1.57).

The effect on ERR/Sv reduction by smoking adjustment was larger for smoking-related cancers than for nonsmoking-related cancers. The ERR/Sv of smoking-related cancers declined from 1.05 (−0.40, 2.79) to 0.36 (−0.95, 1.94) after adjusting for smoking, but for nonsmoking-related cancers, it declined from −0.60 (−2.76, 1.56) to −0.76 (−2.85, 1.33). While the ERR/Sv of smoking-related non-cancer diseases declined from 1.39 (−0.39, 3.56) to 0.79 (−0.84, 2.80) after adjusting for smoking, for nonsmoking-related non-cancer diseases, it declined from 0.26 (−1.73, 2.94) to −0.24 (−2.04, 2.25).

Discussion

The purpose of the present study was to examine whether direct adjustment for smoking reduces radiation-related cancer mortality risk estimates among nuclear workers in Japan. This was demonstrated by a 64% ERR/Sv reduction for all cancers excluding leukaemia, and a 52% ERR/Sv reduction for lung cancer, although the reductions were not significant.

In our previous study [22], we examined adjustments for smoking by utilizing qualitative information on smoking, namely, smoking status (current, former, never, unknown) obtained from individuals who completed questionnaires distributed among Japanese nuclear workers. In the present study, we demonstrate the adjusting effects of smoking by utilizing quantitative
Table 2. ERR/Sv and 90% CI based on likelihood with and without adjustment for smoking by cause of death among Japanese nuclear workers.

| Causes of death | ICD10 codes | Observed Deaths | Without adjustment for smoking ERR/Sv | For smoking ERR/Sv |
|-----------------|-------------|-----------------|----------------------------------------|-------------------|
| All causes      | A00-Z99     | 3038            | 0.97 (0.23, 1.78)                       | 0.45 (−0.22, 1.19) |
| All diseases    | A00-R99     | 2635            | 1.32 (0.40, 2.34)                       | 0.77 (−0.08, 1.72) |
| All non-cancer diseases | A00-B99, D50-R99 | 1228 | 1.87 | 1.28 |
| All cancers     | C00-C97     | 1370            | 0.67 (−0.49, 2.00)                      | 0.16 (−0.90, 1.40) |
| All cancers excluding leukaemia except C91-C95 | C00-C97 | 1326 | 0.80 | 0.29 |
| Oesophageal     | C15         | 87              | 0.15 (−0.39, 2.19)                      | (−0.81, 1.57)     |
| Stomach         | C16         | 218             | 0.36 (−4.12, 4.42)                      | (−4.25, 3.71)     |
| Liver           | C22         | 138             | 4.78 (0.09, 11.68)                      | 3.89 (−0.46, 10.34) |
| Lung            | C33-C34     | 319             | 1.94                                  | 0.94 |
| Leukaemia excluding chronic lymphocytic leukaemia except C91.1 | C91-C95 | 44 | −1.95 (−5.80, 1.89) | (−5.68, 1.68) |
| Smoking-related cancers | C00-C16, C18-C22 | 430 | 1.65 | 1.16 |
| Nonsmoking-related cancers | C00-C15, C18-C22 | 322 | −0.60 | −0.76 |
| Smoking-related non-cancer diseases | C17-C21, C23-C24, C26-C29, C30.1-C30.9, C35-C63, C68-C80. | 624 | 1.39 | 0.79 |
| Nonsmoking-related non-cancer diseases | C17-C21, C23-C24, C26-C29, C30.1-C30.9, C35-C63, C68-C80. | 380 | 0.26 | −0.24 |
| Alcohol-related cancers | C00-C15, C18-C22 | 430 | −1.73 (−2.04, 2.25) | −2.00 (−2.85, 1.33) |
| External causes | V01-Y98     | 385             | −0.04 (−0.48, 4.40)                     | −0.62 (−0.84, 3.74) |

