

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts

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

Songwon Seo¹, Wan Young Lim¹, Dal Nim Lee¹, Jung Un Kim¹, Eun Shil Cha², Ye
Jin Bang², Won Jin Lee², Sunhoo Park¹, Young Woo Jin^{1,*}

¹Laboratory of Low Dose Risk Assessment, National Radiation Emergency Medical
Center, Korea Institute of Radiological and Medical Sciences, Seoul, Korea

²Department 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: ywjjin@kiram.s.re.kr

Word count: 2479 words

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

45 ABSTRACT

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

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

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

72 **Strengths and limitations:**

73 Strengths:

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

78 Limitations:

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

89 INTRODUCTION

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

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

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

128

129 METHODS AND ANALYSIS

130 Study population and design

131 The Korean radiation workers study (KRWS) is a prospective cohort study, and the
132 target population includes approximately 42,000 Korean radiation workers registered

1
2
3 133 with the NSSC from 2016-2017. Korean radiation workers are categorized into 10
4 134 occupations depending on their workplace: nuclear power plant, NDT, industry,
5 135 medical institute (except diagnostic radiation workers), education institute, public
6 136 institute, military, production, and sales. Of these, nuclear power plant workers are in
7 137 the majority with >14,000 workers, followed by NDT and industry workers.[20]
8 138 Average annual doses in the last five years have been reported to be below or near 1
9 139 mSv; however, NDT workers are exposed to the highest doses of 2-4 mSv.[20] The
10 140 number of workers and their annual average radiation doses by occupation in the past
11 141 five years are presented in Figure 1.[20]
12 142 All radiation workers in Korea should receive radiation safety education every year.
13 143 In order to enroll the participants, we will visit each educational location across the
14 144 country between May 24, 2016, and June 30, 2017, to conduct the self-administered
15 145 questionnaire survey and collect informed consent. As of March 31, 2017, of 30,572
16 146 workers that participated in radiation safety education, 22,982 workers have been
17 147 enrolled in the study, which corresponds to a response rate of 75%. Following
18 148 enrollment, we shall combine the data from the questionnaires with dosimetry data
19 149 from the national dose registry, and link the data with secondary health data via
20 150 personal identification numbers. Regarding the secondary health data, cancer
21 151 incidence will be derived from the national cancer registry, overall mortality from the
22 152 national vital statistics registry, and incidence of non-cancer diseases from national
23 153 health examination data. We will continually evaluate the association between
24 154 radiation dose and health effects with long-term follow-up. The study design is
25 155 presented in Figure 2.
26 156

157 **Survey questionnaire and informed consent form**

158 A self-administered questionnaire was developed by referring to the previous cohort
159 studies of Korean diagnostic radiologic technologists and the U.S. Radiologic
160 Technologists (USRT),[23, 24] which was amended through a pilot survey. The
161 questionnaire was composed of 20 questions about general work history and lifestyle
162 factors, and 10 demographic questions for all radiation workers (Table 1). The 20
163 questions asked to all workers covered occupational history, work practices, exposure
164 warnings, medical exposure, medical history, and lifestyle factors. For NDT workers
165 only, we added 11 NDT-specific questions in order to collect more detailed
166 information on their work status and exposure to other harmful agents. These
167 additional questions for NDT workers included specific working types, history of
168 specific health examination, and exposure to other NDT-related harmful agents, such
169 as film developer and cleaning fluids. In addition to the survey questionnaire, an
170 informed consent form was developed based on the Privacy Act in Korea,[25] which
171 included five essential items about the collection and use of personal information,
172 collection and use of identifying information, collection and use of sensitive
173 information, sharing of personal information with third parties, and consent to
174 research participation.
175

176 **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

177

178 **Sample size calculation**

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

188

189 **Analysis plan**

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

191 Once we complete the nationwide survey, survey data for individual workers will be
 192 linked with the national dose registry and health data via personal identification
 193 numbers. The NSSC has been managing workers' radiation doses through monitoring
 194 of individual doses. External and internal doses are collected by measuring effective
 195 doses and committed effective doses quarterly and annually, respectively. The
 196 electronic dose record database for all workers has been available since 1984 in the
 197 Central Registry for Radiation Worker Information. For individuals who were
 198 working before 1984, radiation doses were not documented; therefore, we will
 199 estimate their historical occupational exposure using a dose reconstruction model that
 200 includes predictors such as age, sex, and work place[27]. In addition to radiation dose,
 201 the central registry includes workers' names, sex, job classification, and personal
 202 identification numbers including date of birth. Health information for individual
 203 workers in this study is to be collected from the National Cancer Registry, the
 204 National Vital Statistics Registry, and the National Health Insurance Sharing Service
 205 (NHIS) database (Table 2). National Cancer Registry data includes cancer incidence
 206 data and the National Vital Statistics Registry includes mortality data, which have

1
2
3 207 been available since 1999 and 1991, respectively. The NHISS database consists of
4 208 four major sub-datasets, including an eligibility database, medical treatment database,
5 209 health examination database, and medical care institution database, which have been
6 210 available since 2002[28, 29]. We will predominantly use the first three databases and
7 211 the information derived from these databases includes medical care history, regular
8 212 health check-ups, and socioeconomic variables.
9
10
11
12

13 **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.

14
15
16
17
18
19
20
21
22
23
24
25
26
27

28 216 *Validity and reliability of self-administered questionnaires*

29 217 Information collected from self-administered questionnaires is essential for estimating
30 218 organ doses and determining confounders, which can interpret findings more
31 219 accurately. It is therefore of particular importance that we evaluate the validity and
32 220 reliability of our questionnaires, particularly those measuring work practice and
33 221 lifestyle. Our questionnaire has some items about work history and medical history,
34 222 which we can also ascertain from the National Dose Registry and National Health
35 223 Records (i.e., the cancer registry and NHISS database). We will compare answers to
36 224 these questions with the national records in order to assess the validity of the
37 225 responses to the self-administered questionnaires. For the evaluation of reliability, we
38 226 will compare responses of study participants who were surveyed in both 2016 and
39 227 2017. Intra-class correlation coefficients[30] and kappa coefficients[31, 32] will be
40 228 used as measures of validity and reliability.
41
42
43
44
45

46 230 *Health risk associated with ionizing radiation exposures*

47 231 The primary health outcomes of this study include incidence of cancer or non-cancer
48 232 diseases (such as cataracts and circulatory disease), and mortality. Other outcomes are
49 233 laboratory biomarkers from the NHISS databases, which are possibly associated with
50 234 pre-disease conditions, such as metabolic risk profile (e.g., obesity, high serum
51 235 glucose, cholesterol level, low blood pressure) and abnormal blood cell counts. Age-
52 236 and sex-specific standardized incidence and mortality ratios will be calculated for
53 237 overall comparisons of cancer risk. Study subjects whose doses are below the
54 238 minimum recording level of 0.1 mSv shall be considered as the control group for the
55 239 internal comparison, and national statistics for the general Korean population will be
56
57
58
59
60

1
2
3 240 employed for the external comparison. For individual radiation dose to be used for the
4 241 analysis of a dose-response relationship, we will use organ doses estimated from
5 242 effective dose in the National Dose Registry, and information about work practices
6 243 from the nationwide survey using previous methods applied to the Million Worker
7 244 Study (MWS) [33] and the U.S. Radiologic Technologists (USRT) study.[34] For the
8 245 assessment of dose-response, we will estimate radiation risk per unit of radiation dose
9 246 (i.e., ERR/Gy, EAR/Gy) using a parametric model (Poisson), penalized splines,
10 247 and/or Bayesian semiparametric models[35] with or without adjustment for birth
11 248 cohort and confounding factors, such as lifestyle and socioeconomic status. All the
12 249 analyses will be updated at follow-up intervals of three to five years.
13
14
15
16 250

17 251 **Potential impact and future work**

18 252 We have designed the KRWS to assess health effects among Korean radiation
19 253 workers exposed to protracted low-dose radiation. This is the first prospective cohort
20 254 study of active workers from the entire range of occupations registered with the NSSC.
21 255 Data collected from the nationwide survey will provide detailed information on work
22 256 practices and lifestyle factors, which allows for an in-depth exploration of
23 257 occupational exposure and adjustment for confounding. In addition, individual health
24 258 data derived from the national resources include not only cancer/non-cancer diseases,
25 259 but also pre-disease conditions including laboratory biomarkers, ensuring
26 260 comprehensive and accurate information for the evaluation of health effects from
27 261 radiation exposure. Study findings will be directly relevant to radiation protection for
28 262 radiation workers, and will further provide the basis for recommendations and
29 263 regulations on low-dose radiation safety.

30 264 Besides establishing scientific evidence for radiation-related health effects, we expect
31 265 that this study will contribute to both the prevention of adverse health effects and
32 266 improved communication with radiation workers. We will continue to introduce this
33 267 cohort study and its results via radiation safety education and the study website
34 268 (<http://www.rhs.kr/>), which is a former website for Korean diagnostic radiation
35 269 worker studies [15, 16], that has been combined with the KRWS to increase
36 270 understanding about occupational exposure and health effects. Consequently,
37 271 radiation workers will be encouraged to pay more attention to radiation protection in
38 272 their workplaces, and to accomplish their work duties with a balanced risk judgement
39 273 about potential exposure that is not solely based on perceived risk.

