A Risk Comparison between Lifestyle, Socioeconomic Status, and Radiation: A Cohort Study of Cancer Mortality among Japanese Nuclear Workers (J-EPISODE)

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Abstract—The health effects of low-dose radiation exposure have been a source of controversy. One possible reason is that epidemiological studies that compare radiation risk with other factors, such as lifestyle or socioeconomic status, have been limited. The aim of this study is to conduct a comparison of the cancer risk of mortality as lifestyle or socioeconomic status, and radiation. We assembled a cohort of 41,742 male nuclear workers in Japan who answered a lifestyle questionnaire survey conducted during 2003–2004. To exclude systematic errors caused by missing values, we used multiple imputation and Poisson regression to estimate relative risks and confidence intervals for lifestyle habits, socioeconomic status, and radiation. The total person-y from 2005 to 2010 were 215,000. The mean age and cumulative dose were 54.9 y and 24.8 mSv (10-y lagged dose), respectively. Significantly high relative risks were determined for smoking, alcohol consumption, frequency of medical examination, breakfast intake, sleep, and body mass index. Further, significantly high relative risks of radiation were shown for lung cancer and smoking-related cancers. Since the simultaneous inclusion of radiation and non-radiation variables in the model for relative risk (RR) calculation means that the calculated radiation RR is the result of adjustment by other variables, the risk of cancer from low-dose radiation, if any, is less than smoking and probably less than other lifestyle factors. 

INTRODUCTION

The health effects of high-dose radiation were made visible by studies on atomic bomb survivors (Pierce et al. 1996; Preston et al. 2003; Ozasa et al. 2012). While several studies have been carried out (Kudo et al. 2018a and b; Haylock et al. 2018; Leuraud et al. 2015; Richardson et al. 2015), consensus on the health effects of low-dose radiation has not been established. This suggests that if they exist, these effects are difficult to detect because they are probably less than the risks due to lifestyle or socioeconomic status. However, there is considerable anxiety among the public about the health effects of low-dose radiation, especially after the accident at the Fukushima Daiichi Nuclear Power Plant, and it is often discussed in the context of whether radiation risks exist or not. However, to understand this, a comparison with other lifestyle or socioeconomic factors could be informative. While some studies have reported the results of risk comparisons between radiation and smoking (Cahoon et al. 2017; Kreisheimer et al. 2003; Kudo et al. 2020; Gilbert et al. 2013), those between lifestyle, socioeconomic status, and radiation for individual causes of death remain limited.

Moreover, a cohort study of cancer mortality among Japanese nuclear workers in an epidemiological study on low-dose radiation effects (J-EPISODE: Japanese epidemiological study on low-dose radiation effects) has been conducted since 1990 by the Radiation Effects Association (REA). Information on lifestyle or socioeconomic status was obtained by a questionnaire survey for a part of the cohort, which consisted of 41,742 participants. However, there was some missing data (from 1 to 12% depending on the questions) in their responses. Thus, if a complete case analysis is done, the cohort will be reduced by 25%. In this case, a single imputation or complete case analysis revealed that the results were biased when the missing data did not occur completely at random. One of the solutions was multiple imputation (Rubin 1987; Rubin and Schenker 1991). We have previously compared the risk between death due to radiation and death due to smoking (Kudo et al. 2020). In the
present study, the variables for comparing risk are expanded to compare the risk of cancer death among more factors.

Thus, the aim of this study is to examine the comparison of mortality between lifestyle, socioeconomic status, and radiation for grouped cancers and site-specific cancers. This is accomplished by the simultaneous derivation of relative risks from one cohort by multiple imputation and Poisson regression.

MATERIALS AND METHODS

Ethical approval

The study protocol was based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Japanese Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare (MHLW).

Cohort definition and follow-up of vital status

The present study, J-EPISODE, is a prospective cohort study, and its endpoint was death. To this end, a mortality follow-up was carried out on those workers of Japanese nationality who were registered in the Radiation Dose Registry Center (RADREC) within the REA as of the end of March 1999.

To ascertain workers’ vital status, copies of the residence registration cards (RRCs) were acquired from local government offices. These copies were issued when subjects were alive, and those of deleted RRCs, including death dates or new addresses, were issued when subjects were deceased or had moved away. Obtaining the informed consent of those included in the cohort was performed from 2007 to 2009. The refusal rate was approximately 7%. For those whose data we obtained but who later refused to participate, we ceased all follow-up efforts, and their observed period was censored on the last day on which their vital statuses were known.

To identify the causes of death among deceased participants, linkage with death records was approved for use and provided by MHLW. These records can almost completely ascertain the causes of death because they are based on the national registry. Indices used for record linkage were date of birth, date of death, sex, and municipality code of residence (Iwasaki et al. 2000). In the end, we were able to identify the cause of death for 99.5% of the subjects. The underlying causes of death were coded according to the International Classification of Diseases (ICD), 10th revision. For each variable: smoking [pack-years (pack-y)], alcohol consumption (ethanol in g d⁻¹), health consciousness, frequency of medical examination, breakfast intake, sleep, body mass index (BMI), job category, position, years of education, and cumulative radiation dose. To compare with other studies, smoking was quantified as the total amount of smoking in pack-y for current smokers, while alcohol consumption was quantified as ethanol in g d⁻¹ for current drinkers. The pack-y were defined as follows: the number of cigarettes per day × (1 pack/20 cigarettes) × the number of years between the age at which the individual started to smoke and the age on the survey date. RR of current smokers were estimated by pack-y and defined against never smokers (those with 0 pack-y). In the case of former smokers, the mortality rate differs depending on the years since cessation of smoking. Because the model would be complicated if this was taken into account, the RR of former smokers were not estimated by pack-y but estimated as

