

A Risk Comparison of Non-cancer Mortality between Lifestyle, Socioeconomic Status, and Radiation among Japanese Nuclear Workers (J-EPISODE)

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Abstract—Many epidemiological studies have been conducted to investigate the health effects of low-dose radiation. Most of these investigations have focused on cancer, and fewer studies have examined non-cancer topics than cancer subjects. The purpose of this study is to compare the relative risks of non-cancer mortality from low-dose radiation with lifestyle factors (such as smoking habits) and socioeconomic status (such as years of education). The cohort consisted of 43,692 males who responded to a lifestyle questionnaire survey conducted from 2003 to 2004 among nuclear workers in Japan. Missing questionnaire data were imputed by multiple imputation, each variable was categorized, and the relative risks for the reference group were calculated using Poisson regression. The total number of observed person-years was 300,000, and the mean age and dose were 55.2 y and 24.5 mSv (10-y lagged dose), respectively. For many of the causes of death in this analysis, significantly high risks existed for lifestyle differences, such as smoking, alcohol consumption, frequency of medical examination, breakfast intake, sleep, and BMI, but few for socioeconomic status. Radiation showed no significantly high risks. Taken together, the risk of non-cancer mortality from low-dose radiation is likely smaller than that from lifestyle factors. *Health Phys.* 123(6):464–475; 2022

Key words: cancer; epidemiology; radiation, low-level; risk estimates

INTRODUCTION

STUDIES OF atomic bomb survivors have found an increase in cancer risks due to radiation (Preston et al. 2003; Ozasa et al. 2012). Although those results were based on relatively high-dose,

high-dose-rate exposures, several other studies have found increased cancer risks in cohorts exposed to low-dose, low-dose-rate radiation (Haylock et al. 2018; Shilnikova et al. 2003; Richardson et al. 2015). This increase in cancer from radiation is thought to be caused by damage to DNA (UNSCEAR 2000), and although the pathogenesis of radiation effects on non-cancer is currently unclear, studies on atomic bomb survivors and others have reported increased non-cancer risks from radiation (Preston et al. 2003; Yamada et al. 2004; Muirhead et al. 2009; Shimizu et al. 2010; Ozasa et al. 2012; Gillies et al. 2017; Takahashi et al. 2017; Hinksman et al. 2022; Azizova et al. 2022). These studies that targeted the risks of cancer and non-cancer effects quantified radiation risk in terms of how much mortality was added to 1 Gy exposure. However, studies comparing radiation risks with other factors are limited, especially for non-cancer effects.

Since 1990, the Radiation Effects Association (REA) has been conducting epidemiological studies on cohorts of nuclear power plant workers in Japan. As part of a survey, data on lifestyle habits and socioeconomic status were obtained for each nuclear worker. Using this information, a previous paper comparing the risks of cancer mortality from radiation and other factors showed that the health effects of low-dose radiation, if any, were smaller than those of smoking and some other lifestyle factors (Kudo et al. 2022).

Using the same cohort and methods (multiple imputation and Poisson regression) as in the previous paper, we focused on non-cancer mortality and compared the risks of death. The purpose of this paper is to compare the relative risks of non-cancer deaths due to lifestyle factors, such as smoking, socioeconomic status (including years of education), and radiation exposure among nuclear workers in Japan.

MATERIALS AND METHODS

Ethical approval

This study protocol was based on the Ethical Guidelines for Medical and Health Research Involving Human

¹Institute of Radiation Epidemiology, Radiation Effects Association. The authors declare no conflicts of interest.

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Subjects by the Japanese Ministry of Education, Culture, Sports, Science, and Technology, and Ministry of Health, Labour, and Welfare (MHLW).

Cohort definition and vital status follow-up

The radiation doses of workers at nuclear power facilities in Japan are registered at the Radiation Dose Registry Center (RADREC) in REA. The study cohort consisted of those who met all of the following conditions: (1) those who were registered with RADREC by the end of March 1999 and had been engaged in nuclear power generation, and (2) those with valid responses to the questionnaire on lifestyle.

Vital statuses were confirmed by requesting copies of the residence registration cards (RRCs) from the local government. Certificates of RRCs were issued for survivors, and deleted RRCs were issued for deceased workers. For those who moved away, deleted RRCs were also issued, and in these cases, new requests for issuance were made based on the new addresses.

For those with confirmed deaths, the causes of death were ascertained by linking the death records provided by the MHLW. The matching keys for linkage were date of birth, date of death, sex, and address code at the time of death (Iwasaki et al. 2000). The cause of death was determined for 99.5% of the deaths. The underlying causes of death were coded according to the International Classification of Diseases (ICD), 10th revision.

Dosimetry

The doses provided by RADREC were annual individual effective doses expressed in mSv, including photon, neutron, and internal doses. The photon and neutron doses were the external exposure of equivalent doses at a tissue depth of 10 mm [$H_p(10)$]. When neutron and internal doses were positively detected, they were evaluated by employers and added to the photon doses, but such cases were rare in Japan under normal operations involving periodic inspections and maintenance. Doses below the detectable level were set at 0 mSv. In Japan, the use of nuclear energy began in 1957, and the censor date of the observation period was set in 2010. Therefore, the dose records used in the analysis were from 1957 to 2010.

Lifestyle questionnaire survey

To obtain information on lifestyle and socioeconomic status, a lifestyle survey was conducted from September 2003 to March 2004. The subjects included those who were 40 y of age or older as of 1 July 2003. Those whose cumulative dose was 10 mSv or more as of 31 March 2002, were included, and 40% of those whose cumulative dose was less than 10 mSv were sampled after matching age and region with those of the 10 mSv or more group. The questionnaire was self-administered, and it included questions about lifestyle (e.g., smoking, alcohol consumption) and socioeconomic status (e.g., job category, years of education). It was sent by post to male workers only because the number of female subjects was small for evaluation of radiation risk. Thus, the questionnaires were distributed to 78,064 male workers.