40 274 Lack of statistical power is a major limitation in most epidemiological studies,
41 275 particularly for low-dose ranges (i.e., <100 mSv). Average annual dose for the
42 276 KRWS's population in the past five years is approximately 1 mSv (0-4 mSv
43 277 depending on occupation).[20] Given that there was still a lack of statistical power in
44 278 low-dose ranges in the recent large scale international Nuclear Workers Study
45 279 (INWORKS) with an average individual cumulative dose of 21 mGy,[14] the effect
46 280 size from the expected sample size of this cohort study would not allow a definitive
47 281 conclusion. In order to increase the sample size of the study, it is necessary to expand
48 282 the cohort through continuous enrollment of new radiation workers, and through
49 283 collaborative studies, including with the Korean diagnostic radiation worker cohort,
50
51
52
53
54
55
56
57
58
59
60

1
2
3 284 and international cohorts of similar occupations, such as the INWORKS [14] and the
4 285 USRT.[36] Another limitation is that the current KRWS does not include retired
5 286 workers. Given the average annual occupational doses of 1-3 mSv before 2000,[37]
6 287 the radiation dose of retired workers is expected to be higher, and their ages to be
7 288 higher than those of currently active workers of the KRWS cohort. Thus, it is
8 289 important to include them in any future study as this could possibly increase statistical
9 290 power, via an increase in the number of events and larger exposure variance.[38, 39]
10 291 In addition, collection of biosamples, such as blood and buccal cells, should be
11 292 considered for a comprehensive understanding of biological mechanisms via
12 293 molecular epidemiologic studies of radiation risk.[40] These activities will enhance
13 294 our ability to investigate susceptibility and surrogate biomarkers for assessing
14 295 exposure risk, and to thereby develop more sophisticated dose-response models for
15 296 low-dose risk assessments.
16
17
18
19
20

297

298 **ETHICS AND DISSEMINATION**

299 This study has received ethical approval from the institutional review board of the
300 Korea Institute of Radiological And Medical Sciences (IRB No. K-1603-002-034).
301 All participants provided written informed consent prior to enrollment. The findings
302 of the study will be disseminated through scientific peer-reviewed journals and be
303 provided to the public, including radiation workers, via the study website
304 (<http://www.rhs.kr/>) and onsite radiation safety education.
305

305

306 **Author contributions:** SS and YWJ conceived and designed this study and drafted
307 the manuscript. WRL and DNL are involved in coordination of the nationwide survey.
308 WRL, DNL and JUK are involved in the collection of data and the construction of the
309 cohort database. ESC and YJB designed the survey questionnaire. WJL and SP
310 contributed to the design of the study and provided valuable inputs relevant to study
311 implementation. YWJ obtained funding. All authors reviewed and approved the final
312 manuscript.
313

313

314 **Funding:** This research was supported by the Nuclear Safety Research Program
315 through the Korea Foundation of Nuclear Safety (KOFONS), and granted financial
316 resources by the Nuclear Safety and Security Commission (NSSC) of the Republic of
317 Korea (No. 1503008).
318

318

319 **Competing interests:** None
320

320

321 **Ethics approval:** This study has received ethical approval from the institutional
322 review board of the Korea Institute of Radiological and Medical Sciences (IRB No.
323 K-1603-002-034).
324

324

325 **Provenance and peer review:** Not yet commissioned; to be externally peer reviewed.
326

326

1
2
3 327 **Open Access:** This is an Open Access article distributed in accordance with the
4 328 Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which
5 329 permits others to distribute, remix, adapt, build upon this work non-commercially, and
6 330 license their derivative works on different terms, provided the original work is
7 331 properly cited and the use is non-commercial. See:
8 332 <http://creativecommons.org/licenses/by-nc/4.0/>
9 333

334 REFERENCES

- 335 1. Cardis E, Vrijheid M, Blettner M, et al. The 15-Country Collaborative Study
336 of Cancer Risk among Radiation Workers in the Nuclear Industry:
337 estimates of radiation-related cancer risks. *Radiat Res* 2007;167:396-416.
- 338 2. Seong KM, Seo S, Lee D, et al. Is the Linear No-Threshold Dose-Response
339 Paradigm Still Necessary for the Assessment of Health Effects of Low Dose
340 Radiation? *J Korean Med Sci* 2016;31:S10-23.
- 341 3. National Council on Radiation Protection and Measurements.
342 Uncertainties in the estimation of radiation risks and probability of
343 disease causation, NCRP Report No. 171. Bethesda, MD: National Council
344 on Radiation Protection and Measurements; 2012.
- 345 4. Gilbert ES, Koshurnikova NA, Sokolnikov ME, et al. Lung cancer in Mayak
346 workers. *Radiat Res* 2004;162:505-16.
- 347 5. Hunter N, Kuznetsova IS, Labutina EV, et al. Solid cancer incidence other
348 than lung, liver and bone in Mayak workers: 1948-2004. *Br J Cancer*
349 2013;109:1989-96.
- 350 6. Shilnikova NS, Preston DL, Ron E, et al. Cancer mortality risk among
351 workers at the Mayak nuclear complex. *Radiat Res* 2003;159:787-98.
- 352 7. Rajaraman P, Doody MM, Yu CL, et al. Incidence and mortality risks for
353 circulatory diseases in US radiologic technologists who worked with
354 fluoroscopically guided interventional procedures, 1994-2008. *Occup*
355 *Environ Med* 2016;73:21-7.
- 356 8. Preston DL, Kitahara CM, Freedman DM, et al. Breast cancer risk and
357 protracted low-to-moderate dose occupational radiation exposure in the
358 US Radiologic Technologists Cohort, 1983-2008. *Br J Cancer*
359 2016;115:1105-12.
- 360 9. Matanoski GM, Tonascia JA, Correa-Villasenor A, et al. Cancer risks and
361 low-level radiation in U.S. shipyard workers. *J Radiat Res* 2008;49:83-91.
- 362 10. Richardson DB, Wing S. Leukemia mortality among workers at the
363 Savannah River Site. *Am J Epidemiol* 2007;166:1015-22.
- 364 11. Zablotska LB, Lane RS, and Thompson PA. A reanalysis of cancer mortality
365 in Canadian nuclear workers (1956-1994) based on revised exposure and
366 cohort data. *Br J Cancer* 2014;110:214-23.
- 367 12. Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with
368 chronic external radiation exposure in the French combined cohort of
369 nuclear workers. *Occup Environ Med* 2013;70:630-8.
- 370 13. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from
371 occupational exposure to ionising radiation: retrospective cohort study of
372 workers in France, the United Kingdom, and the United States (INWORKS).
373 *BMJ* 2015;351:h5359.

- 1
2
3 374 14. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of
4 375 death from leukaemia and lymphoma in radiation-monitored workers
5 376 (INWORKS): an international cohort study. *Lancet Haematol*
6 377 2015;2:e276–81.
7 378 15. Lee WJ, Ha M, Hwang SS, et al. The radiologic technologists' health study
8 379 in South Korea: study design and baseline results. *Int Arch Occup Environ*
9 380 *Health* 2015;88:759–68.
10 381 16. Lee J, Cha ES, Jeong M, et al. A national survey of occupational radiation
11 382 exposure among diagnostic radiologic technologists in South Korea.
12 383 *Radiat Prot Dosimetry* 2015;167:525–31.
13 384 17. Choi KH, Ha M, Lee WJ, et al. Cancer risk in diagnostic radiation workers
14 385 in Korea from 1996 to 2002. *Int J Environ Res Public Health* 2013;10:314–
15 386 27.
16 387 18. Jeong M, Jin YW, Yang KH, et al. Radiation exposure and cancer incidence
17 388 in a cohort of nuclear power industry workers in the Republic of Korea,
18 389 1992-2005. *Radiat Environ Biophys* 2010;49:47–55.
19 390 19. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers
20 391 exposed to ionizing radiation in Korea. *J Occup Environ Med* 2008;50:791–
21 392 803.
22 393 20. NSSC, KINS, KINAC. 2015 Nuclear Safety Yearbook , 2016(In Korea).
23 394 21. Korea Occupational Safety and Health Agency: Annual reports of
24 395 occupational disease (2000–2015).
25 396 <http://english.kosha.or.kr/english/content.do?menuId=10412>. (accessed
26 397 29 Mar 2017).
27 398 22. Jin YW, Jeong M, Moon K, et al. Ionizing radiation-induced diseases in
28 399 Korea. *J Korean Med Sci* 2010;25:S70–6.
29 400 23. The U.S. radiologic technologists study.
30 401 <https://radtechstudy.nci.nih.gov/questionnaires.html> (accessed 29 Mar
31 402 2017).
32 403 24. Radiation and health study among radiation workers in Korea.
33 404 <http://www.rhs.kr/method/overview.asp> (accessed 29 Mar 2017).
34 405 25. Personal Information Protection Act, Articles 15 to 22 Section 1 (2014).
35 406 26. Oh CM, Won YJ, Jung KW, et al. Cancer Statistics in Korea: Incidence,
36 407 Mortality, Survival, and Prevalence in 2013. *Cancer Res Treat*
37 408 2016;48:436–50.
38 409 27. Choi Y, Kim J, Lee JJ, et al. Reconstruction of Radiation Dose Received by
39 410 Diagnostic Radiologic Technologists in Korea. *J Prev Med Public Health*
40 411 2016;49:288–300.
41 412 28. Cheol Seong S, Kim YY, Khang YH, et al. Data Resource Profile: The
42 413 National Health Information Database of the National Health Insurance
43 414 Service in South Korea. *Int J Epidemiol* 2016;pii:dyw253 [Epub ahead of
44 415 print]
45 416 29. National Health Insurance Sharing Service in Korea.
46 417 <https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do> (accessed 29 Mar 2017).
47 418 30. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater
48 419 reliability. *Psychol Bull* 1979;86:420–8.
49 420 31. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol*
50 421 1993;46:423–9.

