BMJ Open

Korean radiation workers study (KRWS): a prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017359
Article Type:	Protocol
Date Submitted by the Author:	24-Apr-2017
Complete List of Authors:	Seo, Songwon; Korea Institute of Radiological and Medical Sciences, Lim, Wan Young ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Lee, Dal Nim ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Kim, Jung Un ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Cha, Eun Shil ; Korea University College of Medicine, Department of Preventive Medicine Bang, Ye Jin; Korea University College of Medicine, Department of Preventive Medicine Lee, Won; Korea University College of Medicine, Department of Preventive Medicine Park, Sunhoo; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Jin, Young Woo ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Public health
Keywords:	EPIDEMIOLOGY, OCCUPATIONAL & INDUSTRIAL MEDICINE, PUBLIC HEALTH

Korean radiation workers study (KRWS): a prospective cohort study

Songwon Seo[1], Wan Young Lim[1], Dal Nim Lee[1], Jung Un Kim[1], Eun Shil Cha[2], Ye Jin Bang[2], Won Jin Lee [2], Sunhoo Park[1], Young Woo Jin[1,*]

[1]Laboratory of Low Dose Risk Assessment, National Radiation Emergency Medical Center, Korea Institute of Radiological and Medical Sciences, Seoul, Korea
[2]Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

*Correspondence to: Young Woo Jin, M.D., Ph.D.
National Radiation Emergency Medical Center, Korea Institute of Radiological and Medical Sciences, 75 Nowon-ro, Nowon-gu, Seoul 139-706, Republic of Korea
Tel: +82-2-3399-5800; Fax: +82-2-3399-5870; E-mail: ywjin@kirams.re.kr

Word count: 2479 words

Keywords: radiation worker; epidemiology; cohort; exposure; health

ABSTRACT

Introduction: The cancer risk of radiation exposure in the moderate-to-high dose range has been well established. However, the risk remains unclear at low-dose ranges with protracted low-dose rate exposure, which is typical of occupational exposure. Several epidemiological studies of Korean radiation workers have been conducted, and the data were predominantly collected and analyzed in a retrospective manner. Moreover, relatively highly exposed groups, such as non-destructive testing (NDT) workers, have been neglected. Thus, we have launched a prospective cohort study of all Korean radiation workers to assess the health effects associated with occupational radiation exposure.

Methods and analysis: Approximately 42,000 Korean radiation workers registered with the Nuclear Safety and Security Commission (NSSC) were the target population of this study. Cohort participants are to be enrolled through a nationwide self-administered questionnaire survey between May 24, 2016, and June 30, 2017. As of March 31, 2017, 22,982 workers are enrolled in the study corresponding to a response rate of 75%. Survey data will be linked with the national dose registry, the national cancer registry, the national vital statistics registry, and national health insurance data via personal identification numbers. Age- and sex-specific standardized incidence and mortality ratios will be calculated for overall comparisons of cancer risk. For the assessment of dose-response, excess relative risk (ERR/Gy) and excess absolute risk (EAR/Gy) will be estimated with adjustments for birth year and potential confounders, such as lifestyle factors and socioeconomic status.

Ethics and dissemination: This study has received ethical approval from the institutional review board of the Korea Institute of Radiological and Medical Sciences. All participants provided written informed consent prior to enrollment. The findings of the study will be disseminated through scientific peer-reviewed journals and the study website.

Strengths and limitations:

Strengths:

- Prospective cohort study of "radiation workers", including all occupations
- Data linkage of the national health resources including cancer, non-cancer disease, and laboratory biomarkers
- Adjustment for potential confounding variables

Limitations:

- Limited sample size and retired workers not included in the cohort
- Continued long term follow-up is necessary to extract full value from the cohort

INTRODUCTION

Studies of radiation workers provide an opportunity to assess the health risks of low-dose ionizing radiation. Various epidemiological studies of radiation workers have been conducted in the form of national or international collaborative studies.[1, 2] Due to large uncertainties inherent in low dose radiation studies, including incomplete information on radiation dose, limited sample size, and lack of information on confounders, results from most studies were inconsistent across counties and were predominantly observed without statistical significance.[2, 3] However, adverse health effects, such as cancer and circulatory diseases, have been reported in some single-nation studies, from Russia,[4-6] the U.S.,[7-10] Canada,[11] and France.[12] In addition, a recent international large-scale cohort study indicated an increased risk of cancer from protracted low dose exposure.[13, 14] Although these international efforts have been able to accumulate scientific evidence of health effects in occupationally-exposed populations, findings from these studies at low-dose ranges, particularly <100 mSv, should be interpreted with caution due to wide confidence intervals for risk estimates, heterogeneity of baseline risk, and limited information on confounders. Thus, to supplement international collaborative studies, it is important to evaluate the health effects of low-dose ionizing radiation in national studies reflecting the characteristics of the particular country, including comprehensive information on confounding factors.

In Korea, radiation workers are registered with two independent government agencies depending on their occupation: diagnostic radiation workers under the Centers for Disease Control and Prevention (CDC), and nuclear-related workers under the Nuclear Safety and Security Commission (NSSC). Nuclear-related workers are called “radiation workers” throughout this paper. A prospective cohort study of diagnostic radiation workers was launched about five years ago [15, 16] following the suggestion of an elevated cancer risk in diagnostic medical workers from a retrospective study.[17] For radiation workers, few studies have been conducted, and are predominantly retrospective, which display the healthy worker effect and provide limited evidence of radiation-related cancer risks due to short follow-up and limited information on confounding variables.[18, 19] Moreover, non-destructive testing (NDT) as an occupation has been reported to not only have the highest effective dose,[20] but also accounts for the majority of occupational cancer incidence among all radiation-related occupations.[21, 22] However, NDT workers have been relatively neglected compared with nuclear power plant workers.

Therefore, we have launched a prospective cohort study of all Korean radiation workers, including NDT workers, to assess the health effects associated with protracted low-dose radiation exposure, which has comprehensive information on potential confounding variables and long-term follow-up.

METHODS AND ANALYSIS

Study population and design

The Korean radiation workers study (KRWS) is a prospective cohort study, and the target population includes approximately 42,000 Korean radiation workers registered with the NSSC from 2016-2017. Korean radiation workers are categorized into 10 occupations depending on their workplace: nuclear power plant, NDT, industry, medical institute (except diagnostic radiation workers), education institute, public institute, military, production, and sales. Of these, nuclear power plant workers are in the majority with >14,000 workers, followed by NDT and industry workers.[20] Average annual doses in the last five years have been reported to be below or near 1 mSv; however, NDT workers are exposed to the highest doses of 2-4 mSv.[20] The number of workers and their annual average radiation doses by occupation in the past five years are presented in Figure 1.[20]

All radiation workers in Korea should receive radiation safety education every year. In order to enroll the participants, we will visit each educational location across the country between May 24, 2016, and June 30, 2017, to conduct the self-administered questionnaire survey and collect informed consent. As of March 31, 2017, of 30,572 workers that participated in radiation safety education, 22,982 workers have been enrolled in the study, which corresponds to a response rate of 75%. Following enrollment, we shall combine the data from the questionnaires with dosimetry data from the national dose registry, and link the data with secondary health data via personal identification numbers. Regarding the secondary health data, cancer incidence will be derived from the national cancer registry, overall mortality from the national vital statistics registry, and incidence of non-cancer diseases from national health examination data. We will continually evaluate the association between radiation dose and health effects with long-term follow-up. The study design is presented in Figure 2.

Survey questionnaire and informed consent form

A self-administered questionnaire was developed by referring to the previous cohort studies of Korean diagnostic radiologic technologists and the U.S. Radiologic Technologists (USRT),[23, 24] which was amended through a pilot survey. The questionnaire was composed of 20 questions about general work history and lifestyle factors, and 10 demographic questions for all radiation workers (Table 1). The 20 questions asked to all workers covered occupational history, work practices, exposure warnings, medical exposure, medical history, and lifestyle factors. For NDT workers only, we added 11 NDT-specific questions in order to collect more detailed information on their work status and exposure to other harmful agents. These additional questions for NDT workers included specific working types, history of specific health examination, and exposure to other NDT-related harmful agents, such as film developer and cleaning fluids. In addition to the survey questionnaire, an informed consent form was developed based on the Privacy Act in Korea,[25] which included five essential items about the collection and use of personal information, collection and use of identifying information, collection and use of sensitive information, sharing of personal information with third parties, and consent to research participation.

Table 1. Items collected in the survey questionnaire

Domains	Items
Occupational history	Calendar year of entry, duration of employment, employment status, and frequency of radiation procedures
Work practices	Badge wearing, use of shield wall, wearing of protective equipment, radiation sources, and distance from radiation sources
Experience of high radiation exposure	Warning for exceeding 5 mSv/quarter, and lower white blood cell levels than normal
Medical radiation exposure	Plain radiography, intraoral or panoramic radiography, computed tomography, fluoroscopy, nuclear medicine imaging, nuclear medicine therapy, mammography, interventional radiography, and radiation therapy
Medical history	Cancer, hypertension, stroke, myocardial infarction, angina, cataracts, diabetes, etc. (30 diseases)
Lifestyle factors	Sleep pattern, smoking, alcohol consumption, physical exercise, and night shifts
Demographics	Name, age, sex, education level, marital status, height, weight, and contact details

Sample size calculation

As this study is designed to investigate with long-term follow-up radiation-related health effects for the entire cohort of radiation workers in 2016-2017, a sample size calculation is not deemed relevant. Based on the participation rate of the study from the on-going nationwide survey, we expect that ~29,000 workers (70% of the target population) will be enrolled in the cohort study. In Korea, the crude incidence rate of all cancer types in 2013 was 446 per 100,000 people.[26] Assuming a baseline cancer incidence rate of about 450 per 100,000 person-years and an average follow-up duration of 10-20 years, detectable relative risks would be 1.1-1.15 for a one-sided 5% significance level and 80% power using a Poisson regression model.

Analysis plan

Data linkage of self-administered survey data, dosimetry, and health information

Once we complete the nationwide survey, survey data for individual workers will be linked with the national dose registry and health data via personal identification numbers. The NSSC has been managing workers' radiation doses through monitoring of individual doses. External and internal doses are collected by measuring effective doses and committed effective doses quarterly and annually, respectively. The electronic dose record database for all workers has been available since 1984 in the Central Registry for Radiation Worker Information. For individuals who were working before 1984, radiation doses were not documented; therefore, we will estimate their historical occupational exposure using a dose reconstruction model that includes predictors such as age, sex, and work place[27]. In addition to radiation dose, the central registry includes workers' names, sex, job classification, and personal identification numbers including date of birth. Health information for individual workers in this study is to be collected from the National Cancer Registry, the National Vital Statistics Registry, and the National Health Insurance Sharing Service (NHISS) database (Table 2). National Cancer Registry data includes cancer incidence data and the National Vital Statistics Registry includes mortality data, which have been available since 1999 and 1991, respectively. The NHISS database consists of four major sub-datasets, including an eligibility database, medical treatment database, health examination database, and medical care institution database, which have been available since 2002[28, 29]. We will predominantly use the first three databases and the information derived from these databases includes medical care history, regular health check-ups, and socioeconomic variables.