Variables used for estimation of relative risks

In this study, relative risks (RRs) were calculated for each variable: smoking (pack-y), alcohol consumption (ethanol in grams per day), health consciousness, frequency of medical examination, breakfast intake, sleep, body mass index (BMI), job category, job position, years of education, and cumulative radiation dose. Smoking was quantified as the total amount of smoking in pack-y for current smokers. Pack-y were defined as follows: the number of cigarettes per day \times (1 pack/20 cigarettes) \times the number of years between smoking start date and age on the survey date. The RRs of current smokers were estimated by pack-y and defined against those who had never smoked (never smokers; 0 pack-y). For former smokers, the mortality rate differed depending on the years since cessation.

To simplify the model, the RRs for former smokers were not estimated by pack-y but estimated as a former-smoker group against never smokers. Smoking (pack-y) was defined as follows: 0 [never smoker, reference (hereafter simply ref)]; former smoker, >0 (current smoker); 20– (current smoker); 40– (current smoker); or 60+ (current smoker). Alcohol consumption was quantified as ethanol in grams per day for current drinkers, calculated by the type of alcoholic beverage and frequency of drinking. The RRs for current drinkers were estimated by ethanol in grams per day against never drinkers (0 grams of ethanol per day). The RRs for former drinkers were estimated as the former-drinker group against never drinkers. Alcohol consumption (ethanol in grams per day) was defined as follows: 0 (never drinker, ref) former drinker; >0 (current drinker); 20– (current drinker); 40– (current drinker); or 60+ (current drinker). Health consciousness was defined as follows: good (ref), average, or poor. Frequency of medical examination was defined as follows: every year (ref), sometimes, or almost never. Breakfast intake was defined as follows: every day (ref), sometimes, or almost never. Sleep was defined as follows: well (ref), sometimes not well, or not well. BMI was defined as an individual's weight (kg) divided by the square of height (m) and was defined as follows: <18.5, 18.5– (ref), 25–, or 30+. Job category was defined as follows: design and research (ref), radiological management, operation and investigation, or maintenance. Job position was defined as follows: management (ref), technical advisor, group leader, or staff. Years of education was defined as follows: 13+ (ref), 10–12, or < 10. Radiation dose was defined as follows: <5 (ref), 5–, 10–, 20–, 50–, or 100 + .

Multiple imputation

To improve precision of risk estimates, missing values from the lifestyle questionnaire were imputed by multiple imputation (Rubin 1987; Rubin and Schenker 1991). First, this method creates a regression model with no missing data (i.e., making the Missing At Random assumption that missing

can be explained by other variables) and then uses the missing data estimates and information on variance to randomly generate imputed value to create a pseudo-complete data set (hereafter PCD). In the estimation of imputed values, in order to exclude the influence of initial values, the estimation is performed multiple times. The first part is discarded, and subsequent values are adopted. This discarded portion is called “burn-in.” If there is only one PCD, the uncertainty of missing data completion cannot be taken into account. Therefore, multiple PCDs are generated, and the statistics obtained from each PCD are integrated. This is an overview of the multiple imputation method. A fully conditional specification was used for the imputation algorithm. This method is based on the assumption that the conditional distributions of each variable can be specified by the remaining variables, and it builds an imputation model for each missing variable and iterates the imputation values for each variable (SAS 2014). Smoking status, alcohol consumption, job category, and job position, which were nominal variables, were imputed by discriminant function. Health consciousness, frequency of medical examination, breakfast intake, sleep, and years of education, which were ordinal variables, were imputed by ordinal logistic regression. BMI, pack-y, and ethanol in grams per day, which were continuous variables, were imputed by linear regression. Radiation doses had no missing data. The variables with no missing data were included in the imputation model as auxiliary variables to make the assumption of missing at random more plausible (age at the time of the survey, number of sites where a worker had been engaged, latest prefecture code that verified a worker’s survival status, year of first exposure to radiation, and year of latest exposure to radiation). The indicators of death from all cancers were also added to the auxiliary variables as an endpoint. The number of burn-in was 100, and the number of PCDs created was 30 in this analysis. The MI procedure of SAS was used for imputation (SAS 2014; SAS 2016). The details of multiple imputation were described in a previous paper (Kudo et al. 2022).

Causes of death

The causes of death for which RRs were estimated included all non-cancers (ICD10: A00–B99, D50–R99), circulatory diseases (I00–I99), cardiovascular diseases (I00–I52, I71), cerebrovascular diseases (I60–I69), respiratory diseases (J00–J99), and digestive diseases (K00–K93).

Analysis

The entry date for person-year calculations was set as the date of the questionnaire response. The exit date of the person-years calculation was set as the earliest of the following: (a) date of the latest confirmation of vital status, (b) date of death, or (c) 31 December 2010. Therefore, the individual workers’ observation periods differed, but they were within 2003 to 2010. In the previous paper (Kudo et al. 2022), the

entry date for person-year calculations was set as 2 y after the date of the questionnaire response to exclude the effect of health status at the time of the survey (Goodman et al. 1995). However, in the present paper, the response date was used as the entry date for person-year calculations because the effect was not considered to be large. For comparison with the previous paper (Kudo et al. 2022), we also performed the same analysis with the observation start date being 2 y after the response date, which was conducted as a supplementary analysis.