* Wald-based CI.
* Last estimate is denoted because the ERRs did not converge.
* Buccal and pharynx, oesophageal, stomach, liver, pancreas, nasal cavity, larynx, lung, bladder, kidney, ureter C00-C16, C22, C25, C30.0, C31-C34, C64-C67.
* All solid cancers other than smoking-related cancers C17-C21, C23-C24, C26-C29, C30.1-C30.9, C35-C63, C68-C80.
* Ischaemic heart disease, cerebrovascular disease, abdominal aortic aneurysm, pneumonia, chronic obstructive pulmonary disease, digestive ulcer I20-I25, I60-I69, I71.3, I71.4, J12-J18, J41-J44, K25-K27.
* Circulatory diseases, respiratory diseases and digestive diseases other than smoking-related non-cancers I00-I09, I26-I59, I70-I71.2, I71.5-I99, J00-J11, J19-J40, J45-J99, K00-K24, K28-K93.
* Buccal and pharynx, oesophageal, colorectum, liver.
information, namely, pack-year and years since the cessation of smoking (only among former smokers). In addition, we excluded those workers whose pack-years or years since stopping smoking was unknown. Table 3 summarizes the methods and results of a previous study and the present study. The decreasing effect of ERR/Sv, with an adjustment for smoking, was verified in both studies’ results. In the previous study, we could not distinguish whether a current smoker had a long or short period of smoking, so we thought that adjustment for smoking status included some uncertainty. We have now used smoking as a quantitative variable, namely pack-year and years since cessation of smoking (only among former smokers). Although the results of the present study were similar to those of the previous study, we could treat radiation and smoking as cumulative values in the present study.

The authors of INWORKS reported that the point estimate of ERR/Sv for solid cancers other than lung was similar to that obtained for solid cancers [3]. This implies confounding by smoking had very little effect in this study. The authors of the NRRW-3 study reported that some evidence of an increasing trend with dose from all circulatory diseases may, at least partly, be due to confounding by smoking [2]. Thus, the possibility of confounding by smoking depends on how much smoking is correlated with radiation dose; this varies from population to population. Our Japanese cohort showed a strong confounding effect of smoking [12, 13].

The ERR reduction after adjusting for smoking shows that mortality associated with radiation dose was confounded by smoking. Furthermore, the effects of ERR reduction when adjusted for smoking were larger for smoking-related cancers than nonsmoking-related cancers, supporting the conclusion that confounding effects of smoking exist among Japanese nuclear workers. Therefore, in order to mitigate the possible distortion of radiation risk,
adjustment for smoking is desirable whenever it is suspected that smoking might confound the relationship between mortality and radiation exposure. Although adjustment for smoking does have a greater effect on smoking-related non-cancers and cancers, it also has an effect on nonsmoking-related non-cancers and cancers.

In short, there is a possibility of either the effects of smoking not being fully accounted for or for further confounding by some factor(s) other than smoking.

Table 4 shows ERRs/Sv and 90% CIs for all cancers excluding leukaemia by dose category.

To examine the non-linearity of the dose-response relationship, we fitted quadratic and linear-quadratic models in addition to a linear model; we verified that these results indicated that a quadratic term was not necessary. The fits of the linear, quadratic, and linear-quadratic models were compared for all cancers excluding leukaemia. The quadratic model had a worse fit than the linear or linear-quadratic models. The linear-quadratic model did not show a significant difference in deviance compared to the linear model ($p = 0.108$). Comparing the estimated ERR at 100 mSv for all cancers excluding leukaemia for the linear and non-linear models, all models showed the effects of adjustment for smoking that reduced radiation risk estimates.

Furthermore, we also examined the model for all cancers, excluding leukaemia with effect modification for smoking as follows:

$$\lambda = \lambda_0(a, c, y, r, s)e^{\alpha_1 z_1 + \alpha_2 z_2 + \alpha_3 z_3}(1 + \beta d e^{\beta_1 z_1 + \beta_2 z_2 + \beta_3 z_3}).$$

The estimates of $\beta_1$, $\beta_2$, and $\beta_3$ were not significant, indicating that the model with effect modification by pack-years and years since cessation of smoking are not acceptable: $p$-values were >0.5 for $\beta_1$ and $\beta_2$ and 0.278 for $\beta_3$.

Therefore, we singled out the simple linear model because of the lack of evidence in the data for non-linearity; this made it possible to evaluate radiation dose risk in a way that was comparable with other studies. The results indicate that the ERR reduction supports the importance of adjustment for smoking.
The minimum latent period for all cancers excluding leukaemia is often taken set at 5 years. Therefore, sensitivity analyses were performed under 5- and 15-year lag assumptions for all cancers excluding leukaemia (table 6).

Before adjustment for smoking, the ERRs/Sv were 0.91 (−0.20, 2.22) and 0.86 (−0.45, 2.38), respectively, while after adjustment for smoking, the ERRs/Sv were 0.39 (−0.63, 1.59) and 0.38 (−0.84, 1.81), respectively. Thus, we could verify that adjustment for smoking could reduce ERRs/Sv when lag assumptions were 5, 10, or 15 years.