Table 2. Health data collected from the national sources

National sources	Major items
National Cancer Registry	Cancer code (ICD-10), site, stage, diagnosis method, and date of diagnosis
National Vital Statistics Registry	Date of death and cause of death
National Health Insurance Sharing Service	Eligibility database (14 variables): date of birth, type of eligibility, gender, income level, disability, etc.
	Medical treatment database (56 variables): records of inpatient and outpatient usage (length of stay, treatment costs, services received, etc.), diagnosis (International Classification of Disease-10 codes), prescription, etc.
	Health examination database (41 variables): health behaviors from questionnaire, general health examination data including cancer screening and laboratory tests for blood and urine, etc.

Validity and reliability of self-administered questionnaires

Information collected from self-administered questionnaires is essential for estimating organ doses and determining confounders, which can interpret findings more accurately. It is therefore of particular importance that we evaluate the validity and reliability of our questionnaires, particularly those measuring work practice and lifestyle. Our questionnaire has some items about work history and medical history, which we can also ascertain from the National Dose Registry and National Health Records (i.e., the cancer registry and NHISS database). We will compare answers to these questions with the national records in order to assess the validity of the responses to the self-administered questionnaires. For the evaluation of reliability, we will compare responses of study participants who were surveyed in both 2016 and 2017. Intra-class correlation coefficients[30] and kappa coefficients[31, 32] will be used as measures of validity and reliability.

Health risk associated with ionizing radiation exposures

The primary health outcomes of this study include incidence of cancer or non-cancer diseases (such as cataracts and circulatory disease), and mortality. Other outcomes are laboratory biomarkers from the NHISS databases, which are possibly associated with pre-disease conditions, such as metabolic risk profile (e.g., obesity, high serum glucose, cholesterol level, low blood pressure) and abnormal blood cell counts. Age- and sex-specific standardized incidence and mortality ratios will be calculated for overall comparisons of cancer risk. Study subjects whose doses are below the minimum recording level of 0.1 mSv shall be considered as the control group for the internal comparison, and national statistics for the general Korean population will be employed for the external comparison. For individual radiation dose to be used for the analysis of a dose-response relationship, we will use organ doses estimated from effective dose in the National Dose Registry, and information about work practices from the nationwide survey using previous methods applied to the Million Worker Study (MWS) [33] and the U.S. Radiologic Technologists (USRT) study.[34] For the assessment of dose-response, we will estimate radiation risk per unit of radiation dose (i.e., ERR/Gy, EAR/Gy) using a parametric model (Poisson), penalized splines, and/or Bayesian semiparametric models[35] with or without adjustment for birth cohort and confounding factors, such as lifestyle and socioeconomic status. All the analyses will be updated at follow-up intervals of three to five years.

Potential impact and future work

We have designed the KRWS to assess health effects among Korean radiation workers exposed to protracted low-dose radiation. This is the first prospective cohort study of active workers from the entire range of occupations registered with the NSSC. Data collected from the nationwide survey will provide detailed information on work practices and lifestyle factors, which allows for an in-depth exploration of occupational exposure and adjustment for confounding. In addition, individual health data derived from the national resources include not only cancer/non-cancer diseases, but also pre-disease conditions including laboratory biomarkers, ensuring comprehensive and accurate information for the evaluation of health effects from radiation exposure. Study findings will be directly relevant to radiation protection for radiation workers, and will further provide the basis for recommendations and regulations on low-dose radiation safety.

Besides establishing scientific evidence for radiation-related health effects, we expect that this study will contribute to both the prevention of adverse health effects and improved communication with radiation workers. We will continue to introduce this cohort study and its results via radiation safety education and the study website (http://www.rhs.kr/), which is a former website for Korean diagnostic radiation worker studies [15, 16], that has been combined with the KRWS to increase understanding about occupational exposure and health effects. Consequently, radiation workers will be encouraged to pay more attention to radiation protection in their workplaces, and to accomplish their work duties with a balanced risk judgement about potential exposure that is not solely based on perceived risk.

Lack of statistical power is a major limitation in most epidemiological studies, particularly for low-dose ranges (i.e., <100 mSv). Average annual dose for the KRWS's population in the past five years is approximately 1 mSv (0-4 mSv depending on occupation).[20] Given that there was still a lack of statistical power in low-dose ranges in the recent large scale international Nuclear Workers Study (INWORKS) with an average individual cumulative dose of 21 mGy,[14] the effect size from the expected sample size of this cohort study would not allow a definitive conclusion. In order to increase the sample size of the study, it is necessary to expand the cohort through continuous enrollment of new radiation workers, and through collaborative studies, including with the Korean diagnostic radiation worker cohort, and international cohorts of similar occupations, such as the INWORKS [14] and the USRT.[36] Another limitation is that the current KRWS does not include retired workers. Given the average annual occupational doses of 1-3 mSv before 2000,[37] the radiation dose of retired workers is expected to be higher, and their ages to be higher than those of currently active workers of the KRWS cohort. Thus, it is important to include them in any future study as this could possibly increase statistical power, via an increase in the number of events and larger exposure variance.[38, 39] In addition, collection of biosamples, such as blood and buccal cells, should be considered for a comprehensive understanding of biological mechanisms via molecular epidemiologic studies of radiation risk.[40] These activities will enhance our ability to investigate susceptibility and surrogate biomarkers for assessing exposure risk, and to thereby develop more sophisticated dose-response models for low-dose risk assessments.

ETHICS AND DISSEMINATION

This study has received ethical approval from the institutional review board of the Korea Institute of Radiological And Medical Sciences (IRB No. K-1603-002-034). All participants provided written informed consent prior to enrollment. The findings of the study will be disseminated through scientific peer-reviewed journals and be provided to the public, including radiation workers, via the study website (http://www.rhs.kr/) and onsite radiation safety education.

Author contributions: SS and YWJ conceived and designed this study and drafted the manuscript. WRL and DNL are involved in coordination of the nationwide survey. WRL, DNL and JUK are involved in the collection of data and the construction of the cohort database. ESC and YJB designed the survey questionnaire. WJL and SP contributed to the design of the study and provided valuable inputs relevant to study implementation. YWJ obtained funding. All authors reviewed and approved the final manuscript.

Funding: This research was supported by the Nuclear Safety Research Program through the Korea Foundation of Nuclear Safety (KOFONS), and granted financial resources by the Nuclear Safety and Security Commission (NSSC) of the Republic of Korea (No. 1503008).

Competing interests: None

Ethics approval: This study has received ethical approval from the institutional review board of the Korea Institute of Radiological and Medical Sciences (IRB No. K-1603-002-034).

Provenance and peer review: Not yet commissioned; to be externally peer reviewed.

REFERENCES

1. Cardis E, Vrijheid M, Blettner M, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. *Radiat Res* 2007;167:396-416.
2. Seong KM, Seo S, Lee D, et al. Is the Linear No-Threshold Dose-Response Paradigm Still Necessary for the Assessment of Health Effects of Low Dose Radiation? *J Korean Med Sci* 2016;31:S10–23.
3. National Council on Radiation Protection and Measurements. Uncertainties in the estimation of radiation risks and probability of disease causation, NCRP Report No. 171. Bethesda, MD: National Council on Radiation Protection and Measurements; 2012.
4. Gilbert ES, Koshurnikova NA, Sokolnikov ME, et al. Lung cancer in Mayak workers. *Radiat Res* 2004;162:505–16.
5. Hunter N, Kuznetsova IS, Labutina EV, et al. Solid cancer incidence other than lung, liver and bone in Mayak workers: 1948-2004. *Br J Cancer* 2013;109:1989–96.
6. Shilnikova NS, Preston DL, Ron E, et al. Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat Res* 2003;159:787–98.
7. Rajaraman P, Doody MM, Yu CL, et al. Incidence and mortality risks for circulatory diseases in US radiologic technologists who worked with fluoroscopically guided interventional procedures, 1994-2008. *Occup Environ Med* 2016;73:21–7.
8. Preston DL, Kitahara CM, Freedman DM, et al. Breast cancer risk and protracted low-to-moderate dose occupational radiation exposure in the US Radiologic Technologists Cohort, 1983-2008. *Br J Cancer* 2016;115:1105–12.
9. Matanoski GM, Tonascia JA, Correa-Villasenor A, et al. Cancer risks and low-level radiation in U.S. shipyard workers. *J Radiat Res* 2008;49:83–91.
10. Richardson DB, Wing S. Leukemia mortality among workers at the Savannah River Site. *Am J Epidemiol* 2007;166:1015–22.
11. Zablotska LB, Lane RS, and Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. *Br J Cancer* 2014;110:214–23.
12. Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med* 2013;70:630–8.
13. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). *BMJ* 2015;351:h5359.

14. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. *Lancet Haematol* 2015;2:e276–81.
15. Lee WJ, Ha M, Hwang SS, et al. The radiologic technologists' health study in South Korea: study design and baseline results. *Int Arch Occup Environ Health* 2015;88:759–68.
16. Lee J, Cha ES, Jeong M, et al. A national survey of occupational radiation exposure among diagnostic radiologic technologists in South Korea. *Radiat Prot Dosimetry* 2015;167:525–31.
17. Choi KH, Ha M, Lee WJ, et al. Cancer risk in diagnostic radiation workers in Korea from 1996 to 2002. *Int J Environ Res Public Health* 2013;10:314–27.
18. Jeong M, Jin YW, Yang KH, et al. Radiation exposure and cancer incidence in a cohort of nuclear power industry workers in the Republic of Korea, 1992-2005. *Radiat Environ Biophys* 2010;49:47–55.
19. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers exposed to ionizing radiation in Korea. *J Occup Environ Med* 2008;50:791–803.
20. NSSC, KINS, KINAC. 2015 Nuclear Safety Yearbook , 2016(In Korea).
21. Korea Occupational Safety and Health Agency: Annual reports of occupational disease (2000–2015). http://english.kosha.or.kr/english/content.do?menuId=10412. (accessed 29 Mar 2017).
22. Jin YW, Jeong M, Moon K, et al. Ionizing radiation-induced diseases in Korea. *J Korean Med Sci* 2010;25:S70–6.
23. The U.S. radiologic technologists study. https://radtechstudy.nci.nih.gov/questionnaires.html (accessed 29 Mar 2017).
24. Radiation and health study among radiation workers in Korea. http://www.rhs.kr/method/overview.asp (accessed 29 Mar 2017).
25. Personal Information Protection Act, Articles 15 to 22 Section 1 (2014).
26. Oh CM, Won YJ, Jung KW, et al. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2013. *Cancer Res Treat* 2016;48:436–50.
27. Choi Y, Kim J, Lee JJ, et al. Reconstruction of Radiation Dose Received by Diagnostic Radiologic Technologists in Korea. *J Prev Med Public Health* 2016;49:288–300.
28. Cheol Seong S, Kim YY, Khang YH, et al. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2016;pii:dyw253 [Epub ahead of print]
29. National Health Insurance Sharing Service in Korea. https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do (accessed 29 Mar 2017).
30. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86:420–8.
31. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol* 1993;46:423–9.

32. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and Psychological Measurement* 1960;20:37–46.
33. Bouville A, Toohey ER, Boice JD Jr, et al. Dose reconstruction for the million worker study: status and guidelines. *Health Phys* 2015;108:206–20.
34. Simon SL, Preston DL, Linet MS, et al. Radiation organ doses received in a nationwide cohort of U.S. radiologic technologists: methods and findings. *Radiat Res* 2014;182: 507–28.
35. Furukawa K, Misumi M, Cologne JB, et al. A Bayesian Semiparametric Model for Radiation Dose-Response Estimation. *Risk Anal* 2016;36:1211–23.
36. Boice JD, Mandel JS Jr, Doody MM, et al. A health survey of radiologic technologists. *Cancer* 1992;69:586–98.
37. Choi SY, Kim TH, Chung CK, et al. Analysis of radiation workers' dose records in the Korean National Dose Registry. *Radiat Prot Dosimetry* 2001;95:143–8.
38. McKeown-Eyssen GE, Thomas DC. Sample size determination in case-control studies: the influence of the distribution of exposure. *J Chronic Dis* 1985;38:559–68.
39. White E, Kushi LH, Pepe MS. The effect of exposure variance and exposure measurement error on study sample size: implications for the design of epidemiologic studies. *J Clin Epidemiol* 1993;47:873–80.
40. Pernot E, Hall J, Baatout S, et al. Ionizing radiation biomarkers for potential use in epidemiological studies. *Mutat Res* 2012;751:258–86.

FIGURE LEGENDS

Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

Figure 2. Study design.

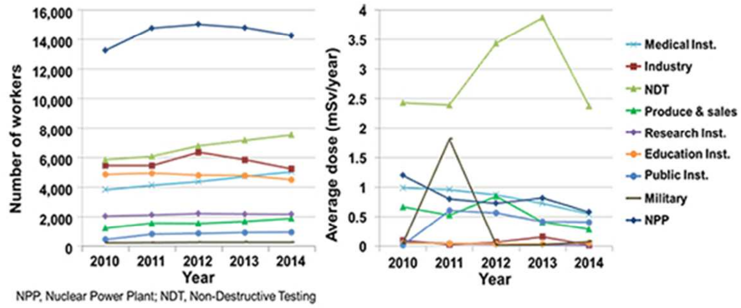

Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

63x42mm (300 x 300 DPI)

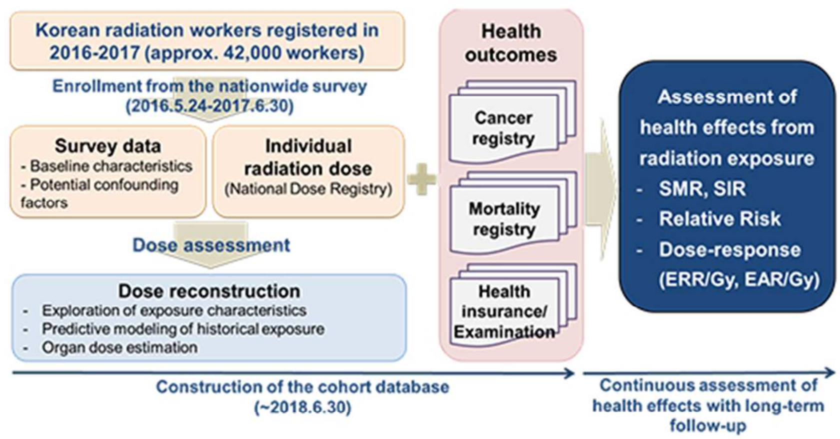

Figure 2. Study design.

Figure 2. Study design.

55x63mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3, 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3, 4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	6 (Will address further details when we submit results of this cohort study)
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6, 7
		(*b*) Describe any methods used to examine subgroups and interactions	6, 7
		(*c*) Explain how missing data were addressed	Will explain this

			when we submit results of this cohort study
		(*d*) If applicable, explain how loss to follow-up was addressed	Will explain this when we submit results of this cohort study
		(*e*) Describe any sensitivity analyses	Will provide them when we submit results of this cohort study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Will provide them when we submit results of this cohort study
		(b) Give reasons for non-participation at each stage	Will provide them when we submit results of this cohort study
		(c) Consider use of a flow diagram	Will provide them when we submit results of this cohort study
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Will provide them when we submit results of this cohort study
		(b) Indicate number of participants with missing data for each variable of interest	Will provide them when we submit results of this cohort

			study
		(c) Summarise follow-up time (eg, average and total amount)	Will provide them when we submit results of this cohort study
Outcome data	15*	Report numbers of outcome events or summary measures over time	Will provide them when we submit results of this cohort study
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Will provide them when we submit results of this cohort study
		(*b*) Report category boundaries when continuous variables were categorized	Will provide them when we submit results of this cohort study
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Will provide them when we submit results of this cohort study
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Will provide them when we submit results of this cohort study
Discussion			
Key results	18	Summarise key results with reference to study objectives	Will provide them when we submit results of this cohort study
Limitations			

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Will provide them when we submit results of this cohort study
Generalisability	21	Discuss the generalisability (external validity) of the study results	Will provide them when we submit results of this cohort study
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Protocol for a prospective cohort study of Korean radiation workers

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017359.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Jun-2017
Complete List of Authors:	Seo, Songwon; Korea Institute of Radiological and Medical Sciences, Lim, Wan Young ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Lee, Dal Nim ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Kim, Jung Un ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Cha, Eun Shil ; Korea University College of Medicine, Department of Preventive Medicine Bang, Ye Jin; Korea University College of Medicine, Department of Preventive Medicine Lee, Won; Korea University College of Medicine, Department of Preventive Medicine Park, Sunhoo; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Jin, Young Woo ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Public health
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, OCCUPATIONAL & INDUSTRIAL MEDICINE

Protocol for a prospective cohort study of Korean radiation workers

Songwon Seo[1], Wan Young Lim[1], Dal Nim Lee[1], Jung Un Kim[1], Eun Shil Cha[2], Ye Jin Bang[2], Won Jin Lee[2], Sunhoo Park[1], Young Woo Jin[1,*]

[1]Laboratory of Low Dose Risk Assessment, National Radiation Emergency Medical Center, Korea Institute of Radiological and Medical Sciences, Seoul, Korea
[2]Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

*Correspondence to: Young Woo Jin, M.D., Ph.D.
National Radiation Emergency Medical Center, Korea Institute of Radiological and Medical Sciences, 75 Nowon-ro, Nowon-gu, Seoul 01812, Republic of Korea
Tel: +82-2-3399-5800; Fax: +82-2-3399-5870; E-mail: ywjin@kirams.re.kr

Word count: 2914 words

Keywords: radiation worker; epidemiology; cohort; exposure; health

ABSTRACT

Introduction: The cancer risk of radiation exposure in the moderate-to-high dose range has been well established. However, the risk remains unclear at low-dose ranges with protracted low-dose rate exposure, which is typical of occupational exposure. Several epidemiological studies of Korean radiation workers have been conducted, but the data were analyzed retrospectively in most cases. Moreover, groups with relatively high exposure, such as industrial radiographers, have been neglected. Therefore, we have launched a prospective cohort study of all Korean radiation workers to assess the health effects associated with occupational radiation exposure.

Methods and analysis: Approximately 42,000 Korean radiation workers registered with the Nuclear Safety and Security Commission from 2016-2017 are the initial target population of this study. Cohort participants are to be enrolled through a nationwide self-administered questionnaire survey between May 24, 2016, and June 30, 2017. As of March 31, 2017, 22,982 workers are enrolled in the study corresponding to a response rate of 75%. This enrollment will be continued at five-year intervals to update information on existing study participants and recruit newly hired workers. Survey data will be linked with the national dose registry, the national cancer registry, the national vital statistics registry, and national health insurance data via personal identification numbers. Age- and sex-specific standardized incidence and mortality ratios will be calculated for overall comparisons of cancer risk. For dose-response assessment, excess relative risk (ERR/Gy) and excess absolute risk (EAR/Gy) will be estimated with adjustments for birth year and potential confounders, such as lifestyle factors and socioeconomic status.

Ethics and dissemination: This study has received ethical approval from the institutional review board of the Korea Institute of Radiological and Medical Sciences. All participants provided written informed consent prior to enrollment. The findings of the study will be disseminated through scientific peer-reviewed journals and the study website.

Strengths and limitations:

Strengths:

- Prospective cohort study of “radiation workers”, including all occupations
- Data linkage of the national health resources including cancer, non-cancer disease, and laboratory biomarkers
- Adjustment for potential confounding variables

Limitations:

- Limited sample size and retired workers not included in the cohort
- Continued long term follow-up is necessary to extract full value from the cohort

INTRODUCTION

Studies of workers in radiation-related occupations provide an opportunity to assess the health risks of low-dose ionizing radiation exposure. Various epidemiological studies of occupational exposure to ionizing radiation have been conducted in the form of national or international collaborative studies.[1, 2] Due to large uncertainties inherent in low dose radiation studies, including incomplete information on radiation dose, limited sample size, and lack of information on confounders, the evidence for an association with radiation, particularly for organ-specific risks, was weak in most studies and more precise risk estimates should be obtained.[2, 3] However, adverse health effects, such as all cancers other than leukemia combined, lung cancer, leukemia excluding chronic lymphocytic leukemia, and circulatory diseases, have been reported in some single-nation studies, from the United Kingdom,[4] Russia,[5-7] the U.S.,[8-12] Canada,[13] and France.[14] In addition, a recent international large-scale cohort study indicated an increased risk of cancer from protracted low dose exposure.[15, 16] Although these international efforts have been able to accumulate scientific evidence of health effects in occupationally-exposed populations and provided more precise dose-response estimates than single-nation studies, findings from these studies at low-dose ranges, particularly <100 mSv, should be still interpreted with caution due to wide confidence intervals for risk estimates and limited information on confounders. Moreover, given that baseline risks possibly differ from nation to nation, generalizations of the findings to other populations should be made with caution. Thus, to supplement international collaborative studies, it is important to evaluate the health effects of low-dose ionizing radiation in national studies reflecting the characteristics of the particular country, including comprehensive information on confounding factors.

In Korea, workers in radiation-related occupations are registered with two independent government agencies depending on their occupation: diagnostic radiation workers under the Centers for Disease Control and Prevention (CDC), and nuclear-related workers under the Nuclear Safety and Security Commission (NSSC). We use the term "radiation workers" for nuclear-related workers henceforth in this paper. A prospective cohort study of diagnostic radiation workers was launched about five years ago[17, 18] following the suggestion of an elevated cancer risk in diagnostic medical workers from a retrospective study.[19] For Korean radiation workers, sparse information is available from two studies that are limited by short follow-up and sparse information on confounding variables.[20, 21] Moreover, industrial radiography which is one of the non-destructive testing (NDT) has been reported to not only have the highest effective dose,[22] but also accounts for the majority of occupational cancer incidence among all radiation-related occupations.[23, 24] However, industrial radiographers have been relatively neglected compared to nuclear power plant workers.

Therefore, we have launched a prospective cohort study of all Korean radiation workers, including industrial radiographers, to assess the health effects associated with protracted low-dose radiation exposure, which has comprehensive information on potential confounding variables and long-term follow-up.

