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Research Article

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The Adjustment Effects of Confounding Factors on Radiation Risk Estimates: Findings from A Japanese Epidemiological Study on Low-Dose Radiation Effects (J-EPISODE)

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Abstract

Purpose: To investigate the degree of any decreasing effects for excess relative risk (ERR) of radiation exposure caused by adjusting for smoking and years of education.

Methods: In this cohort study, we assembled a cohort of 41,742 males who responded to a lifestyle questionnaire survey performed in 2003, were registered in the Radiation Dose Registry as Japanese nuclear workers by the end of March 1999. There were a total of 215,000 person-years, while the number of deaths for all cancers excluding leukemia was 978. Poisson regression was used to quantify ERR per Sv and a comparison of ERRs was performed before adjustment for smoking or years of education and after those adjustments.

Findings: For all cancers excluding leukemia, the ERR/Sv was 0.78 (90%CI: -0.65, 2.20). However, it decreased to 0.31 (-1.03, 1.65) when adjusted for smoking and to 0.42 (-0.94, 1.79) when adjusted for years of education. When adjusting for both smoking and years of education, it decreased to 0.08 (-1.22, 1.39).

Conclusion: Our results demonstrate the importance of collecting lifestyle data and adjusting for them when estimating radiation risk.

Keywords: Radiation epidemiology; Confounding factor; Cancer; Smoking-related cancer

Introduction

Current radiation protection standards are based upon the recommendations of the International Commission on Radiological Protection (ICRP). The dose limits of the ICRP are mainly based on the results of the studies of atomic bomb survivors who were acutely exposed to high-dose rate radiation. However, the causal relationship between low-dose rate radiation and health effects remains unclear despite a number of epidemiological studies undertaken to obtain scientific evidence on the health effects of low-dose and low-dose rate of radiation exposure among radiation workers. One reason is that the estimate of radiation risk is likely to be biased or distorted by confounding factors, such as smoking which are known as one of major risk factors that affect mortality. However, very few published studies have adjusted for smoking.

The Institute of Radiation Epidemiology (IRE) of the Radiation Effects Association (REA) initiated an epidemiological study of Japanese nuclear workers in 1990 (J-EPISODE: Japanese epidemiological study on low-dose radiation effects). The follow-up population consists of nuclear workers of Japanese nationality who were registered with the Radiation Dose Registration Center (RADREC) of the REA as of the end of March 1999. A lifestyle questionnaire survey completed by a part of the follow-up population provided information about lifestyle and socio-economic status. We used this information to quantify the effects of these factors on the radiation risk estimate.

Materials and Methods

The follow-up population consisted of workers of Japanese nationality from all nuclear power plants, research institutes, and fuel processing companies registered in the Radiation Dose Registration Center (RADREC) as of the end of March 1999. We confirmed vital status by requesting copies of the residence registration cards (RRCs) of each subject from their municipalities. The RRCs were issued when the subjects were alive, and deleted RRCs were issued when subjects had deceased or moved. The causes of death were obtained for those whose deaths could be ascertained through the RRCs by linking the records with death records approved for use and provided by the Ministry of Health, Labor, and Welfare, Japan. Indices used for record linkage were date of birth, date of death, sex, and municipality code of residence [1]. The dose records supplied by RADREC to the IRE reported each individual's amount of radiation exposure according to fiscal year. Doses below detectable levels were rated as 0 mSv in the present study. Dose data were available for this study for the entire period from 1957 to 2010 and were used to calculate the cumulative radiation dose for individual workers. Personal dose equivalent Hp (10) values were used in the analysis.

The lifestyle questionnaire was distributed by mail to nuclear facility workers who were 40 years old or more 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 percent of workers with less than 10 mSv exposure were sampled. The questionnaire was self-administered and included questions about smoking, years of education, etc. Of those who replied, 41,742 male workers were assembled as a cohort. Female workers were also followed up but were not included in the analysis because they were too few in number.