Sensitivity analyses of various dose assumptions below the limit of detection (0.05 and 0.1 mSv; see table 7) were also performed for all cancers excluding leukaemia. Before adjustment for smoking, the ERRs/Sv were 0.71 (−0.45, 2.06) and 0.58 (−0.54, 1.90), respectively. After adjustment for smoking, the ERRs/Sv were 0.24 (−0.83, 1.50) and 0.17 (−0.88, 1.41), respectively. Thus, adjustment for smoking showed a large decreasing effect for ERRs/Sv not only when doses below the limit of detection were assumed to be zero but also when assumed to be 0.05 or 0.1 mSv.

Some radiation epidemiology studies used stratification by duration of employment (DOE) to allow for a possible healthy worker survivor effect (HWSE) [1]. We have verified the HWSE by job category and found that it varies in each job category (data not shown). As a result, we think that adjusting for job category is necessary when adjusting for DOE. However, we cannot adjust for this due to a lack of job category information for more than half of the workers. We could only obtain job category information from the second questionnaire survey repliers, as these workers were employed for the longest period. Although some uncertainty was included in the analysis, we examined stratification by DOE (supplemental table 1 is available online at stacks.iop.org/JRP/38/357/mmedia). All causes of death except stomach cancer showed larger ERRs than no stratification by DOE, however, all

### Table 5. ERR at 100 mSv and a 90% CI for all cancers, excluding leukaemia, by linear and non-linear models among Japanese nuclear workers.

| Models               | Without adjustment | With adjustment |
|----------------------|--------------------|-----------------|
| Linear model         |                    |                 |
| ERR at 100 mSv       | 0.08               | 0.03            |
| 90% CI               | (−0.04, 0.22)      | (−0.08, 0.16)   |
| Quadratic model      |                    |                 |
| ERR at 100 mSv       | 0.01               | −0.01           |
| 90% CI               | (−0.05, 0.06)      | (−0.06, 0.04)   |
| Linear-quadratic model |                 |                 |
| ERR at 100 mSv       | 0.19               | 0.13            |
| 90% CI               | (−0.16, 0.54)      | (−0.11, 0.37)   |

*a Wald-based CI.

### Table 6. ERR/Sv and 90% CI for all cancers, excluding leukaemia, by various lag assumptions among Japanese nuclear workers.

| Lag   | Without adjustment | With adjustment |
|-------|--------------------|-----------------|
| 5 years | ERR/Sv            | 0.91            |
|        | 90% CI            | (−0.20, 2.22)   |
| 10 years | ERR/Sv           | 0.80            |
|        | 90% CI            | (−0.39, 2.19)   |
| 15 years | ERR/Sv           | 0.86            |
|        | 90% CI            | (−0.45, 2.38)   |

The minimum latent period for all cancers excluding leukaemia is often taken set at 5 years. Therefore, sensitivity analyses were performed under 5- and 15-year lag assumptions for all cancers excluding leukaemia (table 6).
causes of death showed a decreasing effect for ERRs by adjustment for smoking. When DOE was added to the adjusting variables, the ERR/Sv for all cancers, excluding leukaemia, was 1.55 (0.17, 3.20) before adjusting for smoking, and it decreased to 0.83 (−0.42, 2.32) after adjusting for smoking. When DOE was not added to the adjusting variables, the ERR/Sv for all cancers excluding leukaemia, was 0.80 (−0.39, 2.19) before adjusting for smoking, and it decreased to 0.29 (−0.81, 1.57) after adjusting for smoking. Increases to ERRs/Sv caused by adjustment for DOE were due to a reverse correlation; cumulative doses increased as DOE increases through the HWSE. In particular, liver cancer had a notable increase in regards to its ERR/Sv caused by adjustment for DOE. This was potentially caused by a strong HWSE; however, a conclusive reason is unclear.