Dosimetry

The dose records were supplied by RADREC. Personal dose equivalent $H_p(10)$, which is the operational quantity of effective dose obtained from dosimeter readings, was used in the risk analysis. Here, the effective dose was the sum of the external and internal doses by fiscal year (from April to March of the next year). Moreover, external doses consisted of photons and neutrons. The photon doses were the external exposure records of equivalent doses at a tissue depth of 10 mm [$H_p(10)$]. In cases where neutron and internal doses were positively detected, they were added to external doses. However, such a case is so rare in Japan under routine nuclear work during normal operation, periodic inspections, and maintenance that those doses have little impact on the analysis.

The annual radiation exposure for each worker was calculated by adding doses from all facilities where they worked in a given year. Exposures below the detectable level were set as 0 mSv in the analysis. The present study covers radiation dose records from 1957—when the use of nuclear energy began in Japan—to the end of 2010, which was set as the censored date of the observation period.

Lifestyle questionnaire survey

To examine factors potentially confounding the risk assessment of nuclear workers, a lifestyle questionnaire survey was conducted from September 2003 to March 2004. It was given to a sample of male workers who were 40 y old or more as of 1 July 2003. The questionnaire was self-administered and included questions about lifestyle and socioeconomic status factors such as smoking, job category, years of education, and so on. The questionnaire was distributed by postal mail to all workers exposed to 10 mSv or higher radiation levels as of 31 March 2002, while 40% of workers with less than 10 mSv were sampled. However, the questionnaire was not distributed to female workers because the numbers of deceased females were too small to analyze (approximately 20). Therefore, female workers were excluded from the analysis, and questionnaires were distributed to 78,064 male workers.

Variables used for estimation of relative risks

The aim of this study was to estimate relative risk (RR) for each variable: smoking [pack-years (pack-y)], alcohol consumption (ethanol in g d⁻¹), health consciousness, frequency of medical examination, breakfast intake, sleep, body mass index (BMI), job category, position, years of education, and cumulative radiation dose. To compare with other studies, smoking was quantified as the total amount of smoking in pack-y for current smokers, while alcohol consumption was quantified as ethanol in g d⁻¹ for current drinkers. The pack-y were defined as follows: the number of cigarettes per day × (1 pack/20 cigarettes) × the number of years between the age at which the individual started to smoke and the age on the survey date. RR of current smokers were estimated by pack-y and defined against never smokers (those with 0 pack-y). In the case of former smokers, the mortality rate differs depending on the years since cessation of smoking. Because the model would be complicated if this was taken into account, the RR of former smokers were not estimated by pack-y but estimated as
one former-smoker group against a group of never smokers. Meanwhile, ethanol in g d$^{-1}$ was calculated by the type of liquor and frequency of drinking for current drinkers. RRs of current drinkers were estimated by ethanol in g d$^{-1}$ against never drinkers (ethanol = 0 g d$^{-1}$). RRs of former drinkers were estimated as one former-drinker group against that of never drinkers. Finally, BMI was defined as an individual’s weight (kg) divided by the square of height (m).

### Causes of death

The causes of death for which RRs were estimated included all cancers excluding leukemia (hereafter “all cancers”) (ICD10: C00–C90, C96–C97). Other causes included stomach cancer (C16), liver cancer (C22), colorectal cancer (C18–C21), lung cancer (C33–C34), smoking-related cancers (C00–C16, C22, C25, C30.0, C31–C34, C64–C67), and non-smoking-related cancers (C17–C21, C23–C24, C26–C29, C30.1–C30.9, C35–C63, C68–C80).

### Multiple imputation

There were missing values in the answers to the lifestyle questionnaire. However, as they were not considered as missing completely at random, it was thought that the single imputation analysis or complete case analysis would be biased. Therefore, a multiple imputation method was adopted in three stages (Rubin 1987; Rubin and Schenker 1991) as shown below.

#### Imputation stage

A fully conditional specification was used for the imputation algorithm (SAS 2016). More specifically, conditional on the observed portion of the variable that contains missing data and the variable that does not contain missing data, an imputation model was constructed for each variable. Nominal variables—smoking status, alcohol consumption status, job category, and position—were based on discriminant function. Ordinal variables—health consciousness, frequency of medical examination, breakfast intake, sleep, and years of education—were based on ordinal logistic regression. Continuous variables—BMI, pack-y, and ethanol in g d$^{-1}$—were based on linear regression. Meanwhile, radiation doses from RADREC had no missing data. The following auxiliary variables without any missing data were included in the model to make the missing-at-random assumption more plausible: age at the time of the survey, number of sites where a worker has worked, the latest prefecture code that verified a worker’s survival status, year of first exposure to radiation, and year of latest exposure to radiation. Further, indicators of death by all cancers were also added to the auxiliary variables as the endpoint.