METHODS AND ANALYSIS

Study population and design

The Korean radiation workers study (KRWS) is a prospective cohort study, and the initial target population includes approximately 42,000 Korean radiation workers registered with the NSSC from 2016-2017. Korean radiation workers are categorized into 10 occupations depending on their workplace: nuclear power plant, industrial radiography, industry, medical institute (except diagnostic radiation workers), education institute, public institute, military, production, and sales. Of these, nuclear power plant workers are in the majority with >14,000 workers, followed by industrial radiography and industrial workers.[22] Average annual doses in the last five years have been reported to be below or near 1 mSv; however, industrial radiographers are exposed to the highest doses of 2-4 mSv.[22] The number of workers and their annual average radiation doses by occupation in the past five years are presented in figure 1.[22]

All radiation workers in Korea should receive radiation safety education every year. In order to enroll the participants, we visit each educational location across the country between May 24, 2016, and June 30, 2017, to conduct the self-administered questionnaire survey and collect informed consent. As of March 31, 2017, of 30,572 workers that participated in radiation safety education, 22,982 workers have been enrolled in the study, which corresponds to a response rate of 75%. Following enrollment, we shall combine the data from the questionnaires with dosimetry data from the national dose registry, and link the health data via personal identification numbers. The health data will include cancer incidence data from the national cancer registry, overall mortality data from the national vital statistics registry, and incidence of diseases other than cancer from national health examination data. We will conduct the self-administered questionnaire survey at five-year intervals to update information on existing study participants, recruit newly hired workers, and evaluate the association between radiation dose and health effects on long-term follow-up. The study design is presented in figure 2.

Survey questionnaire and informed consent form

A self-administered questionnaire was developed by referring to the previous cohort studies of Korean diagnostic radiologic technologists and the U.S. Radiologic Technologists (USRT),[25, 26] which was amended through a pilot survey. The questionnaire was composed of 20 questions about general work history and lifestyle factors, and 10 demographic questions for all radiation workers (table 1). The 20 questions asked to all workers covered occupational history, work practices, exposure warnings, medical exposure, medical history, and lifestyle factors. For industry radiographers only, we added 11 NDT-specific questions in order to collect more detailed information on their work status and exposure to other harmful agents. These additional questions for industrial radiographers included specific working types, history of specific health examination, and exposure to other NDT-related harmful agents, such as film developer and cleaning fluids. In addition to the survey questionnaire, an informed consent form was developed based on the Privacy Act in Korea,[27] which included five essential items about the collection and use of personal information, collection and use of identifying information, collection and use of sensitive information, sharing of personal information with third parties, and consent to research participation.

Table 1 Items collected in the survey questionnaire

Domains	Items
Occupational history	Calendar year of hiring, duration of employment, employment status, and frequency of radiation procedures
Work practices	Badge wearing, use of shield wall, wearing of protective equipment, radiation sources, and distance from radiation sources
Experience of high radiation exposure	Warning for exceeding 5 mSv/quarter, and lower white blood cell levels than normal
Medical radiation exposure	Plain radiography, intraoral or panoramic radiography, computed tomography, fluoroscopy, nuclear medicine imaging, nuclear medicine therapy, mammography, interventional radiography, and radiation therapy
Medical history	Cancer, hypertension, stroke, myocardial infarction, angina, cataracts, diabetes, etc. (30 diseases)
Lifestyle factors	Sleep pattern, smoking, alcohol consumption, physical exercise, and night shifts
Demographics	Name, age, sex, education level, marital status, height, weight, and contact details

Dosimetry data and health outcomes

We shall collect radiation doses for individual workers from the Central Registry for Radiation Worker Information (CRRWI) managed by the NSSC. External and internal doses are collected by measuring effective doses and committed effective doses quarterly and annually, respectively, through the electronic dose record database (the National Dose Registry), which has been available under the CRRWI since 1984. Most external doses are measured using thermoluminescent dosimeters (TLD). Film badge dosimeters were used in the past, but not anymore. Doses based on film badge dosimeters are less than 10% of the total dose records.[28] It might be challenging to ensure the inclusion of radiation doses from high-Linear Energy Transfer (LET) exposure (e.g., neutrons) in the current Korean dose reporting system; however, since the proportion of workers with potential high-LET exposure is expected to be less than 5%, the impact of high-LET exposure on risk estimates would be minimal. In addition to radiation dose, the database includes workers' names, sex, job classification, and personal identification numbers including date of birth.[28] For individuals who were working before 1984, radiation doses were not documented; therefore, we will estimate their historical occupational exposure using a dose reconstruction model that includes predictors such as age, sex, and work place.[29] For using individual radiation doses to analyze a dose-response relationship, we will use absorbed organ doses estimated from the effective dose in the National Dose Registry. Absorbed organ dose is estimated based on methods using the ICRP 116 organ dose conversion coefficients and irradiation geometry factors,[30] considering information about work practices, such as use of protective devices and badge location, from the nationwide survey as suggested by the Million Worker Study (MWS)[31] and the USRT study.[32]

Health information for individual workers in this study is to be collected from the National Cancer Registry, the National Vital Statistics Registry, and the National Health Insurance Sharing Service (NHISS) database (table 2). The National Cancer Registry includes cancer incidence data and the National Vital Statistics Registry includes mortality data, which have been available since 1999 and 1992, respectively. The NHISS database consists of four major sub-datasets, including an eligibility database, medical treatment database, health examination database, and medical care institution database, which have been available since 2002.[33, 34] We will predominantly use the first three databases and the information derived from these databases includes medical care history, regular health check-ups, and socioeconomic variables.

Table 2 Health data collected from the national sources

National sources	Major items
National Cancer Registry	Cancer code (ICD-10), site, stage, diagnosis method, and date of diagnosis
National Vital Statistics Registry	Date of death and cause of death
National Health Insurance Sharing Service	Eligibility database (14 variables): date of birth, type of eligibility, gender, income level, disability, etc.
	Medical treatment database (56 variables): records of inpatient and outpatient usage (length of stay, treatment costs, services received, etc.), diagnosis (International Classification of Disease-10 codes), prescription, etc.
	Health examination database (41 variables): health behaviors from questionnaire, general health examination data including cancer screening and laboratory test items (e.g., blood cell counts, cholesterol levels, triglyceride concentration, fasting blood sugar, liver enzyme tests (AST/SGOT, ALT/SGPT, γ-GTP), serum creatinine, urinary protein, and e-GFR), etc.

Validity and reliability of self-administered questionnaires

Information collected from self-administered questionnaires is essential for estimating organ doses and determining confounders, which can interpret findings more accurately. It is therefore of particular importance that we evaluate the validity and reliability of our questionnaires, particularly those measuring work practice and lifestyle. Our questionnaire has items about work history (e.g., employment start date and period, and warning for exceeding 5 mSv) and medical history (e.g., diagnosis of cancer, cataract, and cardiovascular disease), which we can also ascertain from the National Dose Registry and National Health Records (i.e., the cancer registry and NHISS database). We will compare the answers to our questions with the national records in order to assess the validity of the responses to the self-administered questionnaires. For the evaluation of reliability, we will compare responses of study participants who were surveyed in both 2016 and 2017. Intra-class correlation coefficients[35] and kappa coefficients[36, 37] will be used as measures of validity and reliability.

Health risk associated with ionizing radiation exposure

The primary health outcome of this study is cancer incidence. Other outcomes include incidence of non-cancer diseases (e.g., cataracts and circulatory disease), laboratory biomarkers (i.e., laboratory test items) from the NHISS databases, and mortality. The laboratory biomarkers are possibly associated with pre-disease conditions, such as metabolic risk profile (e.g., obesity, high serum glucose, cholesterol level, and low blood pressure) and abnormal blood cell counts. For example, the metabolic risk profile can be considered a surrogate endpoint of cardiovascular disease, and also an independent variable to explore an interaction effect between radiation exposure and metabolic syndrome with regard to cardiovascular disease. Age- and sex-specific standardized incidence and mortality ratios will be calculated for overall comparisons of cancer risk. The national statistics for cancer incidence and mortality among the general Korean population will be employed as the control group for external comparison, and study subjects whose effective doses have not exceeded the minimum recording level of 0.1 mSv/quarter for external exposure and 0.1 mSv/year for internal exposure during their employment according to the National Dose Registry shall be considered as the control group for internal comparison. Risk estimates for radiation exposure are typically presented as excess relative risk (ERR) and excess absolute risk (EAR). The ERR is the relative risk minus 1.0, which refers to the magnitude of the radiation risk relative to the baseline. The EAR refers to the difference between the rate in an exposed and an unexposed population. To quantify the dose-response relationship, we will estimate health risk per unit of radiation dose (i.e., ERR/Gy, EAR/Gy) using a parametric model (Poisson), penalized splines, and/or Bayesian semiparametric models[38] with or without adjustment for birth cohort and confounding factors, such as lifestyle and socioeconomic status. Person-years at risk for the analysis are calculated from date of entry in the study (defined as the latest among the date of the first exposure and date of start of follow-up period in the national health data source) to date of exit (defined as the earliest among the date of health events, date of loss to follow-up and date of end of follow-up). To allow for a possible latency period between radiation exposure and its consequences, cumulative doses will be lagged by 2-5 years for leukemia and 5-10 years for solid cancers. All the analyses will be updated at follow-up intervals of three to five years.

Sample size calculation

As this study is designed to investigate radiation-related health effects with long-term follow-up in a cohort targeting all Korean radiation workers, a sample size calculation is not deemed relevant.

Study limitations and future work

Lack of statistical power is a major limitation in most epidemiological studies, particularly for low-dose ranges (i.e., <100 mSv). Average annual dose for the

KRWS's population in the past five years is approximately 1 mSv (0-4 mSv depending on occupation).[22] Given that there was still a lack of statistical power in low-dose ranges in the recent large scale international Nuclear Workers Study (INWORKS) with an average individual cumulative dose of 21 mGy,[16] this study including a relatively young cohort would not allow a definitive conclusion in a short period of time. In addition, this study is limited in terms of investigation of health effects in women since the proportion of female workers in the cohort is expected to be 10-20%.[28, 39] Thus, it is necessary to expand the cohort through continuous enrollment of new radiation workers with a long follow-up, and through collaborative studies, including with the Korean diagnostic radiation worker cohort, and international cohorts of similar occupations, such as the INWORKS[16] and the USRT.[40] Another limitation is that the current KRWS does not include retired workers and has limited information of radiation doses for those who had worked before 1984 since the electronic National Dose Registry was not available before. As the beginning of nuclear activities in Korea, a research reactor was first introduced at 1962, and the first nuclear power plant opened in 1978.[41] Given that the average annual occupational doses were 1-3 mSv before 2000,[28] the radiation dose of retired workers is expected to be higher, and their ages to be higher than those of currently active workers of the KRWS cohort. Thus, it is important to include them in any future study as this could possibly increase statistical power, via an increase in the number of events and larger exposure variance.[42, 43] In addition, collection of biosamples, such as blood and buccal cells, should be considered for a comprehensive understanding of biological mechanisms via molecular epidemiologic studies of radiation risk.[44] These activities will enhance our ability to investigate susceptibility and surrogate biomarkers for assessing exposure risk, and to thereby develop more sophisticated dose-response models for low-dose risk assessments.