Poisson regression was also used to quantify the RRs of lifestyle, socioeconomic status, and radiation. The model to estimate RRs was a log linear model, which was used in the previous analysis (Kudo et al. 2022). Further, the model to estimate dose response of radiation (excess relative risk per sievert: hereafter ERR Sv⁻¹) as follows. The former is referred to below as eqn (1) and the latter as eqn (2):

$$\lambda = \lambda_0(a, r) \exp(\beta_1 z_1 + \dots + \beta_{11} z_{11}) \quad (1)$$

and

$$\lambda = \lambda_0(a, r) \exp(\beta_1 z_1 + \dots + \beta_{10} z_{10})(1 + \beta z_{11}), \quad (2)$$

where λ is the death rate and λ_0 is the background death rate [stratified by a : 5-y attained age categories (20–, 25–, ... and 100+)]; r = residence, which is divided into eight regional categories within Japan (Kudo et al. 2018a and 2018b, 2022); and z_1 – z_{11} represent the variables used to estimate RRs. More specifically, z_1 was smoking (pack-y), z_2 was alcohol consumption (ethanol in grams per day), z_3 was health consciousness, z_4 was frequency of medical examination, z_5 was breakfast intake, z_6 was sleep, z_7 was BMI, z_8 was job category, z_9 was job position, z_{10} was years of education, and z_{11} was the cumulative radiation dose, assuming a 10-y lag. β_1 – β_{11} represent the coefficient, which means RRs against those 11 reference categories; β in Model 2 represents ERR Sv⁻¹. The person-y table was created by DATAB, and the models were fitted by AMFIT. Both were EPICURE modules (EPICURE 2021).

The RR and standard error for each variable were output for the number of data sets (i.e., 30). The integrated point estimates of RR and the 95% confidence intervals (CIs) of each variable and category were integrated using Rubin’s method (Rubin 1987; Rubin and Schenker 1991). These integrated RRs and variances were calculated using the MIANALYZE procedure by SAS (SAS 2014, 2016).

To estimate the degree of bias, a complete case analysis (CCA) was performed on all the above z_1 – z_{11} with no missing data.

To discuss the observed and excess deaths from smoking and radiation by dose category for all non-cancers and circulatory diseases, eqn (3) as shown below was used. It was a linear and multiplicative joint effect of smoking and radiation. The

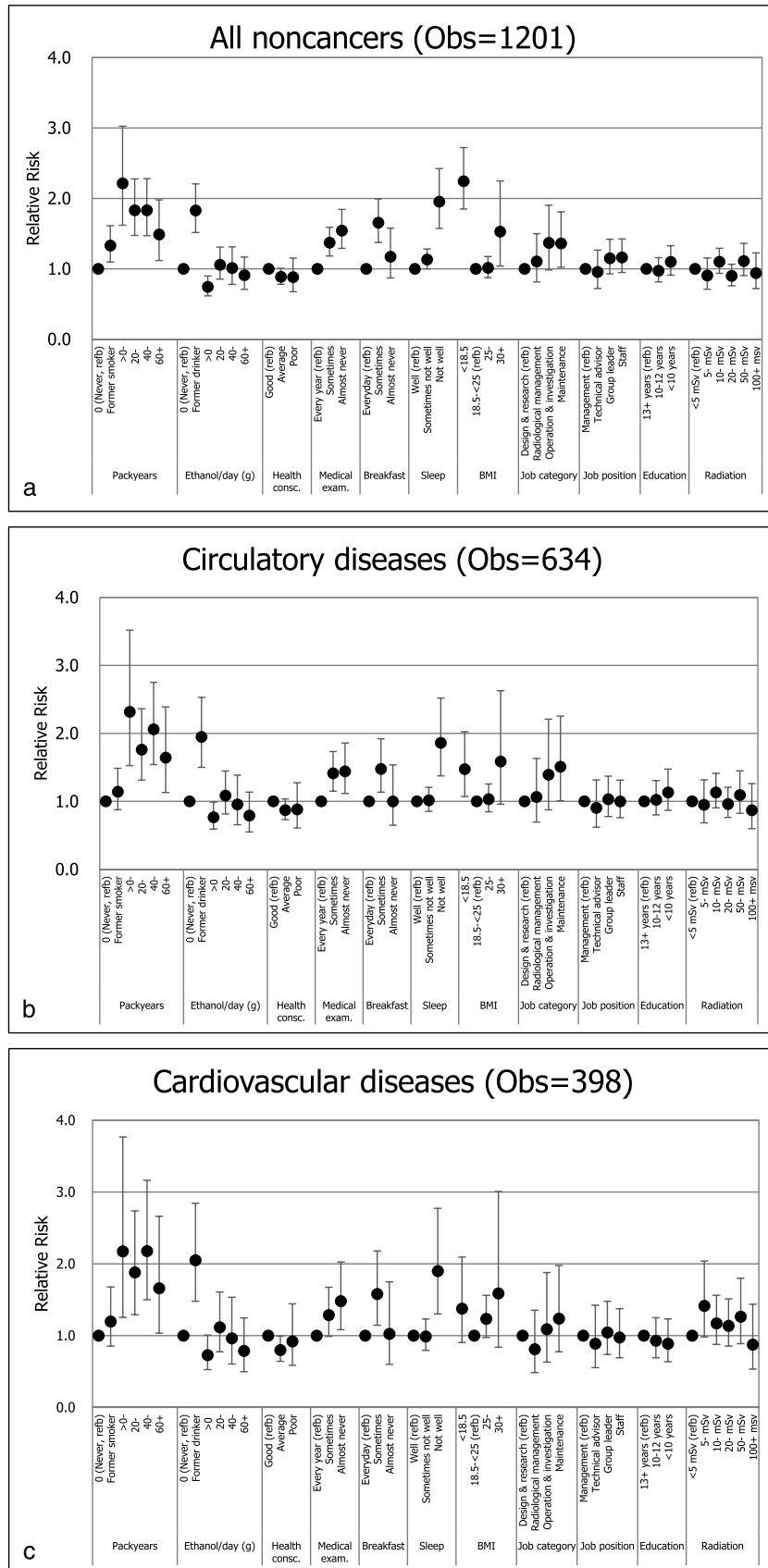


Fig. 1. Continued.