An example of the imputation model of $x_1$ and $x_2$ when $x_1$ (e.g., pack-y) and $x_2$ (e.g., alcohol consumption) are missing is shown below:

$$x_1 = \beta_0 + \beta_1 x_2 + \beta_3 x_3 + \ldots + \beta_7 x_1 + \varepsilon,$$

where $x_1, \ldots, x_7$ are the variables mentioned above, $\beta_1, \ldots, \beta_7$ are the parameters, $\beta_0$ is the intercept, and $\varepsilon$ is the error term. When imputing $x_1$, $x_2$ is assigned by random sample from observed values as an initial value. Missing variable $x_1$ is estimated by the imputation model conditional on the other variables. When imputing $x_2$, the estimated parameters $\beta_1$ and $x_1$ are used as the condition for the imputation model.

This process of estimating the parameters and the imputed values is repeated a certain number of times. However, the values at the beginning of the repeating process are discarded as “burn-in” because they may be affected by the initial value. In this way, multiple data sets (called pseudo-complete data sets) with imputed missing data are created. The number of burn-in was 100, and the created number of pseudo-complete data sets was 30 in this analysis. The MI procedure by SAS was used for imputation (SAS 2014, 2016).

#### Estimation stage

The entry date for person-year (person-y) calculations was set 2 y after the date of response to the questionnaire to prevent any health conditions at that time from affecting the analysis (Goodman et al. 1995). The exit date of the person-y calculation was set as whichever of the following was the earliest: (a) the date of the latest confirmation of vital status, (b) the date of death, or (c) 31 December 2010. Therefore, individual workers’ observation periods differed, but they were within 2005 to 2010.

Next, to select a model for risk comparison, we examined the joint effect of smoking and radiation with reference to the studies of atomic bomb survivors (Pierce et al. 2003; Furukawa et al. 2010; Grant et al. 2017; Cahioun et al. 2017). The target cause of death was lung cancer, and the following Poisson regression models were used:

$$\lambda = \lambda_0(a, r) \exp(q a)(1 + \beta_1 \cdot \text{Smoke} + \beta_2 \cdot \text{Radiation} + \gamma \cdot \text{Smoke} \cdot \text{Radiation}),$$

where $\lambda$ is the death rate, and $\lambda_0$ is the background death rate [stratified by $a$: 5-y attained age categories (20–, 25–, ... and 100+); and $r$: residence, which is divided into eight regional categories within Japan (Kudo et al. 2018a and bb)]. Meanwhile, $q$ is an indicator of a former smoker ($q = 1$ = former smoker, 0 = current and never smoker), and $a$ is a coefficient of $q$. However, calendar periods were not adjusted because the observation period was short (2005–2010). Meanwhile, “Smoke” refers to the pack-y for current smokers, and “Radiation” is the cumulative radiation dose. The unit of pack-y was 20 pack-y, and the unit of radiation was 100 mSv. Therefore, $\beta_1$ represents the smoking ERR per 20 pack-y, and $\beta_2$ represents the radiation ERR per 100 mSv. Here, it is worth noting that if the interaction term $\gamma$ is significant, the joint effect of smoking and radiation is multiplicative; if not, it is additive. As a result of the
analysis, smoking was significant, radiation was not, and the interaction term was not significant (data not shown), suggesting that the joint effect is additive. Additionally, the simple additive model (2), simple multiplicative model (3), generalized additive model (4), and generalized multiplicative model (5) were used:

\[
\lambda = \lambda_0(a, r) \exp(\alpha q)(1 + \beta_1\text{Smoke} + \beta_2\text{Radiation}) \quad (2)
\]

\[
\lambda = \lambda_0(a, r) \exp(\alpha q)(1 + \beta_1\text{Smoke})(1 + \beta_2\text{Radiation}) \quad (3)
\]

\[
\lambda = \lambda_0(a, r) \exp(\alpha q)(1 + \beta_1\text{Smoke} + \beta_2\text{Smoke} \cdot \text{Radiation}) \quad (4)
\]

\[
\lambda = \lambda_0(a, r) \exp(\alpha q)(1 + \beta_1\text{Smoke})(1 + \beta_2\text{Smoke} \cdot \text{Radiation}). \quad (5)
\]

The results were mostly consistent with the common finding that smoking risk (\(\beta_2\)) was significantly high, but radiation risk (\(\beta_3\)) was not significant (Supplementary Table 1, http://links.lww.com/HP/A213). Since radiation was not significant, risk comparison seemed acceptable in both additive and multiplicative models, but when all 11 variables that are used for the estimation of relative risks as described in the above section were included in the model, the multiplicative model did not converge. Consequently, the multiplicative model, which is easy to fit, was used in the following analysis.

Poisson regression was also used to quantify the RRs of lifestyle, socioeconomic status, and radiation based on the number of deaths and person-y after stratification according to the 5-year attained age categories and residence. Here, cumulative dose and attained age were treated as time-dependent variables. The former was lagged 10 y (Gilbert et al. 2013; Haylock et al. 2018; Kreisheimer et al. 2003; Kudo et al. 2018a, 2020; Richardson et al. 2015) and updated every month on the assumption that annual doses were distributed uniformly over each year. The model used to estimate relative risks was a log linear model, which implies multiplicative joint effects:

\[
\lambda = \lambda_0(a, r) \exp(\beta_1z_1 + \ldots + \beta_{11}z_{11}), \quad (6)
\]