Potential impact

We have designed the KRWS to assess health effects among Korean radiation workers exposed to protracted low-dose radiation. This is the first prospective cohort study of active workers from the entire range of occupations registered with the NSSC. Data collected from the nationwide survey will provide detailed information on work practices and lifestyle factors, which allows for an in-depth exploration of occupational exposure and adjustment for confounding factors. In addition, individual health data derived from the national resources include not only cancer/non-cancer diseases, but also pre-disease conditions including laboratory test items, ensuring comprehensive and accurate information for the evaluation of health effects from radiation exposure. Study findings will be directly relevant to radiation protection for radiation workers, and will further provide the basis for recommendations and regulations about low-dose radiation safety.

Besides establishing scientific evidence for radiation-related health effects, we expect that this study will contribute to both the prevention of adverse health effects and improved communication with radiation workers. We will continue to promote this cohort study and its results via radiation safety education and the study website (http://www.rhs.kr/), which is a former website for Korean diagnostic radiation worker studies[17, 18], that has been combined with the KRWS to increase understanding about occupational exposure and health effects. Consequently, radiation workers will be encouraged to pay more attention to radiation protection in their workplaces, and to accomplish their work duties with a balanced risk judgment about potential exposure that is not solely based on perceived risk.

ETHICS AND DISSEMINATION

This study has received ethical approval from the institutional review board of the Korea Institute of Radiological and Medical Sciences (IRB No. K-1603-002-034). All participants provided written informed consent prior to enrollment. The findings of the study will be disseminated through scientific peer-reviewed journals and be provided to the public, including radiation workers, via the study website (http://www.rhs.kr/) and onsite radiation safety education.

Author contributions: SS and YWJ conceived and designed this study and drafted the manuscript. WRL and DNL are involved in coordination of the nationwide survey. WRL, DNL and JUK are involved in the collection of data and the construction of the cohort database. ESC and YJB designed the survey questionnaire. WJL and SP contributed to the design of the study and provided valuable inputs relevant to study implementation. YWJ obtained funding. All authors reviewed and approved the final manuscript.

Funding: This research was supported by the Nuclear Safety Research Program through the Korea Foundation of Nuclear Safety (KOFONS), and granted financial resources by the Nuclear Safety and Security Commission (NSSC) of the Republic of Korea (No. 1503008).

Competing interests: None

Ethics approval: This study has received ethical approval from the institutional review board of the Korea Institute of Radiological and Medical Sciences (IRB No. K-1603-002-034).

Provenance and peer review: Not yet commissioned; to be externally peer reviewed.

REFERENCES

1. Cardis E, Vrijheid M, Blettner M, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. Radiat Res 2007;167:396-416.
2. Seong KM, Seo S, Lee D, et al. Is the Linear No-Threshold Dose-Response Paradigm Still Necessary for the Assessment of Health Effects of Low Dose Radiation? *J Korean Med Sci* 2016;31:S10–23.
3. Navid F, Sondel PM, Barfield R, et al. Phase I trial of a novel anti-GD2 monoclonal antibody, Hu14.18K322A, designed to decrease toxicity in children with refractory or recurrent neuroblastoma. *J Clin Oncol* 2014;32:1445-52
4. Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer* 2009;100:206-12.
5. Gilbert ES, Koshurnikova NA, Sokolnikov ME, et al. Lung cancer in Mayak workers. *Radiat Res* 2004;162:505–16.
6. Hunter N, Kuznetsova IS, Labutina EV, et al. Solid cancer incidence other than lung, liver and bone in Mayak workers: 1948-2004. *Br J Cancer* 2013;109:1989–96.
7. Shilnikova NS, Preston DL, Ron E, et al. Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat Res* 2003;159:787–98.
8. Rajaraman P, Doody MM, Yu CL, et al. Incidence and mortality risks for circulatory diseases in US radiologic technologists who worked with fluoroscopically guided interventional procedures, 1994-2008. *Occup Environ Med* 2016;73:21–7.
9. Preston DL, Kitahara CM, Freedman DM, et al. Breast cancer risk and protracted low-to-moderate dose occupational radiation exposure in the US Radiologic Technologists Cohort, 1983-2008. *Br J Cancer* 2016;115:1105–12.
10. Matanoski GM, Tonascia JA, Correa-Villasenor A, et al. Cancer risks and low-level radiation in U.S. shipyard workers. *J Radiat Res* 2008;49:83–91.
11. Richardson DB, Wing S. Leukemia mortality among workers at the Savannah River Site. *Am J Epidemiol* 2007;166:1015–22.
12. Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer Mortality through 2005 among a Pooled Cohort of U.S. Nuclear Workers Exposed to External Ionizing Radiation. *Radiat Res* 2015;183:620-31
13. Zablotska LB, Lane RS, and Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. *Br J Cancer* 2014;110:214–23.
14. Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med* 2013;70:630–8.
15. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). *BMJ* 2015;351:h5359.
16. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. *Lancet Haematol* 2015;2:e276–81.

17. Lee WJ, Ha M, Hwang SS, et al. The radiologic technologists' health study in South Korea: study design and baseline results. Int Arch Occup Environ Health 2015;88:759–68.
18. Lee J, Cha ES, Jeong M, et al. A national survey of occupational radiation exposure among diagnostic radiologic technologists in South Korea. *Radiat Prot Dosimetry* 2015;167:525–31.
19. Choi KH, Ha M, Lee WJ, et al. Cancer risk in diagnostic radiation workers in Korea from 1996 to 2002. *Int J Environ Res Public Health* 2013;10:314–27.
20. Jeong M, Jin YW, Yang KH, et al. Radiation exposure and cancer incidence in a cohort of nuclear power industry workers in the Republic of Korea, 1992-2005. *Radiat Environ Biophys* 2010;49:47–55.
21. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers exposed to ionizing radiation in Korea. *J Occup Environ Med* 2008;50:791–803.
22. Nuclear Safety and Security Commission, Korea Institute of Nuclear Safety, Korea Institute of Nuclear Nonproliferation and Control. 2015 Nuclear Safety Yearbook (2016).
23. Korea Occupational Safety and Health Agency: Annual reports of occupational disease (2000–2015). http://english.kosha.or.kr/english/content.do?menuId=11436. (accessed 20 Jun 2017).
24. Jin YW, Jeong M, Moon K, et al. Ionizing radiation-induced diseases in Korea. *J Korean Med Sci* 2010;25:S70–6.
25. The U.S. radiologic technologists study. https://radtechstudy.nci.nih.gov/questionnaires.html (accessed 20 Jun 2017).
26. Radiation and health study among radiation workers in Korea. http://www.rhs.kr/method/overview.asp (accessed 20 Jun 2017).
27. Personal Information Protection Act, Articles 15 to 22 Section 1 (2014).
28. Choi SY, Kim TH, Chung CK, et al. Analysis of radiation workers' dose records in the Korean National Dose Registry. *Radiat Prot Dosimetry* 2001;95:143–8.
29. Choi Y, Kim J, Lee JJ, et al. Reconstruction of Radiation Dose Received by Diagnostic Radiologic Technologists in Korea. *J Prev Med Public Health* 2016;49:288–300.
30. Taulbee TD, McCartney KA, Traub R, et al. Implementation of ICRP 116 dose conversion coefficients for reconstruction organ dose in radiation compensation program. *Radiat Prot Dosimetry* 2017;173:131–137.
31. Bouville A, Toohey ER, Boice JD Jr, et al. Dose reconstruction for the million worker study: status and guidelines. *Health Phys* 2015;108:206–20.
32. Simon SL, Preston DL, Linet MS, et al. Radiation organ doses received in a nationwide cohort of U.S. radiologic technologists: methods and findings. *Radiat Res* 2014;182:507–28.
33. Cheol Seong S, Kim YY, Khang YH, et al. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2016;pii:dyw253 [Epub ahead of print]
34. National Health Insurance Sharing Service in Korea. https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do (accessed 20 Jun 2017).
35. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86:420–8.

36. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol* 1993;46:423–9.
37. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and Psychological Measurement* 1960;20:37–46.
38. Furukawa K, Misumi M, Cologne JB, et al. A Bayesian Semiparametric Model for Radiation Dose-Response Estimation. *Risk Anal* 2016;36:1211–23.
39. Jeong JH, Lee JK, Kwon, JW, et al. Occupational Radiaiton Exposure in Korea: 2002. *J Korean Assoc Radiat Protect* 2005;30:175-183.
40. Boice JD, Mandel JS Jr, Doody MM, et al. A health survey of radiologic technologists. *Cancer* 1992;69:586–98.
41. Lim YK, Kim JR., Hwang KH, et al. Investigation of Nuclear Development at the Early Stage in Korea (No. KAERI/CM--1022/2007). Korea Atomic Energy Research Institute 2009.
42. McKeown-Eyssen GE, Thomas DC. Sample size determination in case-control studies: the influence of the distribution of exposure. *J Chronic Dis* 1985;38:559–68.
43. White E, Kushi LH, Pepe MS. The effect of exposure variance and exposure measurement error on study sample size: implications for the design of epidemiologic studies. *J Clin Epidemiol* 1993;47:873–80.
44. Pernot E, Hall J, Baatout S, et al. Ionizing radiation biomarkers for potential use in epidemiological studies. *Mutat Res* 2012;751:258–86.

FIGURE LEGENDS

Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

Figure 2. Study design.

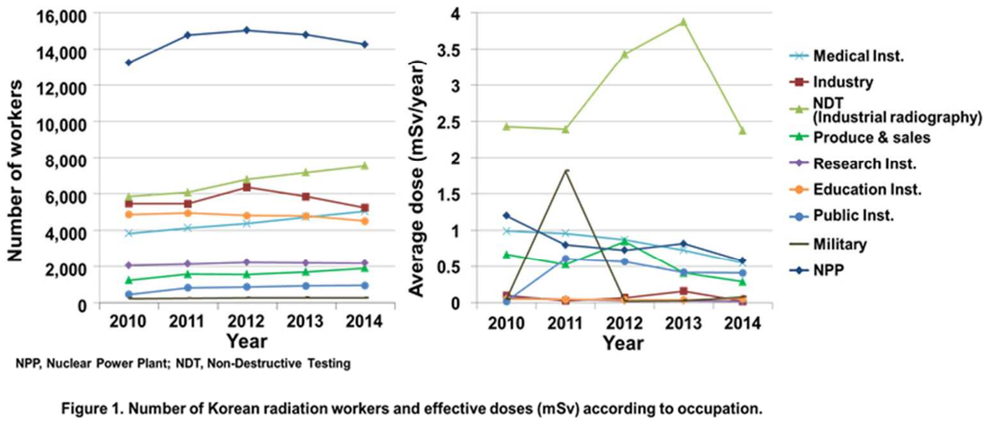

Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

67x46mm (300 x 300 DPI)

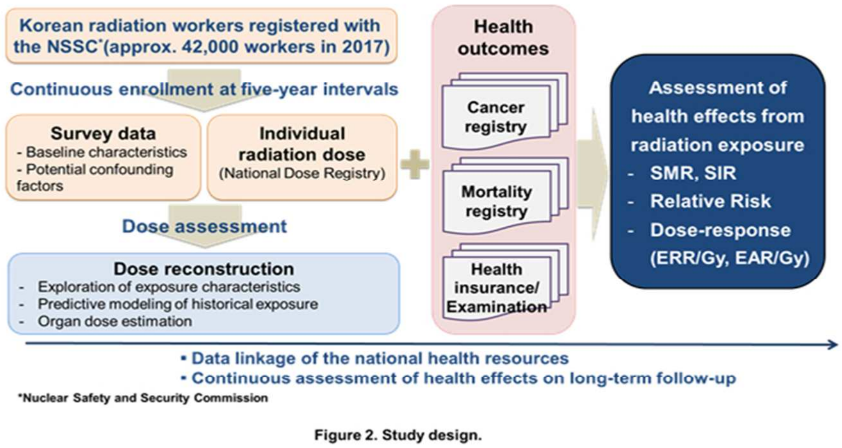

Figure 2. Study design.