- 1
2
3 422 32. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and Psychological Measurement* 1960;20:37–46.
4 423
5 424 33. Bouville A, Toohey ER, Boice JD Jr, et al. Dose reconstruction for the
6 425 million worker study: status and guidelines. *Health Phys* 2015;108:206–
7 426 20.
8 427 34. Simon SL, Preston DL, Linet MS, et al. Radiation organ doses received in a
9 428 nationwide cohort of U.S. radiologic technologists: methods and findings.
10 429 *Radiat Res* 2014;182: 507–28.
11 430 35. Furukawa K, Misumi M, Cologne JB, et al. A Bayesian Semiparametric
12 431 Model for Radiation Dose-Response Estimation. *Risk Anal* 2016;36:1211–
13 432 23.
14 433 36. Boice JD, Mandel JS Jr, Doody MM, et al. A health survey of radiologic
15 434 technologists. *Cancer* 1992;69:586–98.
16 435 37. Choi SY, Kim TH, Chung CK, et al. Analysis of radiation workers' dose
17 436 records in the Korean National Dose Registry. *Radiat Prot Dosimetry*
18 437 2001;95:143–8.
19 438 38. McKeown-Eyssen GE, Thomas DC. Sample size determination in case-
20 439 control studies: the influence of the distribution of exposure. *J Chronic Dis*
21 440 1985;38:559–68.
22 441 39. White E, Kushi LH, Pepe MS. The effect of exposure variance and exposure
23 442 measurement error on study sample size: implications for the design of
24 443 epidemiologic studies. *J Clin Epidemiol* 1993;47:873–80.
25 444 40. Pernot E, Hall J, Baatout S, et al. Ionizing radiation biomarkers for
26 445 potential use in epidemiological studies. *Mutat Res* 2012;751:258–86.
27 446
28 447
29 448
30 449

FIGURE LEGENDS

31 450 **Figure 1.** Number of Korean radiation workers and effective doses (mSv)
32 451 according to occupation.
33 452

34 453 **Figure 2.** Study design.
35 454
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

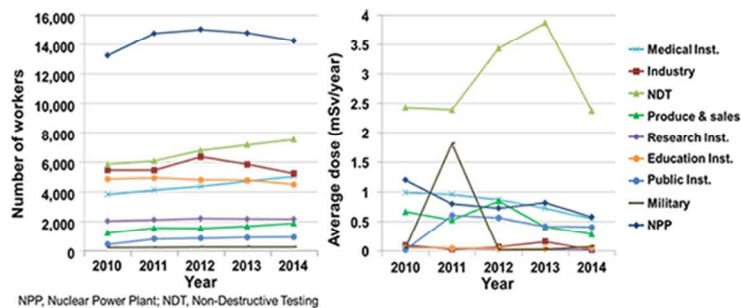


Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

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

63x42mm (300 x 300 DPI)

view only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

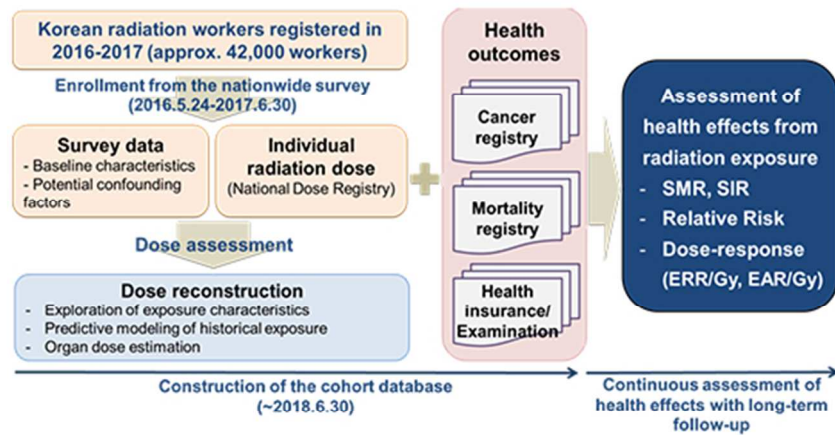


Figure 2. Study design.

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

			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

			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			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Protocol for a prospective cohort study of Korean radiation workers

Songwon Seo¹, Wan Young Lim¹, Dal Nim Lee¹, Jung Un Kim¹, Eun Shil Cha², Ye
Jin Bang², Won Jin Lee², Sunhoo Park¹, Young Woo Jin^{1,*}

¹Laboratory of Low Dose Risk Assessment, National Radiation Emergency Medical
Center, Korea Institute of Radiological and Medical Sciences, Seoul, Korea

²Department 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: ywjjin@kiram.s.re.kr

Word count: 2914 words

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

89 INTRODUCTION

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

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

133 134 **METHODS AND ANALYSIS**

135 **Study population and design**

136 The Korean radiation workers study (KRWS) is a prospective cohort study, and the
137 initial target population includes approximately 42,000 Korean radiation workers
138 registered with the NSSC from 2016-2017. Korean radiation workers are categorized
139 into 10 occupations depending on their workplace: nuclear power plant, industrial
140 radiography, industry, medical institute (except diagnostic radiation workers),
141 education institute, public institute, military, production, and sales. Of these, nuclear
142 power plant workers are in the majority with >14,000 workers, followed by industrial
143 radiography and industrial workers.[22] Average annual doses in the last five years
144 have been reported to be below or near 1 mSv; however, industrial radiographers are
145 exposed to the highest doses of 2-4 mSv.[22] The number of workers and their annual
146 average radiation doses by occupation in the past five years are presented in figure
147 1.[22]

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

163

164 **Survey questionnaire and informed consent form**

165 A self-administered questionnaire was developed by referring to the previous cohort
166 studies of Korean diagnostic radiologic technologists and the U.S. Radiologic
167 Technologists (USRT),[25, 26] which was amended through a pilot survey. The
168 questionnaire was composed of 20 questions about general work history and lifestyle
169 factors, and 10 demographic questions for all radiation workers (table 1). The 20
170 questions asked to all workers covered occupational history, work practices, exposure
171 warnings, medical exposure, medical history, and lifestyle factors. For industry
172 radiographers only, we added 11 NDT-specific questions in order to collect more
173 detailed information on their work status and exposure to other harmful agents. These
174 additional questions for industrial radiographers included specific working types,
175 history of specific health examination, and exposure to other NDT-related harmful
176 agents, such as film developer and cleaning fluids. In addition to the survey

1
2
3 177 questionnaire, an informed consent form was developed based on the Privacy Act in
4 178 Korea,[27] which included five essential items about the collection and use of
5 179 personal information, collection and use of identifying information, collection and use
6 180 of sensitive information, sharing of personal information with third parties, and
7 181 consent to research participation.
8
9 182
10 183

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

184

185 **Dosimetry data and health outcomes**

186 We shall collect radiation doses for individual workers from the Central Registry for
187 Radiation Worker Information (CRRWI) managed by the NSSC. External and
188 internal doses are collected by measuring effective doses and committed effective
189 doses quarterly and annually, respectively, through the electronic dose record
190 database (the National Dose Registry), which has been available under the CRRWI
191 since 1984. Most external doses are measured using thermoluminescent dosimeters
192 (TLD). Film badge dosimeters were used in the past, but not anymore. Doses based
193 on film badge dosimeters are less than 10% of the total dose records.[28] It might be
194 challenging to ensure the inclusion of radiation doses from high-Linear Energy
195 Transfer (LET) exposure (e.g., neutrons) in the current Korean dose reporting system;
196 however, since the proportion of workers with potential high-LET exposure is
197 expected to be less than 5%, the impact of high-LET exposure on risk estimates
198 would be minimal. In addition to radiation dose, the database includes workers'
199 names, sex, job classification, and personal identification numbers including date of
200 birth.[28] For individuals who were working before 1984, radiation doses were not
201 documented; therefore, we will estimate their historical occupational exposure using a
202 dose reconstruction model that includes predictors such as age, sex, and work
203 place.[29] For using individual radiation doses to analyze a dose-response relationship,
204 we will use absorbed organ doses estimated from the effective dose in the National
205 Dose Registry. Absorbed organ dose is estimated based on methods using the ICRP
206 116 organ dose conversion coefficients and irradiation geometry factors,[30]

207 considering information about work practices, such as use of protective devices and
 208 badge location, from the nationwide survey as suggested by the Million Worker Study
 209 (MWS)[31] and the USRT study.[32]
 210 Health information for individual workers in this study is to be collected from the
 211 National Cancer Registry, the National Vital Statistics Registry, and the National
 212 Health Insurance Sharing Service (NHSS) database (table 2). The National Cancer
 213 Registry includes cancer incidence data and the National Vital Statistics Registry
 214 includes mortality data, which have been available since 1999 and 1992, respectively.
 215 The NHSS database consists of four major sub-datasets, including an eligibility
 216 database, medical treatment database, health examination database, and medical care
 217 institution database, which have been available since 2002.[33, 34] We will
 218 predominantly use the first three databases and the information derived from these
 219 databases includes medical care history, regular health check-ups, and socioeconomic
 220 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.

223

224 **Validity and reliability of self-administered questionnaires**

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

1
2
3 237 coefficients[35] and kappa coefficients[36, 37] will be used as measures of validity
4 238 and reliability.