where \(z_{1-11}\) represent the variables that were used to estimate RRs. More specifically, \(z_1\) was smoking (pack-y) defined as 0 (never smoker, reference; hereafter simply ref), former smoker, >0 (current smoker), 20– (current smoker), 40– (current smoker), and 60+ (current smoker). Former smoker was considered to be one category. Next, \(z_2\) was alcohol consumption (ethanol in g d\(^{-1}\)) defined as 0 (never drinker, ref), former drinker, >0 (current drinker), 20– (current drinker), 40– (current drinker), and 60+ (current drinker). The former drinker was considered to be one category for the same reason as for the smokers mentioned above. \(z_3\) was health consciousness defined as good (ref), medium, and bad. \(z_4\) was frequency of medical examination defined as every year (ref), sometimes, and almost never. \(z_5\) was breakfast intake defined as every day (ref), sometimes, and almost never. \(z_6\) was sleep defined as well (ref), sometimes not well, and not well. \(z_7\) was BMI defined as <18.5, 18.5– (ref), 25–, and 30+. \(z_8\) was job category defined as design and research (ref), technical advisor, group leader, and staff. \(z_{10}\) was years of education defined as 13+ (ref), 10–12, and <10. Finally, \(z_{11}\) was the cumulative radiation dose assuming a 10-y lag defined as <5 (ref), 5–, 10–20–, 20–, 50+, and 100+.

Meanwhile, \(\beta_1\) represent the coefficient–relative risk against these 11 reference categories, and 95% confidence intervals described below in the integration stage were calculated. The person-y table was created by DATAB, and the models were fitted by AMPIT. Both were EPICURE modules (EPICURE 2008).

**Integration stage.** Using the point estimates and variances for each RR calculated from the 30 pseudo-complete data sets described in the (1) imputation stage, we calculated the integrated point estimates, and 95% confidence intervals (CIs) of each variable and category were integrated by Rubin’s method (Rubin 1987; Rubin and Schenker 1991) as shown below.

**Integrated relative risk**

\[
\theta = \frac{1}{D} \sum_{d=1}^{D} \hat{\theta}_d,
\]

where \(D\) is the number of pseudo-complete data sets (30 in this analysis), and \(\hat{\theta}_d\) is the relative risk in each pseudo-complete data set. Thus, \(\theta\) is the integrated relative risk—the arithmetic mean of the relative risks of pseudo-complete data sets.

**Integrated variance:**

\[
T = W + \frac{D + 1}{D}B
\]

\[
W = \frac{1}{D} \sum_{d=1}^{D} W_d
\]
Table 1. Number of subjects by each category of items among Japanese nuclear workers.

| Items                  | Category           | Not imputed | PCD #1 | Complete case |
|------------------------|--------------------|-------------|--------|---------------|
| **Smoking**            | 0 (Never, ref)     | 41742 (100%)| 41742 (100%) | 31800 (100%) |
| (Pack-y)               | Former smoker      | 12555 (30%) | 12975 (31%) | 9802 (31%)   |
|                        | >0                 | 2134 (5%)   | 2159 (5%)   | 1733 (5%)    |
|                        | 20−                | 9595 (23%)  | 9864 (24%)  | 7635 (24%)   |
|                        | 40−                | 5508 (13%)  | 5728 (14%)  | 4130 (13%)   |
|                        | 60+                | 2197 (5%)   | 2226 (5%)   | 1611 (5%)    |
|                       | Unknown            | 1259 (3%)   |          |              |
| **Alcohol consumption**| 0 (Never, ref)     | 6450 (15%)  | 7083 (17%) | 5216 (16%)   |
| [Ethanol / day (g)]    | Former drinker     | 2660 (6%)   | 2885 (7%)  | 1808 (6%)    |
|                        | >0                 | 14881 (36%) | 15563 (37%) | 12591 (40%)  |
|                        | 20−                | 6715 (16%)  | 7624 (18%)  | 5725 (18%)   |
|                        | 40−                | 3605 (9%)   | 4209 (10%)  | 3100 (10%)   |
|                        | 60+                | 4129 (10%)  | 4378 (10%)  | 3360 (11%)   |
|                       | Unknown            | 3302 (8%)   |          |              |
| **Health consciousness**| Good (ref)        | 12690 (30%) | 12884 (31%) | 9521 (30%)   |
|                       | Medium             | 26070 (62%) | 26426 (63%) | 20428 (64%)  |
|                       | Bad                | 2399 (6%)   | 2432 (6%)  | 1851 (6%)    |
|                       | Unknown            | 583 (1%)    |          |              |
| **Frequency of medical examination** | Every year (ref) | 33645 (81%) | 34009 (81%) | 26796 (84%)  |
|                        | Sometimes          | 4865 (12%)  | 4951 (12%)  | 3276 (10%)   |
|                        | Almost never       | 2742 (7%)   | 2782 (7%)  | 1728 (5%)    |
|                       | Unknown            | 490 (1%)    |          |              |
| **Breakfast intake**   | Every day (ref)    | 34854 (83%) | 35159 (84%) | 26748 (84%)  |
|                        | Sometimes          | 4044 (10%)  | 4069 (10%)  | 3061 (10%)   |
|                        | Almost never       | 2499 (6%)   | 2514 (6%)  | 1991 (6%)    |
|                       | Unknown            | 345 (1%)    |          |              |
| **Sleep**              | Well (ref)         | 24607 (59%) | 24906 (60%) | 19216 (60%)  |
|                        | Sometimes not well | 15211 (36%) | 15389 (37%) | 11580 (36%)  |
|                        | Not well           | 1436 (3%)   | 1447 (3%)  | 1004 (3%)    |
|                       | Unknown            | 488 (1%)    |          |              |
| **BMI**                | <18.5              | 1125 (3%)   | 1150 (3%)  | 782 (2%)     |
|                        | 18.5− < 25 (ref)   | 28872 (69%) | 29104 (70%) | 22125 (70%)  |
|                        | 25−                | 10496 (25%) | 10596 (25%) | 8227 (26%)   |
|                        | 30+                | 885 (2%)    | 892 (2%)   | 666 (2%)     |
|                       | Unknown            | 364 (1%)    |          |              |
| **Job category**       | Design & research (ref) | 3888 (9%) | 4064 (10%) | 3431 (11%)  |
|                        | Radiological management | 8034 (19%) | 8379 (20%) | 7170 (23%)  |
|                        | Operation & investigation | 5565 (13%) | 5837 (14%) | 4733 (15%)  |
|                        | Maintenance        | 21800 (52%) | 23462 (56%) | 16466 (52%)  |
|                       | Unknown            | 2455 (6%)   |          |              |
| **Position**           | Management (ref)   | 9945 (24%)  | 10535 (25%) | 8956 (28%)   |
|                        | Technical advisor  | 3940 (9%)   | 4361 (10%)  | 3358 (11%)   |
|                        | Group leader       | 10201 (24%) | 12201 (29%) | 8434 (27%)   |
|                        | Staff              | 12708 (30%) | 14645 (35%) | 11052 (35%)  |
|                       | Unknown            | 4948 (12%)  |          |              |
| **Years of education**| 13+ years (ref)    | 12925 (31%) | 13195 (32%) | 11277 (35%)  |
|                        | 10−12 years        | 18940 (45%) | 19670 (47%) | 15416 (48%)  |
|                        | <10 years          | 8236 (20%)  | 8877 (21%)  | 5107 (16%)   |
|                       | Unknown            | 1641 (4%)   |          |              |
| **Radiation**          | <5 mSv (ref)       | 20353 (49%) | 20353 (49%) | 15435 (49%)  |