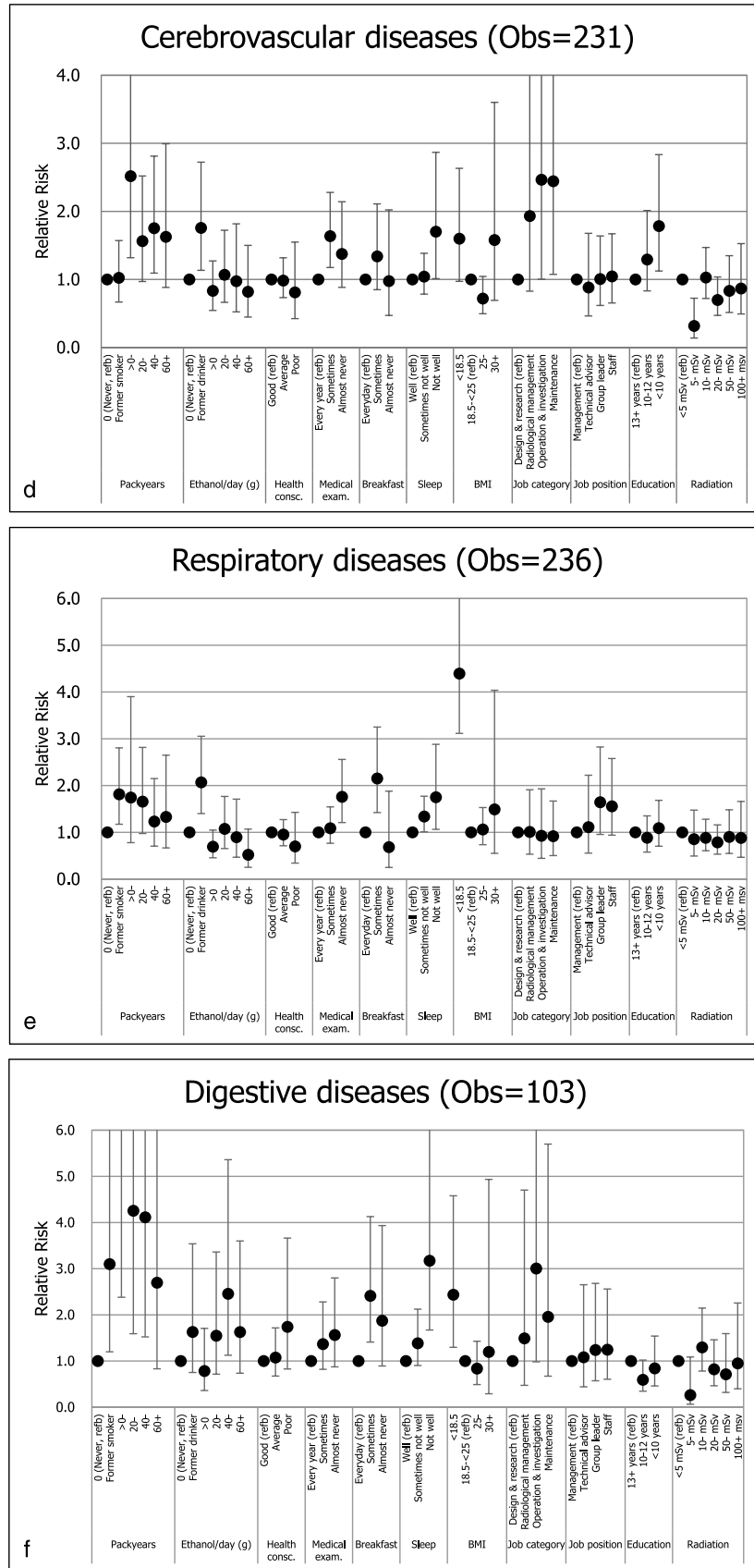


Fig. 1. Relative risks and 95% confidence intervals for lifestyle, socioeconomic status, and radiation of non-cancer mortality among Japanese nuclear workers.

calculation was based on the PCD #1, which was created in imputation stage as stated in multiple imputation:

$$\lambda = \lambda_0 \exp(\alpha_1 a + \alpha_2 r + \alpha_3 q)(1 + \beta_{1i} s_i) \times (1 + \beta_{2i} d_i), \quad (3)$$

where a is an attained age, r is residence, and q is an indicator of a former smoker (1 = former smoker, 0 = current and never smoker). α_1 – α_3 are coefficients of a , r , and q . s_i is the pack-y category for current smoker and never smoker (pack-y = 0). d_i is the radiation dose category. β_{1i} and β_{2i} are the coefficients of s_i and d_i , respectively.

RESULTS

The questionnaire was distributed to 78,064 people, and the cohort consisted of 43,692 subjects. The 34,372 persons not included in the cohort are broken down as follows: 4,522 for unknown destination, 27,637 for no reply, 343 for unable to identify in RADREC, 180 for no answers written in questionnaire, and 1,690 for those who were not followed up after the date of the questionnaire response. The total number of person-years was 300,000 from 2003 to 2010. The mean age and mean 10-y lagged cumulative dose at the date of the survey were 55.2 y and 24.5 mSv, respectively.

Fig. 1 shows the relative risks and 95% CIs by using eqn (1) for each cause of death and category of items (Supplemental Digital Content Table 1, <http://links.lww.com/HP/A231>). For smoking, significantly increasing RRs for all outcomes (all non-cancers, circulatory, cardiovascular, cerebrovascular, respiratory, or digestive diseases) were found (Panels A, B, C, D, E, and F). However, for these causes of death, the dose responses—namely, the RRs of smoking increased as pack-y increased—were unclear. Additionally, for alcohol consumption, significantly increasing RRs of all outcomes were found (Panels A, B, C, D, E, and F). However, all these significantly higher RRs were found in the former-drinker group, with no significantly higher RRs in the current-drinker group without digestive diseases.