5 239

6 240 **Health risk associated with ionizing radiation exposure**

7 241 The primary health outcome of this study is cancer incidence. Other outcomes include
8 242 incidence of non-cancer diseases (e.g., cataracts and circulatory disease), laboratory
9 243 biomarkers (i.e., laboratory test items) from the NHISS databases, and mortality. The
10 244 laboratory biomarkers are possibly associated with pre-disease conditions, such as
11 245 metabolic risk profile (e.g., obesity, high serum glucose, cholesterol level, and low
12 246 blood pressure) and abnormal blood cell counts. For example, the metabolic risk
13 247 profile can be considered a surrogate endpoint of cardiovascular disease, and also an
14 248 independent variable to explore an interaction effect between radiation exposure and
15 249 metabolic syndrome with regard to cardiovascular disease. Age- and sex-specific
16 250 standardized incidence and mortality ratios will be calculated for overall comparisons
17 251 of cancer risk. The national statistics for cancer incidence and mortality among the
18 252 general Korean population will be employed as the control group for external
19 253 comparison, and study subjects whose effective doses have not exceeded the
20 254 minimum recording level of 0.1 mSv/quarter for external exposure and 0.1 mSv/year
21 255 for internal exposure during their employment according to the National Dose
22 256 Registry shall be considered as the control group for internal comparison. Risk
23 257 estimates for radiation exposure are typically presented as excess relative risk (ERR)
24 258 and excess absolute risk (EAR). The ERR is the relative risk minus 1.0, which refers
25 259 to the magnitude of the radiation risk relative to the baseline. The EAR refers to the
26 260 difference between the rate in an exposed and an unexposed population. To quantify
27 261 the dose-response relationship, we will estimate health risk per unit of radiation dose
28 262 (i.e., ERR/Gy, EAR/Gy) using a parametric model (Poisson), penalized splines,
29 263 and/or Bayesian semiparametric models[38] with or without adjustment for birth
30 264 cohort and confounding factors, such as lifestyle and socioeconomic status. Person-
31 265 years at risk for the analysis are calculated from date of entry in the study (defined as
32 266 the latest among the date of the first exposure and date of start of follow-up period in
33 267 the national health data source) to date of exit (defined as the earliest among the date
34 268 of health events, date of loss to follow-up and date of end of follow-up). To allow for
35 269 a possible latency period between radiation exposure and its consequences,
36 270 cumulative doses will be lagged by 2-5 years for leukemia and 5-10 years for solid
37 271 cancers. All the analyses will be updated at follow-up intervals of three to five years.

38 272

39 273 **Sample size calculation**

40 274 As this study is designed to investigate radiation-related health effects with long-term
41 275 follow-up in a cohort targeting all Korean radiation workers, a sample size calculation
42 276 is not deemed relevant.

43 277

44 278 **Study limitations and future work**

45 279 Lack of statistical power is a major limitation in most epidemiological studies,
46 280 particularly for low-dose ranges (i.e., <100 mSv). Average annual dose for the

1
2
3 281 KRWS's population in the past five years is approximately 1 mSv (0-4 mSv
4 282 depending on occupation).[22] Given that there was still a lack of statistical power in
5 283 low-dose ranges in the recent large scale international Nuclear Workers Study
6 284 (INWORKS) with an average individual cumulative dose of 21 mGy,[16] this study
7 285 including a relatively young cohort would not allow a definitive conclusion in a short
8 286 period of time. In addition, this study is limited in terms of investigation of health
9 287 effects in women since the proportion of female workers in the cohort is expected to
10 288 be 10-20%.[28, 39] Thus, it is necessary to expand the cohort through continuous
11 289 enrollment of new radiation workers with a long follow-up, and through collaborative
12 290 studies, including with the Korean diagnostic radiation worker cohort, and
13 291 international cohorts of similar occupations, such as the INWORKS[16] and the
14 292 USRT.[40] Another limitation is that the current KRWS does not include retired
15 293 workers and has limited information of radiation doses for those who had worked
16 294 before 1984 since the electronic National Dose Registry was not available before. As
17 295 the beginning of nuclear activities in Korea, a research reactor was first introduced at
18 296 1962, and the first nuclear power plant opened in 1978.[41] Given that the average
19 297 annual occupational doses were 1-3 mSv before 2000,[28] the radiation dose of
20 298 retired workers is expected to be higher, and their ages to be higher than those of
21 299 currently active workers of the KRWS cohort. Thus, it is important to include them in
22 300 any future study as this could possibly increase statistical power, via an increase in the
23 301 number of events and larger exposure variance.[42, 43] In addition, collection of
24 302 biosamples, such as blood and buccal cells, should be considered for a comprehensive
25 303 understanding of biological mechanisms via molecular epidemiologic studies of
26 304 radiation risk.[44] These activities will enhance our ability to investigate
27 305 susceptibility and surrogate biomarkers for assessing exposure risk, and to thereby
28 306 develop more sophisticated dose-response models for low-dose risk assessments.

29 307

308 **Potential impact**

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

321 Besides establishing scientific evidence for radiation-related health effects, we expect
322 that this study will contribute to both the prevention of adverse health effects and
323 improved communication with radiation workers. We will continue to promote this
324 cohort study and its results via radiation safety education and the study website

1
2
3 325 (<http://www.rhs.kr/>), which is a former website for Korean diagnostic radiation
4 326 worker studies[17, 18], that has been combined with the KRWS to increase
5 327 understanding about occupational exposure and health effects. Consequently,
6 328 radiation workers will be encouraged to pay more attention to radiation protection in
7 329 their workplaces, and to accomplish their work duties with a balanced risk judgment
8 330 about potential exposure that is not solely based on perceived risk.
9 331

332 **ETHICS AND DISSEMINATION**

333 This study has received ethical approval from the institutional review board of the
334 Korea Institute of Radiological and Medical Sciences (IRB No. K-1603-002-034). All
335 participants provided written informed consent prior to enrollment. The findings of
336 the study will be disseminated through scientific peer-reviewed journals and be
337 provided to the public, including radiation workers, via the study website
338 (<http://www.rhs.kr/>) and onsite radiation safety education.
339

340 **Author contributions:** SS and YWJ conceived and designed this study and drafted
341 the manuscript. WRL and DNL are involved in coordination of the nationwide survey.
342 WRL, DNL and JUK are involved in the collection of data and the construction of the
343 cohort database. ESC and YJB designed the survey questionnaire. WJL and SP
344 contributed to the design of the study and provided valuable inputs relevant to study
345 implementation. YWJ obtained funding. All authors reviewed and approved the final
346 manuscript.
347

348 **Funding:** This research was supported by the Nuclear Safety Research Program
349 through the Korea Foundation of Nuclear Safety (KOFONS), and granted financial
350 resources by the Nuclear Safety and Security Commission (NSSC) of the Republic of
351 Korea (No. 1503008).
352

353 **Competing interests:** None
354

355 **Ethics approval:** This study has received ethical approval from the institutional
356 review board of the Korea Institute of Radiological and Medical Sciences (IRB No.
357 K-1603-002-034).
358

359 **Provenance and peer review:** Not yet commissioned; to be externally peer reviewed.
360

361 **Open Access:** This is an Open Access article distributed in accordance with the
362 Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which
363 permits others to distribute, remix, adapt, build upon this work non-commercially, and
364 license their derivative works on different terms, provided the original work is
365 properly cited and the use is non-commercial. See:
366 <http://creativecommons.org/licenses/by-nc/4.0/>
367
368

369 REFERENCES

- 370 1. Cardis E, Vrijheid M, Blettner M, et al. The 15-Country Collaborative Study
371 of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates
372 of radiation-related cancer risks. *Radiat Res* 2007;167:396-416.
- 373 2. Seong KM, Seo S, Lee D, et al. Is the Linear No-Threshold Dose-Response
374 Paradigm Still Necessary for the Assessment of Health Effects of Low Dose
375 Radiation? *J Korean Med Sci* 2016;31:S10–23.
- 376 3. Navid F, Sondel PM, Barfield R, et al. Phase I trial of a novel anti-GD2
377 monoclonal antibody, Hu14.18K322A, designed to decrease toxicity in
378 children with refractory or recurrent neuroblastoma. *J Clin Oncol*
379 2014;32:1445-52
- 380 4. Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence
381 following occupational radiation exposure: third analysis of the National
382 Registry for Radiation Workers. *Br J Cancer* 2009;100:206-12.
- 383 5. Gilbert ES, Koshurnikova NA, Sokolnikov ME, et al. Lung cancer in Mayak
384 workers. *Radiat Res* 2004;162:505–16.
- 385 6. Hunter N, Kuznetsova IS, Labutina EV, et al. Solid cancer incidence other
386 than lung, liver and bone in Mayak workers: 1948-2004. *Br J Cancer*
387 2013;109:1989–96.
- 388 7. Shilnikova NS, Preston DL, Ron E, et al. Cancer mortality risk among
389 workers at the Mayak nuclear complex. *Radiat Res* 2003;159:787–98.
- 390 8. Rajaraman P, Doody MM, Yu CL, et al. Incidence and mortality risks for
391 circulatory diseases in US radiologic technologists who worked with
392 fluoroscopically guided interventional procedures, 1994-2008. *Occup Environ*
393 *Med* 2016;73:21–7.
- 394 9. Preston DL, Kitahara CM, Freedman DM, et al. Breast cancer risk and
395 protracted low-to-moderate dose occupational radiation exposure in the US
396 Radiologic Technologists Cohort, 1983-2008. *Br J Cancer* 2016;115:1105–12.
- 397 10. Matanoski GM, Tonascia JA, Correa-Villasenor A, et al. Cancer risks and
398 low-level radiation in U.S. shipyard workers. *J Radiat Res* 2008;49:83–91.
- 399 11. Richardson DB, Wing S. Leukemia mortality among workers at the Savannah
400 River Site. *Am J Epidemiol* 2007;166:1015–22.
- 401 12. Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer Mortality
402 through 2005 among a Pooled Cohort of U.S. Nuclear Workers Exposed to
403 External Ionizing Radiation. *Radiat Res* 2015;183:620-31
- 404 13. Zablotska LB, Lane RS, and Thompson PA. A reanalysis of cancer mortality
405 in Canadian nuclear workers (1956-1994) based on revised exposure and
406 cohort data. *Br J Cancer* 2014;110:214–23.
- 407 14. Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with
408 chronic external radiation exposure in the French combined cohort of nuclear
409 workers. *Occup Environ Med* 2013;70:630–8.
- 410 15. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from occupational
411 exposure to ionising radiation: retrospective cohort study of workers in France,
412 the United Kingdom, and the United States (INWORKS). *BMJ*
413 2015;351:h5359.
- 414 16. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of
415 death from leukaemia and lymphoma in radiation-monitored workers
416 (INWORKS): an international cohort study. *Lancet Haematol* 2015;2:e276–81.