Continued next page
B = \frac{1}{D-1} \sum_{d=1}^{D} (\bar{\theta}_d - \bar{\theta}_D)^2 ,

where \( T \) is the integrated variance, \( W_d \) is the variance of each pseudo-complete data set, and \( \bar{\theta}_D \) is the arithmetic mean of relative risks of pseudo-complete data sets. These integrated relative risks and variances were calculated using the MIANALYZE procedure by SAS (SAS 2014, 2016).

Comparison with complete case analysis

There were 31,800 workers who responded to all the variables for calculating the relative risk. A complete case analysis was conducted against these respondents to compare with the results based on the multiple imputation for all cancers.

RESULTS

The process of cohort construction is depicted in Fig. 1. The lifestyle questionnaires were distributed to 78,064 workers. Of these, 45,905 workers replied, while the others were in unknown destinations and/or did not reply. In addition, the following were excluded: 1) unable to be identified in RADREC; 2) no answers written in the questionnaire; and 3) no follow-up period, such as those who moved or were deceased before the entry date of the follow-up (September 1, 2005). The remaining 41,742 workers were set as the cohort. Accumulated person-y were 215,000 through 2005 to 2010. The mean age and mean cumulative dose at the date of survey were 54.9 y and 24.8 mSv (10-y-lagged dose), respectively, while the mean duration of employment was 9.9 y. Table 1 shows the number of subjects by each variable before multiple imputation, after imputation (pseudo-complete data set #1), and a complete case analysis. The subjects who were in the unknown category were distributed to other categories by multiple imputation. Therefore, the number of subjects varied by each category and pseudo-complete data sets. Detailed numbers on the subjects are provided in Supplementary Table 2, http://links.lww.com/HP/A214.

Meanwhile, Fig. 2 shows the relative risks and 95% CIs by each cause of death and category of items. More specifically, significantly increasing RRIs of all cancers, stomach cancer, liver cancer, lung cancer, and smoking-related cancers for smoking were seen (Panels A, B, C, E, and F). In these causes of death, dose responses—namely, as pack-y increased, RRs of smoking also increased—were also shown. Additionally, significantly increasing RRs of all cancers, liver cancer, colorectal cancer, and smoking-related cancers for alcohol consumption were seen (Panels A, C, D, and F). However, no significantly increasing RRs for health consciousness were seen. Moreover, significantly increasing RRs of all cancers, smoking-related cancers, and non-smoking-related cancers for frequency of medical examination were seen (Panels A, F, and G). Further, dose responses were seen in all cancers and smoking-related cancers (Panel A, F). Significantly increasing RRs of stomach cancer, colorectal cancer, and non-smoking-related cancers for breakfast intake were seen (Panels B, D, and G). The same was seen with that of liver cancer for sleep (Panel C) and all cancers for BMI (Panel A). However, there were no significantly increasing RRs for job category, position, and years of education. Significantly increasing RRs of lung cancer and smoking-related cancers for radiation were seen (Panel E, F). Finally, detailed relative risks and 95% CIs by each cause of death and category of items are described in Supplementary Table 3, http://links.lww.com/HP/A215. Results from the complete case analysis were different from those that were imputed (Table 2).