The RR of any outcome was not significantly increased for health consciousness. Regarding frequency of medical examination, significantly increasing RRs of all non-cancers, circulatory, cardiovascular, cerebrovascular, and respiratory diseases were found (Panels A, B, C, D, and E). For breakfast intake, significantly increasing RRs of all non-cancers, circulatory, cardiovascular, respiratory, and digestive diseases were found (Panels A, B, C, E, and F). For sleep, significantly increasing RRs for all outcomes were found (Panel A, B, C, D, E, and F). For BMI, significantly increasing RRs for all non-cancers, circulatory, respiratory, and digestive diseases were found (Panel A, B, E, and F).

For job category, significantly increasing RRs of all non-cancers, circulatory, and cerebrovascular diseases were

found (Panel A, B, and D). RR of any outcome was not significantly increased for job position. For years of education, significantly increasing RR of cerebrovascular diseases was found (Panel D).

The RR of any outcome was not significantly increased for radiation. For radiation, in addition to RR per category by using Model 1, ERR Sv⁻¹ was also calculated by using Model 2, but there were no significantly high ERR/Sv among the causes of death included in the analysis. The ERRs were -0.27 (90% CI: -1.61, 1.07) for all non-cancers; -1.01(-2.62, 0.60) for circulatory diseases; -0.89(-2.99, 1.22) for cardiovascular diseases; -1.12(-3.69, 1.45) for cerebrovascular diseases; -0.63(-3.65, 2.40) for respiratory diseases; and 0.76(-4.39, 5.90) for digestive diseases (Supplemental Digital Content Table 1, <http://links.lww.com/HP/A231>). The results from the CCA differed from those that were imputed (Table 1). In comparing the imputed results to the CCA, smoking and BMI showed 5–22% lower RRs, while radiation showed 1–26% lower RRs except in the 100+ mSv category (1% higher). Table 2 provides the information on the observed and excess deaths derived from Model 3 for smoking and radiation by dose category for all non-cancers and circulatory diseases based on the pseudo-complete data set #1. Table 2 also shows the attributable fraction (AF), expressed as the proportion of excess to observed deaths. The AFs of all non-cancers were 20%, 0%, and 0% for smoking only, radiation only, and the smoking-radiation interaction, respectively. The AFs of circulatory diseases were 24%, -1%, and 0% for smoking only, radiation only, and smoking-radiation interaction, respectively. Thus, no excess death occurred due to radiation only or to the interaction of radiation and smoking for either all non-cancers or circulatory diseases.

The results of the supplementary analysis, in which the entry date for person-year calculations was set as 2 y after the date of the questionnaire response, were almost identical to those of the main analysis. However, a significantly higher RR was observed for cerebrovascular disease in the 5-radiation category (Supplemental Digital Content Table 2, <http://links.lww.com/HP/A232>).

DISCUSSION

Principal findings

In this study, we examined direct risk comparisons of non-cancer mortality for lifestyle, socioeconomic status, and radiation. The lifestyle factors of smoking, alcohol consumption, frequency of medical examination, breakfast intake, sleep, BMI, and job category showed significantly increasing RRs. In particular, smoking and BMI showed greater RRs than other factors. Socioeconomic factors showed little evidence of risk compared with the lifestyle factors. Job position showed no risk. Job category showed a significantly high risk

Table 1. Relative risks and 95% CIs for each category of items by imputed and complete case analysis for all non-cancers.

Items	Category	Imputed	Complete case analysis
		RR (95%CI)	RR (95%CI)
Smoking (Pack-y)	0 (Never, ref ^a)	1.00	1.00
	Former smoker	1.33 (1.10–1.61)	1.51 (1.21–1.87)
	>0–	2.21 (1.62–3.03)	2.49 (1.75–3.53)
	20–	1.83 (1.47–2.28)	1.89 (1.47–2.42)
	40–	1.83 (1.47–2.28)	2.01 (1.57–2.58)
	60+	1.49 (1.12–1.98)	1.59 (1.15–2.19)
	Unknown		
Alcohol consumption [Ethanol day ⁻¹ (g)]	0 (Never, ref ^a)	1.00	1.00
	Former drinker	1.83 (1.52–2.21)	2.11 (1.71–2.62)
	>0	0.74 (0.62–0.90)	0.77 (0.63–0.94)
	20–	1.06 (0.85–1.31)	0.99 (0.78–1.25)
	40–	1.01 (0.78–1.31)	1.02 (0.76–1.36)
	60+	0.91 (0.71–1.17)	0.96 (0.74–1.26)
	Unknown		
Health consciousness	Good (ref ^a)	1.00	1.00
	Medium	0.89 (0.78–1.008)	0.89 (0.77–1.03)
	Bad	0.88 (0.68–1.15)	0.82 (0.60–1.13)
	Unknown		
Frequency of medical examination	Every year (ref ^a)	1.00	1.00
	Sometimes	1.37 (1.18–1.59)	1.50 (1.26–1.78)
	Almost never	1.54 (1.29–1.84)	1.53 (1.24–1.88)
	Unknown		
Breakfast intake	Everyday (ref ^a)	1.00	1.00
	Sometimes	1.66 (1.37–1.99)	1.94 (1.58–2.39)
	Almost never	1.17 (0.87–1.58)	1.42 (1.04–1.94)
	Unknown		
Sleep	Well (ref ^a)	1.00	1.00
	Sometimes not well	1.13 (1.00–1.28)	1.09 (0.95–1.26)
	Not well	1.95 (1.58–2.42)	2.39 (1.87–3.04)
	Unknown		
BMI	<18.5	2.24 (1.85–2.72)	2.86 (2.30–3.55)
	18.5– < 25 (ref ^a)	1.00	1.00
	25–	1.02 (0.88–1.18)	1.07 (0.91–1.27)
	30+	1.53 (1.04–2.25)	1.83 (1.18–2.84)
	Unknown		
Job category	Design and research (ref ^a)	1.00	1.00
	Radiological management	1.11 (0.82–1.50)	1.17 (0.86–1.58)
	Operation and investigation	1.37 (0.98–1.90)	1.41 (1.01–1.96)
	Maintenance	1.36 (1.02–1.81)	1.39 (1.04–1.86)
	Unknown		
Job Position	Management (ref ^a)	1.00	1.00
	Technical advisor	0.96 (0.72–1.27)	0.81 (0.61–1.08)
	Group leader	1.15 (0.93–1.42)	1.21 (0.97–1.49)
	Staff	1.16 (0.95–1.43)	1.08 (0.88–1.33)
	Unknown		
Years of education	13+ y (ref ^a)	1.00	1.00
	10–12 y	0.97 (0.82–1.16)	0.99 (0.83–1.18)
	<10 y	1.10 (0.91–1.33)	0.98 (0.80–1.20)
	Unknown		