- 1
2
3 417 17. Lee WJ, Ha M, Hwang SS, et al. The radiologic technologists' health study in
4 418 South Korea: study design and baseline results. *Int Arch Occup Environ*
5 419 *Health* 2015;88:759–68.
6 420 18. Lee J, Cha ES, Jeong M, et al. A national survey of occupational radiation
7 421 exposure among diagnostic radiologic technologists in South Korea. *Radiat*
8 422 *Prot Dosimetry* 2015;167:525–31.
9 423 19. Choi KH, Ha M, Lee WJ, et al. Cancer risk in diagnostic radiation workers in
10 424 Korea from 1996 to 2002. *Int J Environ Res Public Health* 2013;10:314–27.
11 425 20. Jeong M, Jin YW, Yang KH, et al. Radiation exposure and cancer incidence in
12 426 a cohort of nuclear power industry workers in the Republic of Korea, 1992–
13 427 2005. *Radiat Environ Biophys* 2010;49:47–55.
14 428 21. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers
15 429 exposed to ionizing radiation in Korea. *J Occup Environ Med* 2008;50:791–
16 430 803.
17 431 22. Nuclear Safety and Security Commission, Korea Institute of Nuclear Safety,
18 432 Korea Institute of Nuclear Nonproliferation and Control. 2015 Nuclear Safety
19 433 Yearbook (2016).
20 434 23. Korea Occupational Safety and Health Agency: Annual reports of
21 435 occupational disease (2000–2015).
22 436 <http://english.kosha.or.kr/english/content.do?menuId=11436>. (accessed
23 437 20 Jun 2017).
24 438 24. Jin YW, Jeong M, Moon K, et al. Ionizing radiation-induced diseases in Korea.
25 439 *J Korean Med Sci* 2010;25:S70–6.
26 440 25. The U.S. radiologic technologists study.
27 441 <https://radtechstudy.nci.nih.gov/questionnaires.html> (accessed 20 Jun 2017).
28 442 26. Radiation and health study among radiation workers in Korea.
29 443 <http://www.rhs.kr/method/overview.asp> (accessed 20 Jun 2017).
30 444 27. Personal Information Protection Act, Articles 15 to 22 Section 1 (2014).
31 445 28. Choi SY, Kim TH, Chung CK, et al. Analysis of radiation workers' dose
32 446 records in the Korean National Dose Registry. *Radiat Prot Dosimetry*
33 447 2001;95:143–8.
34 448 29. Choi Y, Kim J, Lee JJ, et al. Reconstruction of Radiation Dose Received by
35 449 Diagnostic Radiologic Technologists in Korea. *J Prev Med Public Health*
36 450 2016;49:288–300.
37 451 30. Taulbee TD, McCartney KA, Traub R, et al. Implementation of ICRP 116
38 452 dose conversion coefficients for reconstruction organ dose in radiation
39 453 compensation program. *Radiat Prot Dosimetry* 2017;173:131–137.
40 454 31. Bouville A, Toohey ER, Boice JD Jr, et al. Dose reconstruction for the million
41 455 worker study: status and guidelines. *Health Phys* 2015;108:206–20.
42 456 32. Simon SL, Preston DL, Linet MS, et al. Radiation organ doses received in a
43 457 nationwide cohort of U.S. radiologic technologists: methods and findings.
44 458 *Radiat Res* 2014;182:507–28.
45 459 33. Cheol Seong S, Kim YY, Khang YH, et al. Data Resource Profile: The
46 460 National Health Information Database of the National Health Insurance
47 461 Service in South Korea. *Int J Epidemiol* 2016;pii:dyw253 [Epub ahead of print]
48 462 34. National Health Insurance Sharing Service in Korea.
49 463 <https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do> (accessed 20 Jun 2017).
50 464 35. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability.
51 465 *Psychol Bull* 1979;86:420–8.

- 1
2
3 466 36. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol*
4 467 1993;46:423–9.
5 468 37. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and*
6 469 *Psychological Measurement* 1960;20:37–46.
7 470 38. Furukawa K, Misumi M, Cologne JB, et al. A Bayesian Semiparametric
8 471 Model for Radiation Dose-Response Estimation. *Risk Anal* 2016;36:1211–23.
9 472 39. Jeong JH, Lee JK, Kwon, JW, et al. Occupational Radiation Exposure in
10 473 Korea: 2002. *J Korean Assoc Radiat Protect* 2005;30:175-183.
11 474 40. Boice JD, Mandel JS Jr, Doody MM, et al. A health survey of radiologic
12 475 technologists. *Cancer* 1992;69:586–98.
13 476 41. Lim YK, Kim JR., Hwang KH, et al. Investigation of Nuclear Development at
14 477 the Early Stage in Korea (No. KAERI/CM--1022/2007). Korea Atomic
15 478 Energy Research Institute 2009.
16 479 42. McKeown-Eyssen GE, Thomas DC. Sample size determination in case-
17 480 control studies: the influence of the distribution of exposure. *J Chronic Dis*
18 481 1985;38:559–68.
19 482 43. White E, Kushi LH, Pepe MS. The effect of exposure variance and exposure
20 483 measurement error on study sample size: implications for the design of
21 484 epidemiologic studies. *J Clin Epidemiol* 1993;47:873–80.
22 485 44. Pernot E, Hall J, Baatout S, et al. Ionizing radiation biomarkers for potential
23 486 use in epidemiological studies. *Mutat Res* 2012;751:258–86.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

FIGURE LEGENDS

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

Figure 2. Study design.

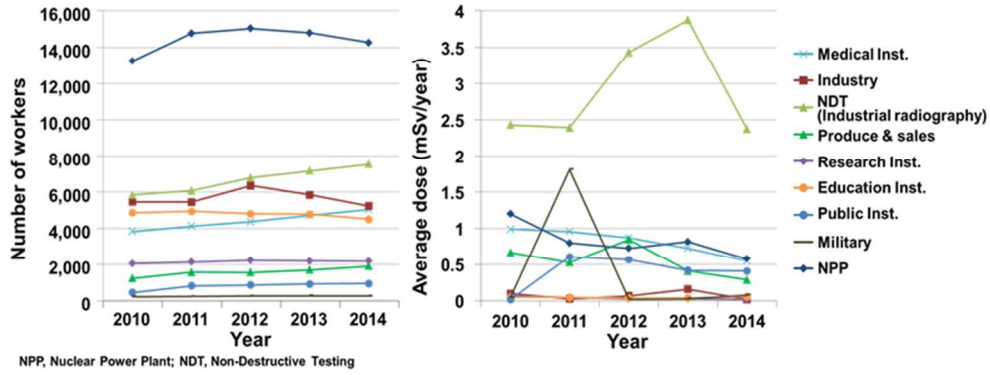


Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

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

67x46mm (300 x 300 DPI)

View only

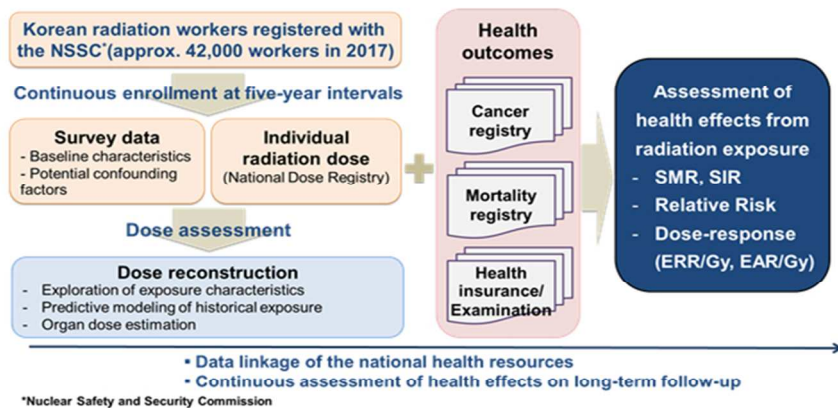


Figure 2. Study design.

Figure 2. Study design.

67x46mm (300 x 300 DPI)

View only

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

			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:	<i>BMJ Open</i>
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

1
2
3 1 **Assessing the health effects associated with occupational radiation exposure in**
4 2 **Korean radiation workers: protocol for a prospective cohort study**
5
6 3
7 4

8 5 Songwon Seo¹, Wan Young Lim¹, Dal Nim Lee¹, Jung Un Kim¹, Eun Shil Cha², Ye
9 6 Jin Bang², Won Jin Lee², Sunhoo Park¹, Young Woo Jin^{1,*}
10 7

11 8 ¹Laboratory of Low Dose Risk Assessment, National Radiation Emergency Medical
12 9 Center, Korea Institute of Radiological and Medical Sciences, Seoul, Korea

13 10 ²Department of Preventive Medicine, Korea University College of Medicine, Seoul,
14 11 Korea
15 12

16 13 *Correspondence to: Young Woo Jin, M.D., Ph.D.