DISCUSSION

Principal findings

In this study, direct risk comparisons between lifestyle, socioeconomic status, radiation, and cancer mortality were examined. Lifestyle factors such as smoking, alcohol consumption, frequency of medical examination, breakfast intake, sleep, and BMI showed significantly increasing RRs. In particular, smoking showed greater RRs than other factors. In contrast, socioeconomic factors—such as job category, position, and years of education—showed no evidence of risk.
Fig. 2. Relative risks and 95% CIs by lifestyle, socioeconomic status, and radiation among Japanese nuclear workers.
Significantly increasing RRs of lung cancer and smoking-related cancers for radiation were also seen. The RR of category 5 mSv was 2.10 (95% CI: 1.34, 3.29), and the RR of category 50 mSv was 1.61 (1.03, 2.51) for lung cancer. These point estimates were larger than the RR for factors other than smoking but smaller than the RR for smoking—especially significantly lower than that for the 40 pack-y and over. Meanwhile, the RR of category 5 mSv was 1.35 (1.02, 1.80)

Table 2. Relative risks and 95% CIs for each category of items by imputed and complete case analysis for all cancers excluding leukemia among Japanese nuclear workers.

| Items                        | Category | Imputed RR (95%CI) | Complete case analysis RR (95%CI) |
|------------------------------|----------|--------------------|----------------------------------|
| Smoking (Pack-y)             | 0 (Never, ref) | 1.00               | 1.00                             |
|                              | Former smoker | 1.51 (1.22–1.86)   | 1.41 (1.14–1.76)                 |
|                              | >0         | 1.66 (1.11–2.50)   | 1.43 (0.92–2.23)                 |
|                              | 20–        | 1.95 (1.53–2.49)   | 1.93 (1.50–2.47)                 |
|                              | 40–        | 1.95 (1.53–2.50)   | 1.79 (1.39–2.30)                 |
|                              | 60+        | 2.71 (2.05–3.57)   | 2.70 (2.04–3.58)                 |
| Alcohol consumption          | 0 (Never, ref) | 1.00               | 1.00                             |
|                              | Former drinker | 1.51 (1.20–1.91)   | 1.94 (1.51–2.50)                 |
|                              | >0         | 0.90 (0.74–1.11)   | 1.07 (0.86–1.33)                 |
|                              | 20–        | 1.18 (0.93–1.49)   | 1.34 (1.05–1.71)                 |
|                              | 40–        | 1.19 (0.89–1.59)   | 1.35 (1.01–1.81)                 |
|                              | 60+        | 1.30 (1.01–1.68)   | 1.52 (1.17–1.97)                 |
| Health consciousness         | Good (ref) | 1.00               | 1.00                             |
|                              | Medium     | 1.08 (0.94–1.24)   | 1.19 (1.02–1.38)                 |
|                              | Bad        | 0.99 (0.72–1.35)   | 1.10 (0.79–1.54)                 |
| Frequency of medical examination | Every year (ref) | 1.00               | 1.00                             |
|                              | Sometimes  | 1.19 (1.01–1.41)   | 1.20 (1.00–1.43)                 |
|                              | Almost never | 1.26 (1.02–1.55)   | 1.37 (1.10–1.70)                 |
| Breakfast intake             | Every day (ref) | 1.00               | 1.00                             |
|                              | Sometimes  | 0.92 (0.71–1.18)   | 0.88 (0.67–1.16)                 |
|                              | Almost never | 1.21 (0.89–1.65)   | 1.35 (0.99–1.82)                 |
| Sleep                        | Well (ref) | 1.00               | 1.00                             |
|                              | Sometimes not well | 1.06 (0.93–1.21)   | 1.05 (0.92–1.21)                 |
|                              | Not well   | 0.93 (0.66–1.30)   | 0.94 (0.65–1.36)                 |
| BMI                          | <18.5      | 1.34 (1.01–1.77)   | 1.10 (0.78–1.55)                 |
|                              | 18.5–25 (ref) | 1.00               | 1.00                             |
|                              | 25–        | 0.94 (0.80–1.10)   | 0.95 (0.81–1.12)                 |
|                              | 30+        | 0.91 (0.54–1.55)   | 1.03 (0.59–1.79)                 |
| Job category                 | Design & research (ref) | 1.00               | 1.00                             |
|                              | Radiological management | 0.99 (0.74–1.32)   | 0.96 (0.73–1.26)                 |
|                              | Operation & investigation | 0.97 (0.70–1.34)   | 0.97 (0.71–1.32)                 |
|                              | Maintenance | 1.01 (0.77–1.34)   | 1.05 (0.81–1.36)                 |
| Position                     | Management (ref) | 1.00               | 1.00                             |
|                              | Technical advisor | 0.96 (0.72–1.27)   | 1.01 (0.78–1.31)                 |
|                              | Group leader | 1.19 (0.94–1.50)   | 1.14 (0.92–1.42)                 |
|                              | Staff      | 1.07 (0.86–1.33)   | 1.02 (0.83–1.25)                 |
| Years of education           | 13+ years (ref) | 1.00               | 1.00                             |
|                              | 10–12 years | 1.14 (0.94–1.37)   | 1.11 (0.93–1.33)                 |
|                              | <10 years  | 1.16 (0.94–1.42)   | 1.23 (1.00–1.50)                 |
| Radiation (Cumulative dose)  | <5 mSv (ref) | 1.00               | 1.00                             |
|                              | 5–50 mSv   | 1.25 (0.98–1.59)   | 1.04 (0.78–1.38)                 |
|                              | 10–20 mSv  | 1.03 (0.85–1.24)   | 1.03 (0.84–1.25)                 |
|                              | 20+ mSv    | 1.08 (0.90–1.29)   | 0.99 (0.81–1.20)                 |
|                              | 50+ mSv    | 1.24 (0.996–1.55)  | 1.20 (0.95–1.52)                 |
|                              | 100+ mSv   | 0.89 (0.65–1.20)   | 0.76 (0.55–1.06)                 |