Continued next page

Table 1. (Continued)

Items	Category	Imputed	Complete case analysis
		RR (95%CI)	RR (95%CI)
Radiation (Cumulative dose)	<5 mSv (ref ^a)	1.00	1.00
	5– mSv	0.91 (0.71–1.16)	1.23 (0.94–1.62)
	10– mSv	1.10 (0.94–1.29)	1.16 (0.96–1.40)
	20– mSv	0.90 (0.76–1.07)	1.06 (0.87–1.28)
	50– mSv	1.11 (0.90–1.36)	1.21 (0.95–1.53)
	100+ msv	0.94 (0.72–1.23)	0.93 (0.68–1.27)

^aReference category.

of all non-cancers, circulatory, and cerebrovascular diseases, and years of education showed a significantly high risk of cerebrovascular diseases.

The results from the CCA were different from the imputed results to some extent. Smoking and radiation showed lower imputed RRs than CCA. These results likely reflect that the multiple imputation, which included auxiliary variables, made the assumption of “missing at random” more plausible and improved the precision of analysis, which was thought to be less biased than the CCA (Rubin 1987; SAS 2014).

Comparisons with previous studies regarding factors other than radiation

Mortality in a Japanese cohort 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). Below, we compare

our results with the findings of these studies. The RRs of the 60+ category of pack-y in both the JPHC and the present analysis were 1.41 (95% CI: 0.95, 2.12) and 1.64 (95% CI: 1.13, 2.39), respectively, for circulatory diseases (Hara et al. 2002). The RRs for the same smoking category were 2.16 (1.47, 3.17) for ischemic heart disease (IHD) in the JACC and 1.66 (1.03, 2.66) for cardiovascular diseases in the present analysis (Ozasa 2007a). The RR of ethanol in grams per day for the 81+ category in the JACC was 0.94 (0.66, 1.36) for IHD; for the 60+ category in the present analysis, it was 0.79 (0.50, 1.25) for cardiovascular diseases (Ozasa 2007b).

When examining frequency of medical examination, IHD in the JACC showed no significantly higher RR, but the present analysis showed significantly higher RR of 1.48 (1.08, 2.03) for cardiovascular diseases. For cerebrovascular diseases, both JACC and the present analysis showed significant RR differences depending on the frequency of medical examinations. In the JACC, the RR for “yes,” with

Table 2. Observed and excess death of smoking and radiation by dose category for all non-cancers and circulatory diseases based on pseudo complete data set #1.

Dose category (mSv)	Observed deaths	Background	Smoking only	AF smoking	Radiation only	AF radiation	Smoking—radiation interaction	AF smoking—radiation
All non-cancers								
<5	541	457.1	105.2259	19%	0.0	0%	0.0	0%
5–	76	63.4	16.94231	22%	0.0	0%	0.0	0%
10–	217	149.9	38.20374	18%	–0.1	0%	0.0	0%
20–	188	158.5	41.99211	22%	–0.2	0%	–0.1	0%
50–	116	81.7	21.3714	18%	–0.2	0%	–0.1	0%
100+	63	51.3	16.47673	26%	–0.3	–1%	–0.1	0%
Total	1201	961.9	240.2	20%	–0.9	0%	–0.2	0%
Circulatory diseases								
<5	280	233.3	67.1218	24%	–0.1	0%	0.0	0%
5–	42	32.5	10.80767	26%	–0.2	0%	–0.1	0%
10–	114	75.6	23.94088	21%	–0.7	–1%	–0.2	0%
20–	105	80.8	26.55251	25%	–1.7	–2%	–0.5	–1%
50–	61	42.1	13.72379	22%	–1.9	–3%	–0.6	–1%
100+	32	26.9	10.65398	33%	–2.8	–9%	–1.1	–4%
Total	634	491.1	152.8	24%	–7.3	–1%	–2.6	0%

the no-screening group as the reference group, was 0.64 (0.46, 0.89), and in the present analysis, the RR for “sometimes,” with every year as the reference group, was 1.64 (1.17, 2.28) (Suzuki 2007). Both studies found that mortality differed significantly by breakfast intake status. The RR of IHD for the skip-breakfast group in JACC was 1.90 (1.13, 3.19), and the RR of cardiovascular diseases for the sometimes group vs. the everyday group in the present analysis was 1.58 (1.14, 2.18) (Iso and Kubota 2007).

In terms of sleep in cardiovascular diseases, the JACC reported no significant difference, while the present analysis showed a significantly higher RR of 1.90 (1.30, 2.77) in the “not-well” group relative to the “sleeps-well” group (Suzuki 2007). Regarding sleep in cerebrovascular diseases, the JACC reported a significantly higher RR of 1.49 (1.30, 1.70) in the group with 9 h or more, relative to the 7–8 h group, and the present analysis showed a significantly higher RR of 1.70 (1.01, 2.87).