17 14 National Radiation Emergency Medical Center, Korea Institute of Radiological and
18 15 Medical Sciences, 75 Nowon-ro, Nowon-gu, Seoul 01812, Republic of Korea
19 16 Tel: +82-2-3399-5800; Fax: +82-2-3399-5870; E-mail: ywjin@kirams.re.kr
20 17

21 18 Word count: 2969 words
22 19

23 20 Keywords: radiation worker; epidemiology; cohort; exposure; health
24 21
25 22
26 23
27 24
28 25
29 26
30 27
31 28
32 29
33 30
34 31
35 32
36 33
37 34
38 35
39 36
40 37
41 38
42 39
43 40
44 41
45 42
46 43
47 44
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

45 ABSTRACT

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

55 **Methods and analysis:** Approximately 42,000 Korean radiation workers registered
56 with the Nuclear Safety and Security Commission from 2016-2017 are the initial
57 target population of this study. Cohort participants are to be enrolled through a
58 nationwide self-administered questionnaire survey between May 24, 2016, and June
59 30, 2017. As of March 31, 2017, 22,982 workers are enrolled in the study
60 corresponding to a response rate of 75%. This enrollment will be continued at five-
61 year intervals to update information on existing study participants and recruit newly
62 hired workers. Survey data will be linked with the national dose registry, the national
63 cancer registry, the national vital statistics registry, and national health insurance data
64 via personal identification numbers. Age- and sex-specific standardized incidence and
65 mortality ratios will be calculated for overall comparisons of cancer risk. For dose-
66 response assessment, excess relative risk (ERR/Gy) and excess absolute risk
67 (EAR/Gy) will be estimated with adjustments for birth year and potential confounders,
68 such as lifestyle factors and socioeconomic status.

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

74 75 **Strengths and limitations:**

76 77 **Strengths:**

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

82 **Limitations:**

- 83 ● Limited sample size and retired workers not included in the cohort
 - 84 ● Continued long term follow-up is necessary to extract full value from the cohort
- 85
86
87
88

89 INTRODUCTION

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

110 In Korea, workers in radiation-related occupations are registered with two
111 independent government agencies depending on their occupation: diagnostic radiation
112 workers under the Centers for Disease Control and Prevention (CDC), and nuclear-
113 related workers under the Nuclear Safety and Security Commission (NSSC). We use
114 the term “radiation workers” for nuclear-related workers henceforth in this paper. A
115 prospective cohort study of diagnostic radiation workers was launched about five
116 years ago[16, 17] following the suggestion of an elevated cancer risk in diagnostic
117 medical workers from a retrospective study.[18] For Korean radiation workers, sparse
118 information is available from two studies that are limited by short follow-up and
119 sparse information on confounding variables.[19, 20] Moreover, industrial
120 radiography, which is one of the non-destructive testing (NDT) technologies, has been
121 reported to not only have the highest effective dose,[21] but also to account for the
122 majority of occupational cancer incidence among all radiation-related occupations.[22,
123 23] However, industrial radiographers have been relatively neglected compared to
124 nuclear power plant workers.

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

129

130 METHODS AND ANALYSIS

131 Study population and design

1
2
3 132 The Korean radiation workers study (KRWS) is a prospective cohort study, and the
4 133 initial target population includes approximately 42,000 Korean radiation workers
5 134 registered with the NSSC from 2016-2017. Korean radiation workers are categorized
6 135 into 10 occupations depending on their workplace: nuclear power plant, industrial
7 136 radiography, industry, medical institute (except diagnostic radiation workers),
8 137 education institute, public institute, military, production, and sales. Of these, nuclear
9 138 power plant workers are in the majority with >14,000 workers, followed by industrial
10 139 radiography and industrial workers.[21] Average annual effective doses, which are
11 140 the sum of the external dose ($H_p(10)$) and the committed effective dose, in the last
12 141 five years have been reported to be below or near 1 mSv; however, industrial
13 142 radiographers are exposed to the highest doses of 2-4 mSv.[21] The number of
14 143 workers and their annual average effective doses by occupation in the past five years
15 144 are presented in figure 1.[21]

16 145 All radiation workers in Korea should receive radiation safety education every year.
17 146 In order to enroll the participants, we visited each educational location across the
18 147 country between May 24, 2016, and June 30, 2017, to conduct the self-administered
19 148 questionnaire survey and collect informed consent, the details of which are described
20 149 in the following section. As of March 31, 2017, of 30,572 workers that participated in
21 150 radiation safety education, 22,982 workers have been enrolled in the study, which
22 151 corresponds to a response rate of 75%. Following enrollment, we shall combine the
23 152 data from the questionnaires with dosimetry data from the national dose registry, and
24 153 link the health data via personal identification numbers. The health data will include
25 154 cancer incidence data from the national cancer registry, overall mortality data from
26 155 the national vital statistics registry, and incidence of diseases other than cancer from
27 156 national health examination data. We will conduct the self-administered questionnaire
28 157 survey at five-year intervals to update information on existing study participants,
29 158 recruit newly hired workers, and evaluate the association between radiation dose and
30 159 health effects on long-term follow-up. The study design is presented in figure 2.

31 160

32 161 **Survey questionnaire and informed consent form**

33 162 A self-administered questionnaire was developed by referring to the previous cohort
34 163 studies of Korean diagnostic radiologic technologists and the U.S. Radiologic
35 164 Technologists (USRT),[24, 25] which was amended through a pilot survey. The
36 165 questionnaire was composed of 20 questions about general work history and lifestyle
37 166 factors, and 10 demographic questions for all radiation workers (table 1). The 20
38 167 questions asked to all workers covered occupational history, work practices, exposure
39 168 warnings, medical exposure, medical history, and lifestyle factors. For industry
40 169 radiographers only, we added 11 NDT-specific questions in order to collect more
41 170 detailed information on their work status and exposure to other harmful agents. These
42 171 additional questions for industrial radiographers included specific working types,
43 172 history of specific health examination, and exposure to other NDT-related harmful
44 173 agents, such as film developer and cleaning fluids. In addition to the survey
45 174 questionnaire, an informed consent form was developed based on the Privacy Act in
46 175 Korea,[26] which included five essential items about the collection and use of

176 personal information, collection and use of identifying information, collection and use
 177 of sensitive information, sharing of personal information with third parties, and
 178 consent to research participation.

179

180 **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

181

182 **Dosimetry data**

183 We shall collect radiation doses for individual workers from the Central Registry for
 184 Radiation Worker Information (CRRWI) managed by the NSSC. External and
 185 internal doses are collected by measuring personal dose equivalent, $H_p(10)$, and
 186 committed effective doses quarterly and annually, respectively, through the electronic
 187 dose record database (the National Dose Registry), which has been available under
 188 the CRRWI since 1984. Most external doses are measured using thermoluminescent
 189 dosimeters (TLD); optically stimulated luminescence dosimeters (OSLD) are only
 190 applied in limited fields.[27] Film badge dosimeters were used in the past, but are no
 191 longer used. Doses based on film badge dosimeters are less than 10% of the total dose
 192 records.[28] It might be challenging to ensure the inclusion of radiation doses from
 193 high-Linear Energy Transfer (LET) exposure (e.g., neutrons) in the current Korean
 194 dose reporting system in which $H_p(10)$ for neutrons is included but it is not separated
 195 from $H_p(10)$ for photons; however, since the proportion of workers with potential
 196 high-LET exposure is expected to be less than 5%, the impact of high-LET exposure
 197 on risk estimates would be minimal. Committed effective doses are reported only for
 198 workers whose annual committed effective dose is likely to exceed 2 mSv/year. In
 199 addition to radiation dose, the database includes workers' names, sex, job
 200 classification, and personal identification numbers including date of birth.[28] For
 201 individuals who were working before 1984, radiation doses were not documented;
 202 therefore, we will estimate their historical occupational exposure using a dose
 203 reconstruction model that includes predictors such as age, sex, and work place.[29]
 204 For using individual radiation doses to analyze a dose-response relationship, we will
 205 use organ absorbed doses estimated from the effective dose from the external

206 exposure in the National Dose Registry. Absorbed organ dose is estimated based on
 207 methods using the ICRP 116 organ dose conversion coefficients and irradiation
 208 geometry factors,[30] considering information about work practices, such as use of
 209 protective devices and badge location, from the nationwide survey as suggested by the
 210 Million Worker Study (MWS)[31] and the USRT study.[32]

211

212 **Health outcomes**

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

224

225 **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.

226

227 **Validity and reliability of self-administered questionnaires**

228 Information collected from self-administered questionnaires is essential for estimating
 229 organ doses and determining confounders, which can interpret findings more
 230 accurately. It is therefore of particular importance that we evaluate the validity and
 231 reliability of our questionnaires, particularly those measuring work practice and
 232 lifestyle. Our questionnaire contains items about work history (e.g., employment start
 233 date and period, and warning for exceeding 5 mSv) and medical history (e.g.,
 234 diagnosis of cancer, cataract, and cardiovascular disease), which we can also ascertain
 235 from the National Dose Registry and National Health Records (i.e., the cancer registry

1
2
3 236 and NHISS database). We will compare the answers to our questions with the national
4 237 records in order to assess the validity of the responses to the self-administered
5 238 questionnaires. For the evaluation of reliability, we will compare responses of study
6 239 participants who were surveyed in both 2016 and 2017. Intra-class correlation
7 240 coefficients[35] and kappa coefficients[36, 37] will be used as measures of validity
8 241 and reliability.
9 242