67x46mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	7 (Will address further details when we submit results of this cohort study)
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Will explain this

			when we submit results of this cohort study
		(*d*) If applicable, explain how loss to follow-up was addressed	7 (Will address further details when we submit results of this cohort study)
		(*e*) Describe any sensitivity analyses	Will provide them when we submit results of this cohort study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Will provide them when we submit results of this cohort study
		(b) Give reasons for non-participation at each stage	Will provide them when we submit results of this cohort study
		(c) Consider use of a flow diagram	Will provide them when we submit results of this cohort study
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Will provide them when we submit results of this cohort study
		(b) Indicate number of participants with missing data for each variable of interest	Will provide them when we submit results of this cohort

			study
		(c) Summarise follow-up time (eg, average and total amount)	Will provide them when we submit results of this cohort study
Outcome data	15*	Report numbers of outcome events or summary measures over time	Will provide them when we submit results of this cohort study
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Will provide them when we submit results of this cohort study
		(*b*) Report category boundaries when continuous variables were categorized	Will provide them when we submit results of this cohort study
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Will provide them when we submit results of this cohort study
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Will provide them when we submit results of this cohort study
Discussion			
Key results	18	Summarise key results with reference to study objectives	Will provide them when we submit results of this cohort study
Limitations			

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Will provide them when we submit results of this cohort study
Generalisability	21	Discuss the generalisability (external validity) of the study results	Will provide them when we submit results of this cohort study
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Assessing the health effects associated with occupational radiation exposure in Korean radiation workers: protocol for a prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017359.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Aug-2017
Complete List of Authors:	Seo, Songwon; Korea Institute of Radiological and Medical Sciences, Lim, Wan Young ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Lee, Dal Nim ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Kim, Jung Un ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Cha, Eun Shil ; Korea University College of Medicine, Department of Preventive Medicine Bang, Ye Jin; Korea University College of Medicine, Department of Preventive Medicine Lee, Won; Korea University College of Medicine, Department of Preventive Medicine Park, Sunhoo; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center Jin, Young Woo ; Korea Institute of Radiological and Medical Sciences, National Radiation Emergency Medical Center
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Public health
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, OCCUPATIONAL & INDUSTRIAL MEDICINE

SCHOLARONE™ Manuscripts

Assessing the health effects associated with occupational radiation exposure in Korean radiation workers: protocol for a prospective cohort study

Songwon Seo[1], Wan Young Lim[1], Dal Nim Lee[1], Jung Un Kim[1], Eun Shil Cha[2], Ye Jin Bang[2], Won Jin Lee[2], Sunhoo Park[1], Young Woo Jin[1,*]

[1]Laboratory of Low Dose Risk Assessment, National Radiation Emergency Medical Center, Korea Institute of Radiological and Medical Sciences, Seoul, Korea
[2]Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

*Correspondence to: Young Woo Jin, M.D., Ph.D.
National Radiation Emergency Medical Center, Korea Institute of Radiological and Medical Sciences, 75 Nowon-ro, Nowon-gu, Seoul 01812, Republic of Korea
Tel: +82-2-3399-5800; Fax: +82-2-3399-5870; E-mail: ywjin@kirams.re.kr

Word count: 2969 words

Keywords: radiation worker; epidemiology; cohort; exposure; health

ABSTRACT

Introduction: The cancer risk of radiation exposure in the moderate-to-high dose range has been well established. However, the risk remains unclear at low-dose ranges with protracted low-dose rate exposure, which is typical of occupational exposure. Several epidemiological studies of Korean radiation workers have been conducted, but the data were analyzed retrospectively in most cases. Moreover, groups with relatively high exposure, such as industrial radiographers, have been neglected. Therefore, we have launched a prospective cohort study of all Korean radiation workers to assess the health effects associated with occupational radiation exposure.

Methods and analysis: Approximately 42,000 Korean radiation workers registered with the Nuclear Safety and Security Commission from 2016-2017 are the initial target population of this study. Cohort participants are to be enrolled through a nationwide self-administered questionnaire survey between May 24, 2016, and June 30, 2017. As of March 31, 2017, 22,982 workers are enrolled in the study corresponding to a response rate of 75%. This enrollment will be continued at five-year intervals to update information on existing study participants and recruit newly hired workers. Survey data will be linked with the national dose registry, the national cancer registry, the national vital statistics registry, and national health insurance data via personal identification numbers. Age- and sex-specific standardized incidence and mortality ratios will be calculated for overall comparisons of cancer risk. For dose-response assessment, excess relative risk (ERR/Gy) and excess absolute risk (EAR/Gy) will be estimated with adjustments for birth year and potential confounders, such as lifestyle factors and socioeconomic status.

Ethics and dissemination: This study has received ethical approval from the institutional review board of the Korea Institute of Radiological and Medical Sciences. All participants provided written informed consent prior to enrollment. The findings of the study will be disseminated through scientific peer-reviewed journals and the study website.

Strengths and limitations:

Strengths:

- Prospective cohort study of “radiation workers,” including all occupations
- Data linkage of the national health resources including cancer, non-cancer disease, and laboratory biomarkers
- Adjustment for potential confounding variables

Limitations:

- Limited sample size and retired workers not included in the cohort
- Continued long term follow-up is necessary to extract full value from the cohort

INTRODUCTION

Studies of workers in radiation-related occupations provide an opportunity to assess the health risks of low-dose ionizing radiation exposure. Various epidemiological studies of occupational exposure to ionizing radiation have been conducted in the form of national or international collaborative studies.[1, 2] Adverse health effects, such as all cancers other than leukemia combined, lung cancer, leukemia excluding chronic lymphocytic leukemia, and circulatory diseases, have been reported in some single-nation studies, from the United Kingdom,[3] Russia,[4-6] the U.S.,[7-11] Canada,[12] and France.[13] In addition, a recent international large-scale cohort study indicated an increased risk of cancer from protracted low dose exposure.[14, 15] Although these international efforts have been able to accumulate scientific evidence of health effects in occupationally-exposed populations and provided more precise dose-response estimates than single-nation studies, findings from these studies at low-dose ranges, particularly <100 mSv, should be still interpreted with caution due to wide confidence intervals for risk estimates and limited information on confounders. Moreover, given that baseline risks possibly differ from nation to nation, generalizations of the findings to other populations should be made with caution. Thus, to supplement international collaborative studies, it is important to evaluate the health effects of low-dose ionizing radiation in national studies reflecting the characteristics of the particular country, including comprehensive information on confounding factors.

In Korea, workers in radiation-related occupations are registered with two independent government agencies depending on their occupation: diagnostic radiation workers under the Centers for Disease Control and Prevention (CDC), and nuclear-related workers under the Nuclear Safety and Security Commission (NSSC). We use the term “radiation workers” for nuclear-related workers henceforth in this paper. A prospective cohort study of diagnostic radiation workers was launched about five years ago[16, 17] following the suggestion of an elevated cancer risk in diagnostic medical workers from a retrospective study.[18] For Korean radiation workers, sparse information is available from two studies that are limited by short follow-up and sparse information on confounding variables.[19, 20] Moreover, industrial radiography, which is one of the non-destructive testing (NDT) technologies, has been reported to not only have the highest effective dose,[21] but also to account for the majority of occupational cancer incidence among all radiation-related occupations.[22, 23] However, industrial radiographers have been relatively neglected compared to nuclear power plant workers.

Therefore, we have launched a prospective cohort study of all Korean radiation workers, including industrial radiographers, to assess the health effects associated with protracted low-dose radiation exposure, which has comprehensive information on potential confounding variables and long-term follow-up.

METHODS AND ANALYSIS

Study population and design

The Korean radiation workers study (KRWS) is a prospective cohort study, and the initial target population includes approximately 42,000 Korean radiation workers registered with the NSSC from 2016-2017. Korean radiation workers are categorized into 10 occupations depending on their workplace: nuclear power plant, industrial radiography, industry, medical institute (except diagnostic radiation workers), education institute, public institute, military, production, and sales. Of these, nuclear power plant workers are in the majority with >14,000 workers, followed by industrial radiography and industrial workers.[21] Average annual effective doses, which are the sum of the external dose ($H_p(10)$) and the committed effective dose, in the last five years have been reported to be below or near 1 mSv; however, industrial radiographers are exposed to the highest doses of 2-4 mSv.[21] The number of workers and their annual average effective doses by occupation in the past five years are presented in figure 1.[21]

All radiation workers in Korea should receive radiation safety education every year. In order to enroll the participants, we visited each educational location across the country between May 24, 2016, and June 30, 2017, to conduct the self-administered questionnaire survey and collect informed consent, the details of which are described in the following section. As of March 31, 2017, of 30,572 workers that participated in radiation safety education, 22,982 workers have been enrolled in the study, which corresponds to a response rate of 75%. Following enrollment, we shall combine the data from the questionnaires with dosimetry data from the national dose registry, and link the health data via personal identification numbers. The health data will include cancer incidence data from the national cancer registry, overall mortality data from the national vital statistics registry, and incidence of diseases other than cancer from national health examination data. We will conduct the self-administered questionnaire survey at five-year intervals to update information on existing study participants, recruit newly hired workers, and evaluate the association between radiation dose and health effects on long-term follow-up. The study design is presented in figure 2.

Survey questionnaire and informed consent form

A self-administered questionnaire was developed by referring to the previous cohort studies of Korean diagnostic radiologic technologists and the U.S. Radiologic Technologists (USRT),[24, 25] which was amended through a pilot survey. The questionnaire was composed of 20 questions about general work history and lifestyle factors, and 10 demographic questions for all radiation workers (table 1). The 20 questions asked to all workers covered occupational history, work practices, exposure warnings, medical exposure, medical history, and lifestyle factors. For industry radiographers only, we added 11 NDT-specific questions in order to collect more detailed information on their work status and exposure to other harmful agents. These additional questions for industrial radiographers included specific working types, history of specific health examination, and exposure to other NDT-related harmful agents, such as film developer and cleaning fluids. In addition to the survey questionnaire, an informed consent form was developed based on the Privacy Act in Korea,[26] which included five essential items about the collection and use of personal information, collection and use of identifying information, collection and use of sensitive information, sharing of personal information with third parties, and consent to research participation.