For BMI, the RR of the 30+ group relative to the reference group (18.5–25) was 2.27 (1.25, 4.15) for IHD in the JACC and 1.59 (0.96, 2.63) for circulatory diseases in the present analysis. The RR of 30+ for cerebrovascular diseases was 1.34 (1.11, 1.63) in the JACC and 1.58 (0.69, 3.60) in the present analysis (Fujino 2007a).

Differences in RR by job category were not found in the JACC (Fujino 2007b), but the present analysis showed significantly higher RRs of staff to management, 1.36 (1.02, 1.81) for all non-cancers, 1.51 (1.01, 2.25) for circulatory diseases, and 2.44 (1.07, 5.55) for cerebrovascular diseases. When considering job position, no significantly higher RRs were found in the present analysis, and we could not find any comparable data related to job position. Differences in the RRs of cerebrovascular diseases by years of education were found in both the JACC and the current study. For the JACC, the RR was 0.76 (0.62, 0.92) for 19+ y, with 15 y or less as the reference group—in the present analysis, the RR was 1.78 (1.12, 2.83) for <10 y, with 13+ y as the reference group (Fujino 2007a).

The results of our study and those of previous studies are in good agreement, with overlapping CIs even when significance differs. The risk of non-cancer mortality from lifestyle and socioeconomic status seen in our study is consistent with other studies.

Comparisons with previous studies regarding radiation

The point estimates of ERR Sv^{-1} derived by Model 2 in this study were distributed from -1.12 to 0.76 (Supplemental Digital Content Table 1, <http://links.lww.com/HP/A231>). In INWORKS, the ERR Sv^{-1} were 0.19 (90% CI: $0.07, 0.30$) for all non-cancers and 0.22 (0.08, 0.37) for circulatory diseases (Gillies et al. 2017). In NRRW, the ERR Sv^{-1} was 0.251 (90% CI: $0.03, 0.49$) for circulatory diseases (Muirhead et al. 2009). Furthermore, in the study on atomic bomb survi-

vors, the ERR Gy^{-1} was 0.11 (95% CI: $0.05, 0.17$) for circulatory diseases (Ozasa et al. 2012). Therefore, the ERR Sv^{-1} derived from the present analysis could be regarded as comparable with these studies.

For each dose category of our study, there was no clear dose response for all non-cancers and cardiovascular diseases. Cardiovascular disease rose in the 5 to <10 mSv category, followed by a plateau, and the RR was below 1 in the 100+ mSv category. The NRRW analysis showed a similar trend for cerebrovascular disease in the larger dose range, with an increase in risk in the very low dose range, followed by a plateau and then a slight decrease at 200 mSv or higher (Hinksman et al. 2022). The authors suggest that the trend toward lower risk in the high-dose group (200+) may be healthy worker survivor effect. In INWORKS, the risk of cerebrovascular disease also tends to increase in the low-dose range and plateau at doses above 200 mSv (Gillies et al. 2017). Our results showed no such trend for cerebrovascular disease but rather significantly lower estimates in the 5 to <10 mSv category. Mayak shows a significantly higher risk of ischemic stroke among male residents, $\text{ERR Gy}^{-1} = 0.43$ (95%CI: $0.08, 0.99$), but this is with adjustment for alpha radiation; without this adjustment, ERR Gy^{-1} falls to 0.17 (95%CI: $-0.05, 0.52$), and becomes insignificant (Azizova et al. 2022). However, the authors mention the uncertainty of the alpha dose estimation as a limitation of the study. ERR Sv^{-1} for cerebrovascular disease in our study was also not significant at -1.12 (95%CI: $-3.69, 1.45$).

The difference between NRRW, Mayak, and our results in cerebrovascular disease may be due to the difference in the number of observed deaths: 3,219 in NRRW and 1,168 in the Mayak no resident subcohorts compared to 231 in our study, less than one-tenth of NRRW and one-fifth of Mayak. Cardiovascular and cerebrovascular diseases in our study showed high or low RRs in the 5 to <10 mSv category, with a trend toward an RR approaching 1 in the higher dose groups, but this trend is biologically unlikely and difficult to explain from the current data. Fig. 2 shows the percentages for each dose group for at-risk current smokers and those with <13 y of education, but there were no specific differences in the 5 to <10 mSv category for both current smokers and those with <13 y of education. The RR in the 5 to <10 mSv category for circulatory diseases was almost one [0.95 ($0.68, 1.32$)] and was not significant, including both cardiovascular and cerebrovascular diseases. These findings suggest that the higher RR observed at 5 to <10 mSv for cardiovascular diseases and significantly lower RR observed at 5 to <10 mSv for cerebrovascular diseases could be considered to have happened by chance.

Respiratory disease showed a gradual negative decreasing trend. Digestive diseases showed no clear dose response and, like cerebrovascular diseases, showed a fairly low point estimate of 0.26 (0.06, 1.09) in the 5 to <10 mSv category,