aReference category.
and the RR of category 50 mSv was 1.32 (1.02, 1.71) for smoking-related cancer. These point estimates were larger than the RR for factors other than smoking and alcohol consumption but smaller than the RR for smoking, the category of former drinker, and 60+ category of ethanol consumption—especially significantly lower than that for ≥40 pack-y of smoking. Here, the comparison of radiation and smoking risk is unit-dependent, but these results suggest that the radiation risk, if any, is less than that of smoking. Further, our previous analysis comparing the risks of radiation and smoking in a larger cohort suggested that the radiation risk, if any, was less than the smoking risk (Kudo 2020). The present results are similar in this respect.

However, the results from complete case analyses were different from the imputed results to some extent. This probably reflected the fact that the multiple imputation was thought to be less biased than the non-imputed or complete case analysis. In addition, multiple imputation, which included auxiliary variables, made the assumption of missing-at-random more plausible and improved the precision of the analysis (Rubin 1987; SAS 2014).

Table 3 provides information on the observed and excess deaths of smoking and radiation by dose category and pack-y category for lung cancer and smoking-related cancers based on the pseudo complete data set #1 among Japanese nuclear workers. The model was a linear and multiplicative joint effect of smoking and radiation as follows:

$$\lambda = \lambda_0 \exp(\alpha_1 a + \alpha_2 r + \alpha_3 q)(1 + \beta_1 s_i)(1 + \beta_2 d_i),$$

where $a$ is an attained age, $r$ is residence, and $q$ is an indicator of a former smoker ($1 = \text{former smoker}$, $0 = \text{current and never smoker}$). Further, $\alpha_1 - \alpha_3$ is a coefficient of $a$, $r$, and $q$; $s_i$ is the pack-y category for current and never smokers (pack-y = 0); and $d_i$ is the radiation dose category. Finally, $\beta_1$ and $\beta_2$ are coefficients of $s_i$ and $d_i$, respectively.

Table 3 also shows the attributable fraction (AF), which is expressed as the proportion of excess to observed deaths. The AFs for lung cancer were 48%, 1%, and 2% for smoking only, radiation only, and smoking-radiation interaction, respectively. In this context, a study of atomic bomb survivors found that the AFs for solid cancer derived by males were 30%, 6%, and 2% (Grant 2017). Our results suggest that the AF of radiation may have been smaller because the average dose of the cohort was lower than that of the atomic bomb survivors, which in turn may have caused the AF of smoking to be relatively higher. In addition, the difference between our results for lung cancer and those of the atomic bomb survivors for solid cancers may also be a factor. For lung cancer, excess deaths of radiation only increased with increasing dose category, but conversely, it decreased for smoking-related cancers.

**Comparison with other studies in terms of factors other than radiation**

Mortality by several risk factors was also evaluated in the Japan Collaborative Cohort Study for Evaluation on Cancer (JACC) and the Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study). The RRs for all cancers in the present analysis were compatible with the above studies for the most part. For example, the RRs of the 60+ category of pack-y in both the present analysis and the JACC were 2.71 (2.05, 3.57) and 2.48 (95% CI: 2.13, 2.90), respectively (Ozasa 2007a). The RRs of the 30+ category of pack-y in the present analysis and the JPHC were 1.95 (1.53, 2.49)

### Table 3. Observed and excess death of smoking and radiation by dose category for lung cancer and smoking-related cancers based on pseudo complete data set #1 among Japanese nuclear workers.