243 **Health risk associated with ionizing radiation exposure**

244 The primary health outcome of this study is cancer incidence. Other outcomes include
245 incidence of non-cancer diseases (e.g., cataracts and circulatory disease), laboratory
246 biomarkers (i.e., laboratory test items) from the NHISS databases, and mortality. The
247 laboratory biomarkers are possibly associated with pre-disease conditions, such as
248 metabolic risk profile (e.g., obesity, high serum glucose, cholesterol level, and low
249 blood pressure) and abnormal blood cell counts. For example, the metabolic risk
250 profile can be considered a surrogate endpoint of cardiovascular disease, and also an
251 independent variable to explore an interaction effect between radiation exposure and
252 metabolic syndrome with regard to cardiovascular disease. Age- and sex-specific
253 standardized incidence and mortality ratios will be calculated for overall comparisons
254 of cancer risk. The national statistics for cancer incidence and mortality among the
255 general Korean population will be employed as the control group for external
256 comparison, and study subjects whose effective doses (the sum of the external dose
257 ($H_p(10)$) and the committed effective dose) have not exceeded the minimum recording
258 level of 0.1 mSv/quarter for external exposure and 0.1 mSv/year for internal exposure
259 during their employment according to the National Dose Registry shall be considered
260 as the control group for internal comparison. Risk estimates for radiation exposure are
261 typically presented as excess relative risk (ERR) and excess absolute risk (EAR). The
262 ERR is the relative risk minus 1.0, which refers to the magnitude of the radiation risk
263 relative to the baseline. The EAR refers to the difference between the rate in an
264 exposed and an unexposed population. To quantify the dose-response relationship, we
265 will estimate health risk per unit of organ absorbed dose (i.e., ERR/Gy, EAR/Gy)
266 using a parametric model (Poisson), penalized splines, and/or Bayesian
267 semiparametric models[38] with or without adjustment for birth cohort and
268 confounding factors, such as lifestyle and socioeconomic status. Committed effective
269 dose will be used as another confounder for sensitivity analyses considering internal
270 exposure, using an adjusted analysis and a stratified analysis. Person-years at risk for
271 the analysis are calculated from date of entry in the study (defined as the latest among
272 the date of the first exposure and date of start of follow-up period in the national
273 health data source) to date of exit (defined as the earliest among the date of health
274 events, date of loss to follow-up and date of end of follow-up). To allow for a possible
275 latency period between radiation exposure and its consequences, cumulative doses
276 will be lagged by 2-5 years for leukemia and 5-10 years for solid cancers. All the
277 analyses will be updated at follow-up intervals of three to five years.
278

279 **Sample size calculation**

1
2
3 280 As this study is designed to investigate radiation-related health effects with long-term
4 281 follow-up in a cohort targeting all Korean radiation workers, a sample size calculation
5 282 is not deemed relevant.
6
7 283

8 284 **Study limitations and future work**

9 285 Lack of statistical power is a major limitation in most epidemiological studies,
10 286 particularly for low-dose ranges (i.e., <100 mSv). Average annual dose for the
11 287 KRWS's population in the past five years is approximately 1 mSv (0-4 mSv
12 288 depending on occupation).[21] Given that there was still a lack of statistical power in
13 289 low-dose ranges in the recent large scale international Nuclear Workers Study
14 290 (INWORKS) with an average individual cumulative dose of 21 mGy,[15] this study
15 291 including a relatively young cohort would not allow a definitive conclusion in a short
16 292 period of time. In addition, this study is limited in terms of investigation of health
17 293 effects in women since the proportion of female workers in the cohort is expected to
18 294 be 10-20%.[28, 39] Thus, it is necessary to expand the cohort through continuous
19 295 enrollment of new radiation workers with a long follow-up, and through collaborative
20 296 studies, including with the Korean diagnostic radiation worker cohort, and
21 297 international cohorts of similar occupations, such as the INWORKS[15] and the
22 298 USRT.[40] Another limitation is that the current KRWS does not include retired
23 299 workers and has limited information of radiation doses for those who had worked
24 300 before 1984 since the electronic National Dose Registry was not available before. As
25 301 the beginning of nuclear activities in Korea, a research reactor was first introduced at
26 302 1962, and the first nuclear power plant opened in 1978.[41] Given that the average
27 303 annual occupational doses were 1-3 mSv before 2000,[28] the radiation dose of
28 304 retired workers is expected to be higher, and their ages to be higher than those of
29 305 currently active workers of the KRWS cohort. Thus, it is important to include them in
30 306 potential future studies, as this could possibly increase statistical power, via an
31 307 increase in the number of events and larger exposure variance.[42, 43] In addition,
32 308 collection of biosamples, such as blood and buccal cells, should be considered for a
33 309 comprehensive understanding of biological mechanisms via molecular epidemiologic
34 310 studies of radiation risk.[44] These activities will enhance our ability to investigate
35 311 susceptibility and surrogate biomarkers for assessing exposure risk, and to thereby
36 312 develop more sophisticated dose-response models for low-dose risk assessments.
37
38
39
40
41
42
43
44
45

46 314 **Potential impact**

47 315 We have designed the KRWS to assess health effects among Korean radiation
48 316 workers exposed to protracted low-dose radiation. This is the first prospective cohort
49 317 study of active workers from the entire range of occupations registered with the NSSC.
50 318 Data collected from the nationwide survey will provide detailed information on work
51 319 practices and lifestyle factors, which allows for an in-depth exploration of
52 320 occupational exposure and adjustment for confounding factors. In addition, individual
53 321 health data derived from the national resources include not only cancer/non-cancer
54 322 diseases, but also pre-disease conditions including laboratory test items, ensuring
55 323 comprehensive and accurate information for the evaluation of health effects from
56
57
58
59
60

1
2
3 324 radiation exposure. Study findings will be directly relevant to radiation protection for
4 325 radiation workers, and will further provide the basis for recommendations and
5 326 regulations about low-dose radiation safety.

6
7 327 Besides establishing scientific evidence for radiation-related health effects, we expect
8 328 that this study will contribute to both the prevention of adverse health effects and
9 329 improved communication with radiation workers. We will continue to promote this
10 330 cohort study and its results via radiation safety education and the study website
11 331 (<http://www.rhs.kr/>), which is a former website for Korean diagnostic radiation
12 332 worker studies[16, 17], that has been combined with the KRWS to increase
13 333 understanding about occupational exposure and health effects. Consequently,
14 334 radiation workers will be encouraged to pay more attention to radiation protection in
15 335 their workplaces, and to accomplish their work duties with a balanced risk judgment
16 336 about potential exposure that is not solely based on perceived risk.

17 337

20 338 **ETHICS AND DISSEMINATION**

21 339 This study has received ethical approval from the institutional review board of the
22 340 Korea Institute of Radiological and Medical Sciences (IRB No. K-1603-002-034). All
23 341 participants provided written informed consent prior to enrollment. The findings of
24 342 the study will be disseminated through scientific peer-reviewed journals and be
25 343 provided to the public, including radiation workers, via the study website
26 344 (<http://www.rhs.kr/>) and onsite radiation safety education.

27 345

28 346 **Author contributions:** SS and YWJ conceived and designed this study and drafted
29 347 the manuscript. WRL and DNL are involved in coordination of the nationwide survey.
30 348 WRL, DNL and JUK are involved in the collection of data and the construction of the
31 349 cohort database. ESC and YJB designed the survey questionnaire. WJL and SP
32 350 contributed to the design of the study and provided valuable inputs relevant to study
33 351 implementation. YWJ obtained funding. All authors reviewed and approved the final
34 352 manuscript.

35 353

36 354 **Funding:** This research was supported by the Nuclear Safety Research Program
37 355 through the Korea Foundation of Nuclear Safety (KOFONS), and granted financial
38 356 resources by the Nuclear Safety and Security Commission (NSSC) of the Republic of
39 357 Korea (No. 1503008).

40 358

41 359 **Competing interests:** None

42 360

43 361 **Ethics approval:** This study has received ethical approval from the institutional
44 362 review board of the Korea Institute of Radiological and Medical Sciences (IRB No.
45 363 K-1603-002-034).

46 364

47 365 **Provenance and peer review:** Not yet commissioned; to be externally peer reviewed.

48 366

1
2
3 367 **Open Access:** This is an Open Access article distributed in accordance with the
4 368 Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which
5 369 permits others to distribute, remix, adapt, build upon this work non-commercially, and
6 370 license their derivative works on different terms, provided the original work is
7 371 properly cited and the use is non-commercial. See:
8 372 <http://creativecommons.org/licenses/by-nc/4.0/>
9
10 373

11 374 **Acknowledgments:**

12 375 The authors express gratitude to Kijung Lim from the Korea Foundation of Nuclear
13 376 Safety (KOFONS) for providing his professional knowledge regarding the National
14 377 Dose Registry for radiation workers.
15
16 378