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We used the person-years method for the death rate denominator and observed deaths for the death rate numerator. The person-years is obtained by summing the number of observed years for each member of the cohort. All individuals contributed person-years at risk, excluding the first two years from the date of reply to the questionnaire [2], 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 analyze radiation risks based on the number of deaths and the person years cross-classified by the attained age (20-, 25-, ... 100+), area of residence (divided into eight areas within Japan), time-dependent radiation dose (<0.005, 0.005-, 0.01-, 0.02-, 0.05-, 0.1+ Sv), smoking status (current, former, never, unknown), and years of education (<10, 10-, 13+, unknown). No adjustment was made for calendar period because the follow-up period was short (2005–2010). Each stratum of the cross-classification included the number of deaths, the number of person years, and the person-weighted mean values of attained age, radiation dose. The model used to estimate radiation risks was a linear excess relative risk (ERR) model:

$$\lambda = \lambda_0(\mathrm{a,r})e^{\alpha 1z1+\alpha 2z2}(1+\beta \mathrm{d})$$

where λ is the death rate at dose, λ_0 is the background death rate (stratified by a: attained age and r: residence), d is the person-year weighted cumulative dose in Sv, z_1 represents the category of smoking status and z_2 represents the category of years of education in each stratum. The parameters α_1 and α_2 represents the coefficient of z_1 and z_2, respectively. β is the ERR per Sv (ERR/Sv). ERR expressed as relative risk (RR) minus one, is equal to a portion of the RR accounted for by radiation dose. We calculated 90% Wald-based confidence intervals. The cross-tabulation and model fitting were performed using the Epicure statistical package [3]. We used this model to examine the confounding effects of smoking and years of education by comparing the ERRs of radiation risks with and without adjustment for smoking and years of education. Cumulative doses were lagged by 10 years.

Results

Approximately 215,000 person-years were accumulated from 2005 to 2010 for 41,742 members of the cohort. The arithmetic mean and standard deviation of age were 54.9 and 9.6 years respectively; the mean cumulative dose was 25.6 mSv at the date on which responders completed the questionnaire.

Regarding all cancers excluding leukemia, adjustment for only attained age and residence (hereafter "basic adjustment") gave an ERR of 0.78. This value decreased to 0.31 when adjusted for smoking. Adjustment for years of education also decreased the ERR value similarly to smoking, to 0.42, and this value further declined to 0.08 with adjustment for both smoking and years of education (Table 1).

Regarding for smoking-related cancer, basic adjustment gave an ERR of 0.68. Adjustment for smoking showed a large decrease to 0.08, whereas adjustment for years of education gave an ERR of 0.35, and adjustment for both smoking and years of education gave an ERR of -0.09 (Table 1).

Discussion

The reduction in ERR following adjustment for smoking was due to the correlation with radiation [4]. The correlation of radiation dose with smoking reflected the differences in smoking rates among job status groups. For example, the group of workers who were engaged in maintenance or repair of pressure vessels, pumps, etc. made up a higher proportion of the high-dose group and also had higher smoking rates.

Adjustment	All cancers excluding leukemia (Obs=978)	Smoking-related cancer[a] (Obs=704)
	ERR/Sv (90% CI)	ERR/Sv (90% CI)
Basic[b]	0.78 (-0.65, 2.20)	0.68 (-0.97, 2.33)
Basic+Smoking	0.31 (-1.03, 1.65)	0.08 (-1.44, 1.60)
Basic+Years of education	0.42 (-0.94, 1.79)	0.35 (-1.24, 1.94)
Basic+Smoking+Years of education	0.08 (-1.22, 1.39)	-0.09 (-1.58, 1.39)
Basic (Excluding lung cancer)	0.19 (-1.36, 1.74)	-0.35 (-2.17, 1.46)

[a]Buccal and pharynx, esophagus, stomach, liver, pancreas, nasal cavity, larynx, lung, bladder, kidney, ureter.
[b]Adjusted only for attained age and residence.

Table 1: The excess relative risk (ERR) for all cancers, excluding leukemia and smoking-related cancer, in nuclear facility workers in Japan.

Sterling et al. have reported the following strong pattern in smoking behavior: 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 [5]. The positive correlation between radiation dose and smoking shown in the present study might therefore reflect the fact that blue-collar workers were more likely to smoke.

An indirect method that excluded lung cancer from all cancers has often been used as a surrogate for adjusting for smoking. However, the ERRs obtained by excluding lung cancer from all cancers excluding leukemia or smoking-related cancers were not similar to the ERRs obtained by adjusting for smoking.

Adjustment for years of education also decreased the ERRs. This reduction was caused by the correlation between radiation and years of education. This correlation possibly arose due to differences in the socioeconomic status of workers in each dose category.

Conclusion

We demonstrated the effect of adjustment for a confounding factor on the reduction of radiation risk estimates. Our results indicate the importance of collecting lifestyle data and adjusting for them when estimating radiation risk.

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Conflicts of Interest

The authors have no conflicts of interest.

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This study protocol conformed to the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labor, and Welfare, Japan and the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The protocol was reviewed and approved by the Research Ethics Committee of the REA.

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