Table 1 Items collected in the survey questionnaire

Domains	Items
Occupational history	Calendar year of hiring, duration of employment, employment status, and frequency of radiation procedures
Work practices	Badge wearing, use of shield wall, wearing of protective equipment, radiation sources, and distance from radiation sources
Experience of high radiation exposure	Warning for exceeding 5 mSv/quarter, and lower white blood cell levels than normal
Medical radiation exposure	Plain radiography, intraoral or panoramic radiography, computed tomography, fluoroscopy, nuclear medicine imaging, nuclear medicine therapy, mammography, interventional radiography, and radiation therapy
Medical history	Cancer, hypertension, stroke, myocardial infarction, angina, cataracts, diabetes, etc. (30 diseases)
Lifestyle factors	Sleep pattern, smoking, alcohol consumption, physical exercise, and night shifts
Demographics	Name, age, sex, education level, marital status, height, weight, and contact details

Dosimetry data

We shall collect radiation doses for individual workers from the Central Registry for Radiation Worker Information (CRRWI) managed by the NSSC. External and internal doses are collected by measuring personal dose equivalent, $H_p(10)$, and committed effective doses quarterly and annually, respectively, through the electronic dose record database (the National Dose Registry), which has been available under the CRRWI since 1984. Most external doses are measured using thermoluminescent dosimeters (TLD); optically stimulated luminescence dosimeters (OSLD) are only applied in limited fields.[27] Film badge dosimeters were used in the past, but are no longer used. Doses based on film badge dosimeters are less than 10% of the total dose records.[28] It might be challenging to ensure the inclusion of radiation doses from high-Linear Energy Transfer (LET) exposure (e.g., neutrons) in the current Korean dose reporting system in which $H_p(10)$ for neutrons is included but it is not separated from $H_p(10)$ for photons; however, since the proportion of workers with potential high-LET exposure is expected to be less than 5%, the impact of high-LET exposure on risk estimates would be minimal. Committed effective doses are reported only for workers whose annual committed effective dose is likely to exceed 2 mSv/year. In addition to radiation dose, the database includes workers' names, sex, job classification, and personal identification numbers including date of birth.[28] For individuals who were working before 1984, radiation doses were not documented; therefore, we will estimate their historical occupational exposure using a dose reconstruction model that includes predictors such as age, sex, and work place.[29] For using individual radiation doses to analyze a dose-response relationship, we will use organ absorbed doses estimated from the effective dose from the external exposure in the National Dose Registry. Absorbed organ dose is estimated based on methods using the ICRP 116 organ dose conversion coefficients and irradiation geometry factors,[30] considering information about work practices, such as use of protective devices and badge location, from the nationwide survey as suggested by the Million Worker Study (MWS)[31] and the USRT study.[32]

Health outcomes

Health information for individual workers in this study is to be collected from the National Cancer Registry, the National Vital Statistics Registry, and the National Health Insurance Sharing Service (NHISS) database (table 2). The National Cancer Registry includes cancer incidence data and the National Vital Statistics Registry includes mortality data, which have been available since 1999 and 1992, respectively. The NHISS database consists of four major sub-datasets, including an eligibility database, medical treatment database, health examination database, and medical care institution database, which have been available since 2002.[33, 34] We will predominantly use the first three databases and the information derived from these databases includes medical care history, regular health check-ups, and socioeconomic variables.

Table 2 Health data collected from the national sources

National sources	Major items
National Cancer Registry	Cancer code (ICD-10), site, stage, diagnosis method, and date of diagnosis
National Vital Statistics Registry	Date of death and cause of death
National Health Insurance Sharing Service	Eligibility database (14 variables): date of birth, type of eligibility, gender, income level, disability, etc.
	Medical treatment database (56 variables): records of inpatient and outpatient usage (length of stay, treatment costs, services received, etc.), diagnosis (International Classification of Disease-10 codes), prescription, etc.
	Health examination database (41 variables): health behaviors from questionnaire, general health examination data including cancer screening and laboratory test items (e.g., blood cell counts, cholesterol levels, triglyceride concentration, fasting blood sugar, liver enzyme tests (AST/SGOT, ALT/SGPT, γ-GTP), serum creatinine, urinary protein, and e-GFR), etc.

Validity and reliability of self-administered questionnaires

Information collected from self-administered questionnaires is essential for estimating organ doses and determining confounders, which can interpret findings more accurately. It is therefore of particular importance that we evaluate the validity and reliability of our questionnaires, particularly those measuring work practice and lifestyle. Our questionnaire contains items about work history (e.g., employment start date and period, and warning for exceeding 5 mSv) and medical history (e.g., diagnosis of cancer, cataract, and cardiovascular disease), which we can also ascertain from the National Dose Registry and National Health Records (i.e., the cancer registry and NHISS database). We will compare the answers to our questions with the national records in order to assess the validity of the responses to the self-administered questionnaires. For the evaluation of reliability, we will compare responses of study participants who were surveyed in both 2016 and 2017. Intra-class correlation coefficients[35] and kappa coefficients[36, 37] will be used as measures of validity and reliability.

Health risk associated with ionizing radiation exposure

The primary health outcome of this study is cancer incidence. Other outcomes include incidence of non-cancer diseases (e.g., cataracts and circulatory disease), laboratory biomarkers (i.e., laboratory test items) from the NHISS databases, and mortality. The laboratory biomarkers are possibly associated with pre-disease conditions, such as metabolic risk profile (e.g., obesity, high serum glucose, cholesterol level, and low blood pressure) and abnormal blood cell counts. For example, the metabolic risk profile can be considered a surrogate endpoint of cardiovascular disease, and also an independent variable to explore an interaction effect between radiation exposure and metabolic syndrome with regard to cardiovascular disease. Age- and sex-specific standardized incidence and mortality ratios will be calculated for overall comparisons of cancer risk. The national statistics for cancer incidence and mortality among the general Korean population will be employed as the control group for external comparison, and study subjects whose effective doses (the sum of the external dose ($H_p(10)$) and the committed effective dose) have not exceeded the minimum recording level of 0.1 mSv/quarter for external exposure and 0.1 mSv/year for internal exposure during their employment according to the National Dose Registry shall be considered as the control group for internal comparison. Risk estimates for radiation exposure are typically presented as excess relative risk (ERR) and excess absolute risk (EAR). The ERR is the relative risk minus 1.0, which refers to the magnitude of the radiation risk relative to the baseline. The EAR refers to the difference between the rate in an exposed and an unexposed population. To quantify the dose-response relationship, we will estimate health risk per unit of organ absorbed dose (i.e., ERR/Gy, EAR/Gy) using a parametric model (Poisson), penalized splines, and/or Bayesian semiparametric models[38] with or without adjustment for birth cohort and confounding factors, such as lifestyle and socioeconomic status. Committed effective dose will be used as another confounder for sensitivity analyses considering internal exposure, using an adjusted analysis and a stratified analysis. Person-years at risk for the analysis are calculated from date of entry in the study (defined as the latest among the date of the first exposure and date of start of follow-up period in the national health data source) to date of exit (defined as the earliest among the date of health events, date of loss to follow-up and date of end of follow-up). To allow for a possible latency period between radiation exposure and its consequences, cumulative doses will be lagged by 2-5 years for leukemia and 5-10 years for solid cancers. All the analyses will be updated at follow-up intervals of three to five years.

Sample size calculation

As this study is designed to investigate radiation-related health effects with long-term follow-up in a cohort targeting all Korean radiation workers, a sample size calculation is not deemed relevant.

Study limitations and future work

Lack of statistical power is a major limitation in most epidemiological studies, particularly for low-dose ranges (i.e., <100 mSv). Average annual dose for the KRWS's population in the past five years is approximately 1 mSv (0-4 mSv depending on occupation).[21] Given that there was still a lack of statistical power in low-dose ranges in the recent large scale international Nuclear Workers Study (INWORKS) with an average individual cumulative dose of 21 mGy,[15] this study including a relatively young cohort would not allow a definitive conclusion in a short period of time. In addition, this study is limited in terms of investigation of health effects in women since the proportion of female workers in the cohort is expected to be 10-20%.[28, 39] Thus, it is necessary to expand the cohort through continuous enrollment of new radiation workers with a long follow-up, and through collaborative studies, including with the Korean diagnostic radiation worker cohort, and international cohorts of similar occupations, such as the INWORKS[15] and the USRT.[40] Another limitation is that the current KRWS does not include retired workers and has limited information of radiation doses for those who had worked before 1984 since the electronic National Dose Registry was not available before. As the beginning of nuclear activities in Korea, a research reactor was first introduced at 1962, and the first nuclear power plant opened in 1978.[41] Given that the average annual occupational doses were 1-3 mSv before 2000,[28] the radiation dose of retired workers is expected to be higher, and their ages to be higher than those of currently active workers of the KRWS cohort. Thus, it is important to include them in potential future studies, as this could possibly increase statistical power, via an increase in the number of events and larger exposure variance.[42, 43] In addition, collection of biosamples, such as blood and buccal cells, should be considered for a comprehensive understanding of biological mechanisms via molecular epidemiologic studies of radiation risk.[44] These activities will enhance our ability to investigate susceptibility and surrogate biomarkers for assessing exposure risk, and to thereby develop more sophisticated dose-response models for low-dose risk assessments.

Potential impact

We have designed the KRWS to assess health effects among Korean radiation workers exposed to protracted low-dose radiation. This is the first prospective cohort study of active workers from the entire range of occupations registered with the NSSC. Data collected from the nationwide survey will provide detailed information on work practices and lifestyle factors, which allows for an in-depth exploration of occupational exposure and adjustment for confounding factors. In addition, individual health data derived from the national resources include not only cancer/non-cancer diseases, but also pre-disease conditions including laboratory test items, ensuring comprehensive and accurate information for the evaluation of health effects from radiation exposure. Study findings will be directly relevant to radiation protection for radiation workers, and will further provide the basis for recommendations and regulations about low-dose radiation safety.

Besides establishing scientific evidence for radiation-related health effects, we expect that this study will contribute to both the prevention of adverse health effects and improved communication with radiation workers. We will continue to promote this cohort study and its results via radiation safety education and the study website (http://www.rhs.kr/), which is a former website for Korean diagnostic radiation worker studies[16, 17], that has been combined with the KRWS to increase understanding about occupational exposure and health effects. Consequently, radiation workers will be encouraged to pay more attention to radiation protection in their workplaces, and to accomplish their work duties with a balanced risk judgment about potential exposure that is not solely based on perceived risk.

ETHICS AND DISSEMINATION

This study has received ethical approval from the institutional review board of the Korea Institute of Radiological and Medical Sciences (IRB No. K-1603-002-034). All participants provided written informed consent prior to enrollment. The findings of the study will be disseminated through scientific peer-reviewed journals and be provided to the public, including radiation workers, via the study website (http://www.rhs.kr/) and onsite radiation safety education.

Author contributions: SS and YWJ conceived and designed this study and drafted the manuscript. WRL and DNL are involved in coordination of the nationwide survey. WRL, DNL and JUK are involved in the collection of data and the construction of the cohort database. ESC and YJB designed the survey questionnaire. WJL and SP contributed to the design of the study and provided valuable inputs relevant to study implementation. YWJ obtained funding. All authors reviewed and approved the final manuscript.