17 379 **REFERENCES**

- 18 380 1. Cardis E, Vrijheid M, Blettner M, et al. The 15-country collaborative study
19 381 of cancer risk among radiation workers in the nuclear industry: estimates
20 382 of radiation-related cancer risks. *Radiat Res* 2007;167:396-416.
21 383 2. Seong KM, Seo S, Lee D, et al. Is the linear no-threshold dose-response
22 384 paradigm still necessary for the assessment of health effects of low dose
23 385 radiation? *J Korean Med Sci* 2016;31:S10-23.
24 386 3. Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence
25 387 following occupational radiation exposure: third analysis of the National
26 388 Registry for Radiation Workers. *Br J Cancer* 2009;100:206-12.
27 389 4. Gilbert ES, Koshurnikova NA, Sokolnikov ME, et al. Lung cancer in Mayak
28 390 workers. *Radiat Res* 2004;162:505-16.
29 391 5. Hunter N, Kuznetsova IS, Labutina EV, et al. Solid cancer incidence other
30 392 than lung, liver and bone in Mayak workers: 1948-2004. *Br J Cancer*
31 393 2013;109:1989-96.
32 394 6. Shilnikova NS, Preston DL, Ron E, et al. Cancer mortality risk among
33 395 workers at the Mayak nuclear complex. *Radiat Res* 2003;159:787-98.
34 396 7. Rajaraman P, Doody MM, Yu CL, et al. Incidence and mortality risks for
35 397 circulatory diseases in US radiologic technologists who worked with
36 398 fluoroscopically guided interventional procedures, 1994-2008. *Occup Environ*
37 399 *Med* 2016;73:21-7.
38 400 8. Preston DL, Kitahara CM, Freedman DM, et al. Breast cancer risk and
39 401 protracted low-to-moderate dose occupational radiation exposure in the US
40 402 Radiologic Technologists Cohort, 1983-2008. *Br J Cancer* 2016;115:1105-12.
41 403 9. Matanoski GM, Tonascia JA, Correa-Villasenor A, et al. Cancer risks and
42 404 low-level radiation in U.S. shipyard workers. *J Radiat Res* 2008;49:83-91.
43 405 10. Richardson DB, Wing S. Leukemia mortality among workers at the Savannah
44 406 River Site. *Am J Epidemiol* 2007;166:1015-22.
45 407 11. Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer mortality
46 408 through 2005 among a pooled cohort of U.S. nuclear workers exposed to
47 409 external ionizing radiation. *Radiat Res* 2015;183:620-31
48 410 12. Zablotska LB, Lane RS, and Thompson PA. A reanalysis of cancer mortality
49 411 in Canadian nuclear workers (1956-1994) based on revised exposure and
50 412 cohort data. *Br J Cancer* 2014;110:214-23.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 413 13. Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with
4 414 chronic external radiation exposure in the French combined cohort of nuclear
5 415 workers. *Occup Environ Med* 2013;70:630–8.
- 6 416 14. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from occupational
7 417 exposure to ionising radiation: retrospective cohort study of workers in France,
8 418 the United Kingdom, and the United States (INWORKS). *BMJ*
9 419 2015;351:h5359.
- 10 420 15. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of
11 421 death from leukaemia and lymphoma in radiation-monitored workers
12 422 (INWORKS): an international cohort study. *Lancet Haematol* 2015;2:e276–81.
- 13 423 16. Lee WJ, Ha M, Hwang SS, et al. The radiologic technologists' health study in
14 424 South Korea: study design and baseline results. *Int Arch Occup Environ*
15 425 *Health* 2015;88:759–68.
- 16 426 17. Lee J, Cha ES, Jeong M, et al. A national survey of occupational radiation
17 427 exposure among diagnostic radiologic technologists in South Korea. *Radiat*
18 428 *Prot Dosimetry* 2015;167:525–31.
- 19 429 18. Choi KH, Ha M, Lee WJ, et al. Cancer risk in diagnostic radiation workers in
20 430 Korea from 1996 to 2002. *Int J Environ Res Public Health* 2013;10:314–27.
- 21 431 19. Jeong M, Jin YW, Yang KH, et al. Radiation exposure and cancer incidence in
22 432 a cohort of nuclear power industry workers in the Republic of Korea, 1992–
23 433 2005. *Radiat Environ Biophys* 2010;49:47–55.
- 24 434 20. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers
25 435 exposed to ionizing radiation in Korea. *J Occup Environ Med* 2008;50:791–
26 436 803.
- 27 437 21. Nuclear Safety and Security Commission, Korea Institute of Nuclear Safety,
28 438 Korea Institute of Nuclear Nonproliferation and Control. 2015 Nuclear Safety
29 439 Yearbook (2016).
- 30 440 22. Korea Occupational Safety and Health Agency: Annual reports of
31 441 occupational disease (2000–2015).
32 442 <http://english.kosha.or.kr/english/content.do?menuId=11436>. (accessed
33 443 20 Jun 2017).
- 34 444 23. Jin YW, Jeong M, Moon K, et al. Ionizing radiation-induced diseases in Korea.
35 445 *J Korean Med Sci* 2010;25:S70–6.
- 36 446 24. The U.S. radiologic technologists study.
37 447 <https://radtechstudy.nci.nih.gov/questionnaires.html> (accessed 20 Jun 2017).
- 38 448 25. Radiation and health study among radiation workers in Korea.
39 449 <http://www.rhs.kr/method/overview.asp> (accessed 20 Jun 2017).
- 40 450 26. Personal Information Protection Act, Articles 15 to 22 Section 1 (2014).
- 41 451 27. Lee WH, Kim SC, Ahn SM. Comparison on the Dosimetry of TLD and OSLD
42 452 Used in Nuclear Medicine. *Journal of the Korea Contents Association* 2012;
43 453 12:329-34.
- 44 454 28. Choi SY, Kim TH, Chung CK, et al. Analysis of radiation workers' dose
45 455 records in the Korean National Dose Registry. *Radiat Prot Dosimetry*
46 456 2001;95:143–8.
- 47 457 29. Choi Y, Kim J, Lee JJ, et al. Reconstruction of radiation dose received by
48 458 diagnostic radiologic technologists in Korea. *J Prev Med Public Health*
49 459 2016;49:288–300.
- 50 460 30. Taulbee TD, McCartney KA, Traub R, et al. Implementation of ICRP 116
51 461 dose conversion coefficients for reconstruction organ dose in radiation
52 462 compensation program. *Radiat Prot Dosimetry* 2017;173:131–137.

- 1
2
3 463 31. Bouville A, Toohey ER, Boice JD Jr, et al. Dose reconstruction for the million
4 464 worker study: status and guidelines. *Health Phys* 2015;108:206–20.
5 465 32. Simon SL, Preston DL, Linet MS, et al. Radiation organ doses received in a
6 466 nationwide cohort of U.S. radiologic technologists: methods and findings.
7 467 *Radiat Res* 2014;182:507–28.
8 468 33. Cheol Seong S, Kim YY, Khang YH, et al. Data Resource Profile: The
9 469 National Health Information Database of the National Health Insurance
10 470 Service in South Korea. *Int J Epidemiol* 2016;pii:dyw253 [Epub ahead of print]
11 471 34. National Health Insurance Sharing Service in Korea.
12 472 <https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do> (accessed 20 Jun 2017).
13 473 35. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability.
14 474 *Psychol Bull* 1979;86:420–8.
15 475 36. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol*
16 476 1993;46:423–9.
17 477 37. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and*
18 478 *Psychological Measurement* 1960;20:37–46.
19 479 38. Furukawa K, Misumi M, Cologne JB, et al. A Bayesian semiparametric model
20 480 for radiation dose-response estimation. *Risk Anal* 2016;36:1211–23.
21 481 39. Jeong JH, Lee JK, Kwon, JW, et al. Occupational radiation exposure in Korea:
22 482 2002. *J Korean Assoc Radiat Protect* 2005;30:175-183.
23 483 40. Boice JD, Mandel JS Jr, Doody MM, et al. A health survey of radiologic
24 484 technologists. *Cancer* 1992;69:586–98.
25 485 41. Lim YK, Kim JR., Hwang KH, et al. Investigation of nuclear development at
26 486 the early stage in Korea (No. KAERI/CM--1022/2007). Korea Atomic Energy
27 487 Research Institute 2009.
28 488 42. McKeown-Eyssen GE, Thomas DC. Sample size determination in case-
29 489 control studies: the influence of the distribution of exposure. *J Chronic Dis*
30 490 1985;38:559–68.
31 491 43. White E, Kushi LH, Pepe MS. The effect of exposure variance and exposure
32 492 measurement error on study sample size: implications for the design of
33 493 epidemiologic studies. *J Clin Epidemiol* 1993;47:873–80.
34 494 44. Pernot E, Hall J, Baatout S, et al. Ionizing radiation biomarkers for potential
35 495 use in epidemiological studies. *Mutat Res* 2012;751:258–86.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

FIGURE LEGENDS

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

Figure 2. Study design.

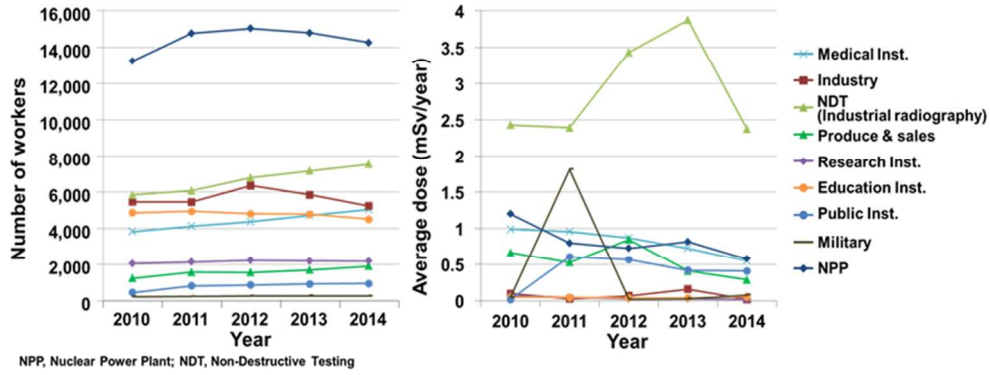


Figure 1. Number of Korean radiation workers and effective doses (mSv) according to occupation.

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

67x46mm (300 x 300 DPI)

View only

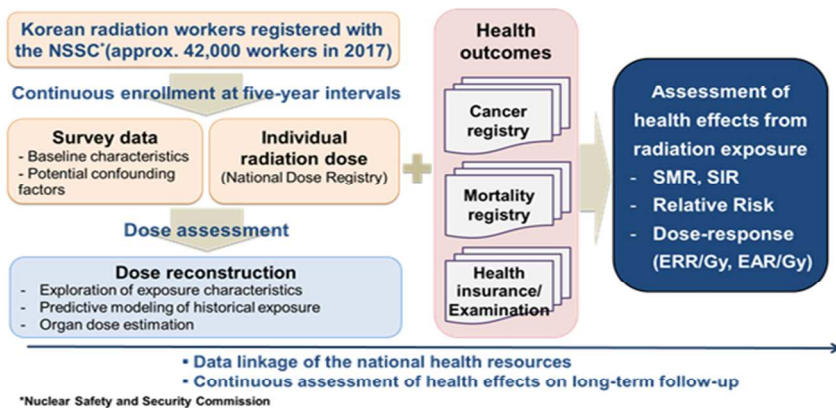


Figure 2. Study design.

Figure 2. Study design.

67x46mm (300 x 300 DPI)

View only

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

			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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

			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.