| Dose category (mSv) | Observed deaths Background Smoking only AF smoking Radiation only AF radiation Smoking-radiation interaction AF smoking-radiation |
|---------------------|-----------------|----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Lung cancer         |                 |                      |                 |                 |                 |                 |                 |
| <5                  | 84              | 54.9                 | 49.6            | 59%             | 0.0             | 0%              | 0.0             | 0%              |
| 5–                  | 26              | 7.3                  | 7.9             | 30%             | 0.1             | 0%              | 0.1             | 0%              |
| 10–                 | 43              | 18.7                 | 18.8            | 44%             | 0.3             | 1%              | 0.3             | 1%              |
| 20–                 | 44              | 18.9                 | 20.4            | 46%             | 0.7             | 2%              | 0.8             | 2%              |
| 50–                 | 27              | 9.8                  | 10.3            | 38%             | 0.8             | 3%              | 0.9             | 3%              |
| 100+                | 13              | 5.8                  | 7.9             | 61%             | 1.1             | 9%              | 1.6             | 12%             |
| Total               | 237             | 115.3                | 114.9           | 48%             | 3.1             | 1%              | 3.7             | 2%              |
| Smoking-related cancers |             |                      |                 |                 |                 |                 |                 |
| <5                  | 291             | 215.9                | 112.3           | 39%             | −0.1            | 0%              | 0.0             | 0%              |
| 5–                  | 58              | 29.6                 | 17.6            | 30%             | −0.1            | 0%              | −0.1            | 0%              |
| 10–                 | 114             | 72.9                 | 42.2            | 37%             | −0.6            | −1%             | −0.3            | 0%              |
| 20–                 | 135             | 75.4                 | 45.5            | 34%             | −1.4            | −1%             | −0.8            | −1%             |
| 50–                 | 75              | 38.4                 | 23.0            | 31%             | −1.5            | −2%             | −0.9            | −1%             |
| 100+                | 31              | 23.7                 | 17.2            | 55%             | −2.1            | −7%             | −1.6            | −5%             |
| Total               | 704             | 455.9                | 257.7           | 37%             | −5.8            | −1%             | −3.8            | −1%             |
and 1.83 (95% CI: 1.34, 2.51), respectively (Hara et al. 2002). The RRs of the 60+ category of ethanol $g^{-1} \text{d}^{-1}$ in the present analysis and the 81+ category of the JACC were 1.30 (1.01, 1.68) and 1.39 (1.20, 1.60), respectively (Ozasa 2007b). However, slightly higher RRs of smoking and alcohol consumption were seen in site-specific cancers in the present analysis relative to the JACC, although the CIs overlapped. The RRs of the 60+ category of smoking in the present analysis and the JACC were 2.76 (1.35, 5.62) and 1.57 (1.09, 2.25) for stomach cancer, 2.58 (1.20, 5.52) and 1.81 (1.14, 2.87) for liver cancer, and 12.52 (6.05, 25.90) and 7.85 (5.65, 10.9) for lung cancer, respectively (Ozasa 2007a). In addition, we found larger RRs of alcohol consumption in the present analysis than in the JACC. The RRs of the maximum category for liver cancer were 1.87 (0.82, 4.27) and 1.47 (0.96, 2.25) for the present analysis and JACC, respectively (Ozasa 2007b). Considering the difference in categories (the present analysis was 60+ and JACC was 81+), the RRs in the present analysis seemed higher. However, these discrepancies may be reflections of differences in cohort structure—the present analysis was based on an occupational cohort, and JACC and JPHC were based on an inhabitant cohort (Ohno et al. 2001; Hara et al. 2002). Moreover, the differences in age or baseline risk might contribute to this discrepancy. More specifically, significantly high RRs of alcohol consumption were shown for smoking-related cancer in the present analysis. This was likely because some cancers related to alcohol consumption were included in the smoking-related cancer category—for example, esophagus and liver cancers (Ozasa 2007a and b). Further, significantly high RRs were shown in the frequency of medical examination for all cancers, breakfast intake for stomach and colorectal cancers, sleep for liver cancer, and BMI for all cancers; however, the CIs of present analysis overlapped with the CIs of JACC (Suzuki 2007; Iso and Kubota 2007; Fujino 2007a).

Furthermore, significant differences in health effects by socioeconomic factors have been reported by some studies (Fujino 2007b; Kagamimori et al. 2009), but no significant differences were shown in this analysis. The cohort of this study was an occupation cohort. Thus, some differences between RRs of the present analysis and other studies were found, but their CIs overlapped. Therefore, the cancer mortality rates caused by lifestyle or socioeconomic status that were derived from our analysis could be regarded as compatible with other studies.

Comparison with other studies in terms of radiation

The CIs of radiation for all cancers that were derived from previous analyses overlapped with international nuclear worker studies for all cancers other than leukemia (Richardson et al. 2015), a UK national registry for radiation workers of all malignant neoplasms (excluding leukemia) (Haylock et al. 2018), and under 0.5 Gy categories of a study on atomic bomb survivors (Ozasa et al. 2012). Therefore, risk estimate on cancer mortality based on radiation, which was derived from our analysis, could be regarded as compatible with these studies.

Limitations

Some limitations of the present analysis should be acknowledged. First, the deficiency of statistical power is the greatest limitation. The total person-y were 215,000, and the number of observed deaths for all cancers was 978. These person-y and numbers of observed deaths might be insufficient for detecting risks by each variable and category, especially in site-specific cancer. Second, as shown in Fig. 1, the cohort of this study was the 41,742 respondents to the lifestyle questionnaire, but the number of those to whom the questionnaire was distributed was 78,064; the remaining 36,322 individuals did not respond. The mean ages of the 41,742 and 36,322 subjects in September 2003 were 54.9 and 53.7 y, respectively, and the mean radiation doses were 24.8 mSv and 20.9 mSv, respectively, with no significant difference between them. However, the fact that only about half of those who received the questionnaires responded to the survey suggests the existence of a potential bias. Third, there was a possibility that unadjusted confounding factors were present. Although dose response was not found, significantly high RRs of radiation were found in lung and smoking-related cancers. However, no significantly high RRs of radiation were found for non-smoking related cancers. These results may suggest that there are some unadjusted confounding factors related to both radiation and smoking.

CONCLUSION

The RRs of lifestyle, socioeconomic status, and radiation derived from this analysis were compatible with other studies. Despite the limitations, significantly high RRs of smoking, alcohol consumption, frequency of medical examination, breakfast intake, sleep, BMI, and radiation were found. Additionally, dose responses of RRs of smoking and frequency of medical examination were also found in the present analysis. Moreover, the results of this analysis showed that smoking is a major risk factor. Since the simultaneous inclusion of radiation and non-radiation variables in the model for RR calculation means that the calculated radiation RR is the result of adjustment by other variables, the risk of cancer from low-dose radiation, if any, is less than smoking and probably less than other lifestyle factors. The results offer worthwhile evidence in terms of the minimization of bias by using multiple imputation and estimation of RRs for several causes of death, variables, and categories from one simultaneous cohort.
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