Funding: This research was supported by the Nuclear Safety Research Program through the Korea Foundation of Nuclear Safety (KOFONS), and granted financial resources by the Nuclear Safety and Security Commission (NSSC) of the Republic of Korea (No. 1503008).

Competing interests: None

Ethics approval: This study has received ethical approval from the institutional review board of the Korea Institute of Radiological and Medical Sciences (IRB No. K-1603-002-034).

Provenance and peer review: Not yet commissioned; to be externally peer reviewed.

Acknowledgments:

The authors express gratitude to Kijung Lim from the Korea Foundation of Nuclear Safety (KOFONS) for providing his professional knowledge regarding the National Dose Registry for radiation workers.

REFERENCES

1. Cardis E, Vrijheid M, Blettner M, et al. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. *Radiat Res* 2007;167:396-416.
2. Seong KM, Seo S, Lee D, et al. Is the linear no-threshold dose-response paradigm still necessary for the assessment of health effects of low dose radiation? *J Korean Med Sci* 2016;31:S10–23.
3. Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer* 2009;100:206-12.
4. Gilbert ES, Koshurnikova NA, Sokolnikov ME, et al. Lung cancer in Mayak workers. *Radiat Res* 2004;162:505–16.
5. Hunter N, Kuznetsova IS, Labutina EV, et al. Solid cancer incidence other than lung, liver and bone in Mayak workers: 1948-2004. *Br J Cancer* 2013;109:1989–96.
6. Shilnikova NS, Preston DL, Ron E, et al. Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat Res* 2003;159:787–98.
7. Rajaraman P, Doody MM, Yu CL, et al. Incidence and mortality risks for circulatory diseases in US radiologic technologists who worked with fluoroscopically guided interventional procedures, 1994-2008. *Occup Environ Med* 2016;73:21–7.
8. Preston DL, Kitahara CM, Freedman DM, et al. Breast cancer risk and protracted low-to-moderate dose occupational radiation exposure in the US Radiologic Technologists Cohort, 1983-2008. *Br J Cancer* 2016;115:1105–12.
9. Matanoski GM, Tonascia JA, Correa-Villasenor A, et al. Cancer risks and low-level radiation in U.S. shipyard workers. *J Radiat Res* 2008;49:83–91.
10. Richardson DB, Wing S. Leukemia mortality among workers at the Savannah River Site. *Am J Epidemiol* 2007;166:1015–22.
11. Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. *Radiat Res* 2015;183:620-31
12. Zablotska LB, Lane RS, and Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. *Br J Cancer* 2014;110:214–23.

13. Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med* 2013;70:630–8.
14. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). *BMJ* 2015;351:h5359.
15. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. *Lancet Haematol* 2015;2:e276–81.
16. Lee WJ, Ha M, Hwang SS, et al. The radiologic technologists' health study in South Korea: study design and baseline results. Int Arch Occup Environ Health 2015;88:759–68.
17. Lee J, Cha ES, Jeong M, et al. A national survey of occupational radiation exposure among diagnostic radiologic technologists in South Korea. *Radiat Prot Dosimetry* 2015;167:525–31.
18. Choi KH, Ha M, Lee WJ, et al. Cancer risk in diagnostic radiation workers in Korea from 1996 to 2002. *Int J Environ Res Public Health* 2013;10:314–27.
19. Jeong M, Jin YW, Yang KH, et al. Radiation exposure and cancer incidence in a cohort of nuclear power industry workers in the Republic of Korea, 1992-2005. *Radiat Environ Biophys* 2010;49:47–55.
20. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers exposed to ionizing radiation in Korea. *J Occup Environ Med* 2008;50:791–803.
21. Nuclear Safety and Security Commission, Korea Institute of Nuclear Safety, Korea Institute of Nuclear Nonproliferation and Control. 2015 Nuclear Safety Yearbook (2016).
22. Korea Occupational Safety and Health Agency: Annual reports of occupational disease (2000–2015). http://english.kosha.or.kr/english/content.do?menuId=11436. (accessed 20 Jun 2017).
23. Jin YW, Jeong M, Moon K, et al. Ionizing radiation-induced diseases in Korea. *J Korean Med Sci* 2010;25:S70–6.
24. The U.S. radiologic technologists study. https://radtechstudy.nci.nih.gov/questionnaires.html (accessed 20 Jun 2017).
25. Radiation and health study among radiation workers in Korea. http://www.rhs.kr/method/overview.asp (accessed 20 Jun 2017).
26. Personal Information Protection Act, Articles 15 to 22 Section 1 (2014).
27. Lee WH, Kim SC, Ahn SM. Comparison on the Dosimetry of TLD and OSLD Used in Nuclear Medicine. *Journal of the Korea Contents Association* 2012; 12:329-34.
28. Choi SY, Kim TH, Chung CK, et al. Analysis of radiation workers' dose records in the Korean National Dose Registry. *Radiat Prot Dosimetry* 2001;95:143–8.
29. Choi Y, Kim J, Lee JJ, et al. Reconstruction of radiation dose received by diagnostic radiologic technologists in Korea. *J Prev Med Public Health* 2016;49:288–300.
30. Taulbee TD, McCartney KA, Traub R, et al. Implementation of ICRP 116 dose conversion coefficients for reconstruction organ dose in radiation compensation program. *Radiat Prot Dosimetry* 2017;173:131–137.

31. Bouville A, Toohey ER, Boice JD Jr, et al. Dose reconstruction for the million worker study: status and guidelines. *Health Phys* 2015;108:206–20.
32. Simon SL, Preston DL, Linet MS, et al. Radiation organ doses received in a nationwide cohort of U.S. radiologic technologists: methods and findings. *Radiat Res* 2014;182:507–28.
33. Cheol Seong S, Kim YY, Khang YH, et al. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2016;pii:dyw253 [Epub ahead of print]
34. National Health Insurance Sharing Service in Korea. https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do (accessed 20 Jun 2017).
35. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86:420–8.
36. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol* 1993;46:423–9.
37. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and Psychological Measurement* 1960;20:37–46.
38. Furukawa K, Misumi M, Cologne JB, et al. A Bayesian semiparametric model for radiation dose-response estimation. *Risk Anal* 2016;36:1211–23.
39. Jeong JH, Lee JK, Kwon, JW, et al. Occupational radiaiton exposure in Korea: 2002. *J Korean Assoc Radiat Protect* 2005;30:175-183.
40. Boice JD, Mandel JS Jr, Doody MM, et al. A health survey of radiologic technologists. *Cancer* 1992;69:586–98.
41. Lim YK, Kim JR., Hwang KH, et al. Investigation of nuclear development at the early stage in Korea (No. KAERI/CM--1022/2007). Korea Atomic Energy Research Institute 2009.
42. McKeown-Eyssen GE, Thomas DC. Sample size determination in case-control studies: the influence of the distribution of exposure. *J Chronic Dis* 1985;38:559–68.
43. White E, Kushi LH, Pepe MS. The effect of exposure variance and exposure measurement error on study sample size: implications for the design of epidemiologic studies. *J Clin Epidemiol* 1993;47:873–80.
44. Pernot E, Hall J, Baatout S, et al. Ionizing radiation biomarkers for potential use in epidemiological studies. *Mutat Res* 2012;751:258–86.

FIGURE LEGENDS

Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

Figure 2. Study design.

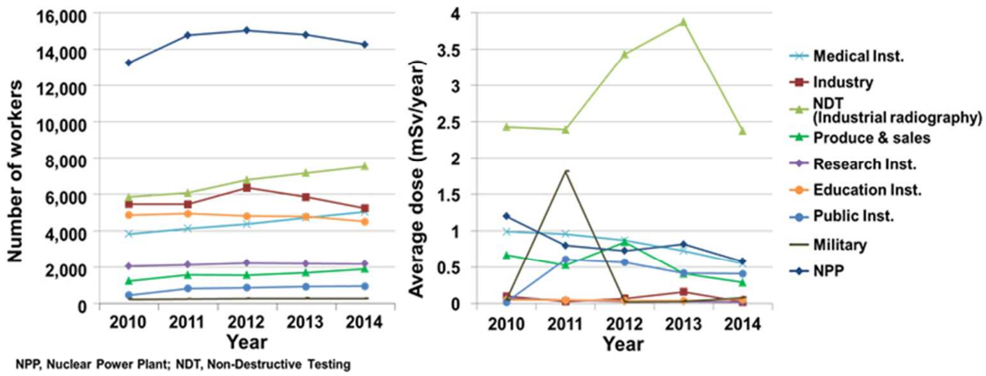

Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

67x46mm (300 x 300 DPI)

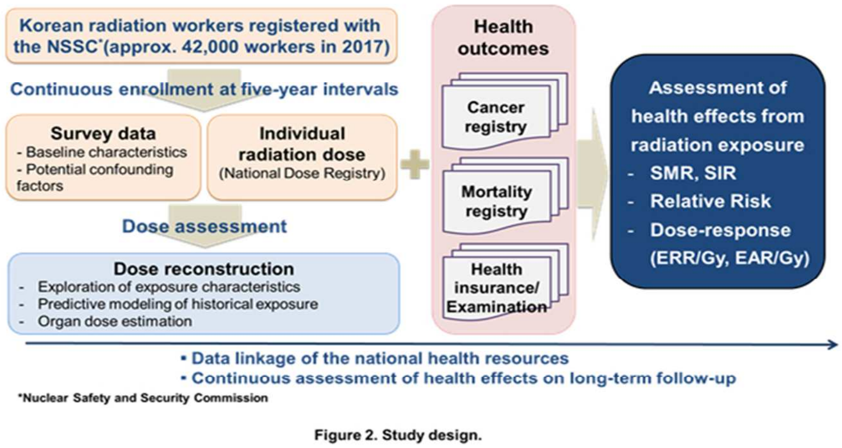

Figure 2. Study design.

67x46mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	7 (Will address further details when we submit results of this cohort study)
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Will explain this

			when we submit results of this cohort study
		(*d*) If applicable, explain how loss to follow-up was addressed	7 (Will address further details when we submit results of this cohort study)
		(*e*) Describe any sensitivity analyses	Will provide them when we submit results of this cohort study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Will provide them when we submit results of this cohort study
		(b) Give reasons for non-participation at each stage	Will provide them when we submit results of this cohort study
		(c) Consider use of a flow diagram	Will provide them when we submit results of this cohort study
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Will provide them when we submit results of this cohort study
		(b) Indicate number of participants with missing data for each variable of interest	Will provide them when we submit results of this cohort

			study
		(c) Summarise follow-up time (eg, average and total amount)	Will provide them when we submit results of this cohort study
Outcome data	15*	Report numbers of outcome events or summary measures over time	Will provide them when we submit results of this cohort study
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Will provide them when we submit results of this cohort study
		(*b*) Report category boundaries when continuous variables were categorized	Will provide them when we submit results of this cohort study
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Will provide them when we submit results of this cohort study
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Will provide them when we submit results of this cohort study
Discussion			
Key results	18	Summarise key results with reference to study objectives	Will provide them when we submit results of this cohort study
Limitations			

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Will provide them when we submit results of this cohort study
Generalisability	21	Discuss the generalisability (external validity) of the study results	Will provide them when we submit results of this cohort study
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.