Generally, Asian countries that have nuclear power plants show higher male smoking rates than INWORKS countries (USA, UK, France) [23]. So, the importance of adjustment for smoking was considered pressing in Asian countries, while in INWORKS countries, the importance of adjustment for smoking may be small, or at least smaller, although smoking patterns may have been different in the past. Nevertheless, the key point is the degree of correlation between smoking and radiation dose; this could be influenced by the fact that blue-collar workers are more likely than white-collar workers to smoke [24, 25]. The correlation of radiation dose with smoking in this study reflected the differences in smoking rates among job status groups; the group of workers who engaged in the maintenance or repair of nuclear reactor equipment—namely blue-collar workers—made up a higher proportion of the high-dose group and had higher smoking rates. Sterling et al reported the following strong pattern in smoking behaviour [24]: smoking is much more prevalent among occupational groups (and social strata) that also have greater exposure to hazards in the workplace, whereas it is much less prevalent among groups less exposed to these hazards. The positive correlation of radiation dose with smoking shown in this study might be at least partly attributable to the fact that blue-collar workers are more likely to smoke. In addition, the group of workers who had comparatively fewer years of education made up a higher proportion of the high-dose group and had higher smoking rates.

Murata et al reported that heavy consumption of alcohol was related to radiation exposure [12]. Their cohort consisted of repliers to the first questionnaire survey, namely, 48 281 workers. Akiba and Mizuno found a highly significant trend of alcohol-related cancers with cumulative doses in the Japanese nuclear worker cohort and suggested confounding by alcohol by the fact that the ERR/Sv for all cancers, excluding leukaemia, decreased from 1.26 (95% CI: −0.27, 3.00) to 0.20 (−1.42, 2.09) when alcohol-related cancers were excluded [26]. Their cohort was 200 583 workers, including repliers to the first and second questionnaire surveys and followed through 2002. However, the correlation between radiation

| Dose assumptions below the limit of detection, mSv | Without adjustment | With adjustment |
|-----------------------------------------------|-------------------|----------------|
| 0 ERR/Sv                                      | 0.80 (−0.39, 2.19) | 0.29 (−0.81, 1.57) |
| 0.05 ERR/Sv                                   | 0.71 (−0.45, 2.06) | 0.24 (−0.83, 1.50) |
| 0.1 ERR/Sv                                    | 0.58 (−0.54, 1.90) | 0.17 (−0.88, 1.41) |
dose and alcohol consumption was not found in the present study. The ERR/Sv for alcohol-related cancers was 1.65 (−0.48, 4.40) before adjustment for alcohol, and after adjustment for alcohol, the ERR/Sv was 1.63 (−0.50, 4.37). Therefore, the ERR/Sv after adjusting for alcohol was similar to what was obtained without adjusting for alcohol. The cohort of the present study consisted of repliers to the first and second questionnaire surveys, namely, 71,733 workers were followed through 2010. Concerning the quality of information of the questionnaire, the response rate was 69.5%. Within the group that answered both surveys, those who answered with the same smoking status was 83%, and those who showed discrepant answers, such as ‘current smoker’ in the first survey and ‘never smoker’ in the second survey, was 0.6%. Considering the reasonable quality of information, the divergence in results between these studies was likely to be caused by differences in both the cohorts and the follow-up periods. Almost all alcohol-related cancers are also smoking-related cancers, so an ERR/Sv reduction after adjustment for smoking was shown in alcohol-related cancers (table 2).

After adjusting for smoking, the ERR/Sv of liver cancer showed a smaller decrease than other causes of death, suggesting the existence of other factors, such as the contribution of the hepatitis virus, or that radiation itself may increase mortality outcomes in liver cancer or that the observed increase in liver cancer risk may be caused by chance. However, the results of similar studies in other countries show no significant increase in liver cancer with radiation dose [1, 2, 27]. A third lifestyle questionnaire survey is now underway and includes questions about individuals’ medical history of hepatitis virus, cirrhosis, and liver cancer. We will be able to obtain more information about confounding factors by using this survey. The results of this survey may produce a firmer conclusion in our study.

External causes also showed a decrease in ERR/Sv after adjusting for smoking. One half of external causes was made up of suicide, and smoking is a known marker of depression [28, 29]. The ERR/Sv reduction for external causes might be caused by a correlation between smoking and suicide due to depression. We have tried to verify whether the ERR/Sv for suicide decreases by adjusting for smoking or not; however, the ERR/Sv for suicide did not converge.

**Conclusion**

We adjusted for smoking directly and quantified the confounding effects of smoking on radiation risks among Japanese nuclear workers. Thus, smoking was shown to have a large effect in estimating radiation risks, especially with regard to smoking-related cancers. But the adjustment for smoking might not fully account for the confounding effect of smoking, and other confounders may still be present.

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