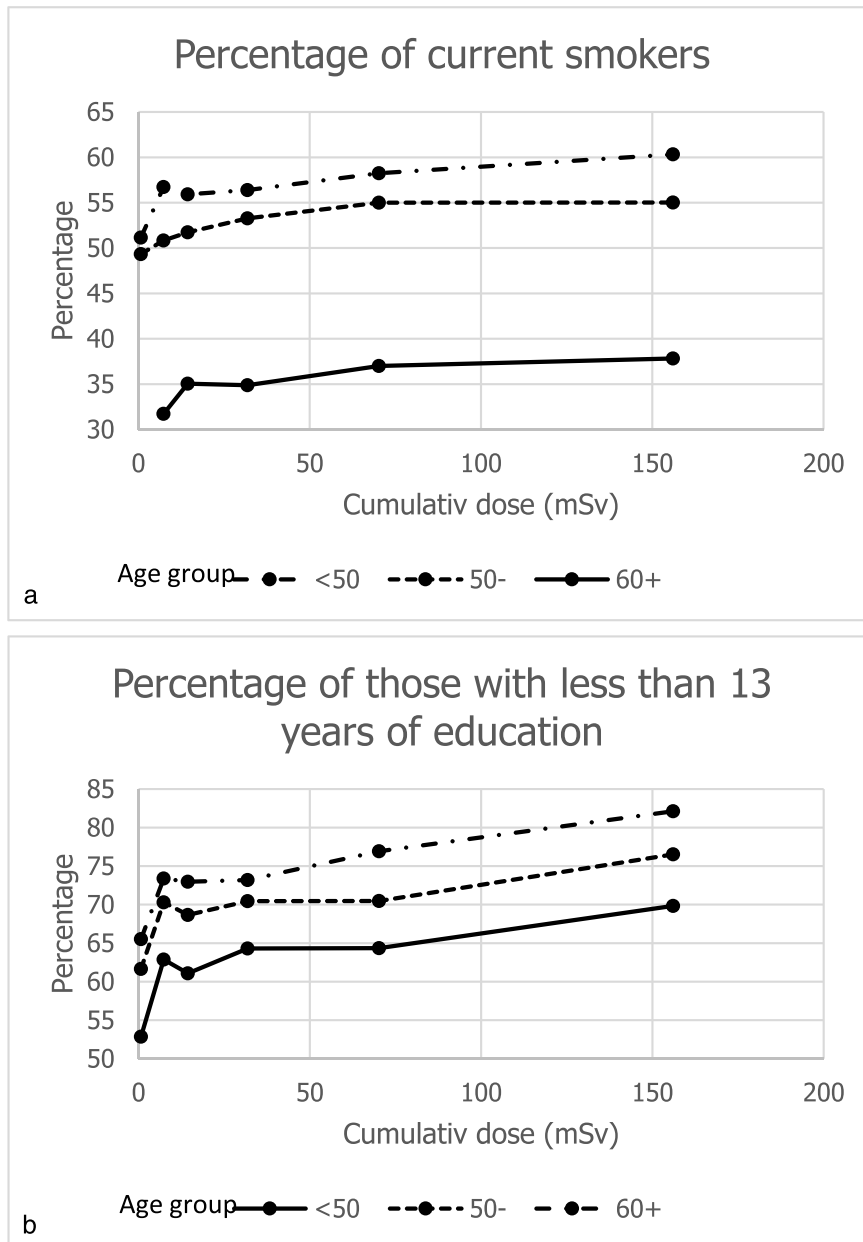


Fig. 2. Percentage of current smokers and those with less than 13 years of education by dose and age group.

although not significant. Because of the small number of observed deaths (103), the confidence intervals for the RRs are wide for both variables.

In the LSS, a significantly higher ERR Gy⁻¹ [0.96 (95% CI: 0.28, 1.92)] was found in rheumatic VHD, with a large contribution from the early observation period from 1950 to 1968, which the authors attributed to the more severe destruction caused by the atomic bombs in the proximity of the survivors (i.e., higher dose survivors) (Takahashi et al. 2017). The authors suggest that this may be due to a higher incidence of rheumatic fever after streptococcal infection due to poor sanitary conditions among those exposed in close proximity (i.e., high-dose survivors), where

the destruction caused by the atomic bombs was more severe, indicating a possible confounding between radiation and rheumatic fever.

The biological effects of radiation on deaths from non-cancer diseases are not clear. Biological studies report that ionizing radiation causes cellular senescence (Lowe and Raj 2014), while others suggest that radiation is associated with an inhibitory rather than an accelerating effect on atherosclerosis (Roedel et al. 2002; Mitchel et al. 2011). It has also been suggested that acute doses (>1 Gy) are considered to have an inflammatory effect, while low doses (<0.5 Gy) may potentially have an anti-inflammatory effect and slow the progression of cardiovascular disease (Rodel et al.

2007; Stewart et al. 2013), and the ICRP report also classifies radiation-induced cardiovascular disease as a tissue response effect (ICRP 2012). The ICRP report classifies radiation-induced cardiovascular disease as a tissue response effect, with a threshold of 0.5 Gy for such effects.

The lack of a significantly higher radiation risk in either eqn (1) or eqn (2) in this study may be the result of the low mean dose of 24.8 mSv, as well as adjustment for factors other than radiation.

Limitations

The greatest limitation is deficient statistical power from the small cohort size and short observation period. The total number of person-years was 300,000, and the number of observed deaths for all non-cancers was 1,201. This short observation period and small number of observed deaths, which were divided into categories for each variable, resulted in wider confidence intervals for the RRs. Significantly higher RRs were found for many causes of death and lifestyle factors, such as smoking and alcohol consumption, but few were found for job category, job position, and years of education. This could mean that differences in socioeconomic status may not affect mortality as much as lifestyle, but it could also mean that these factors did not appear as significant risks because of the lack of power to detect them.

As noted above, questionnaires were distributed to 78,064 people, but only about half (43,692) were included in the cohort for this analysis. To examine selection bias, the ages and cumulative doses of the 43,692 in the cohort were compared with those of the remaining 34,372, whose ages at the time of the survey were nearly equal—55.2 and 53.3 years, respectively. The cumulative doses were 24.5 mSv and 21.1 mSv, respectively, with the cohort having the highest cumulative dose in the category. This difference is due to the selective inclusion of the high-dose group in the cohort, but it is unlikely that a definite bias exists between the two groups.

CONCLUSION

The non-cancer mortality risks of lifestyle, socioeconomic status, and radiation identified in this study were comparable to those reported in previous studies. Despite the limitations of cohort size and observation period, significantly high RRs of smoking, alcohol consumption, frequency of medical examination, breakfast intake, sleep, BMI, job category, and years of education were found. These estimates are comparable with those from previous studies. Radiation showed no significantly high risks, and these estimates were also comparable with previous studies. Taken together, the risk of non-cancer mortality from low-dose radiation is likely smaller than the risk from lifestyle differences.

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