Project Title: Combined analysis of mortality among nuclear workers

Final Report

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Abstract

The objective of this project was to conduct a pooled analysis of US worker data for employees of 5 major facilities selected based on cohort size, availability of demographic and employment history information, and completeness of radiation monitoring data: Oak Ridge National Laboratory, Savannah River Site, Hanford site, Idaho National Laboratory, and Portsmouth Naval Shipyard. An update of vital status follow-up of each cohort had been conducted recently, making the proposed analysis feasible. The combined study of US workers was undertaken and has permitted us to address questions regarding variation in radiation risks with time-since-exposure and age-at-exposure, as well as variation in radiation risks by type of cancer. We proposed state-of-the-art methods to minimize bias due to confounding, sensitivity analyses to assess the impact of exposure misclassification, and innovative regression models to assess effect measure modification and between-cohort heterogeneity in radiation risks. Moreover, a causal interpretation of epidemiological study findings is strengthened by evidence of reproducibility and consistency. Therefore, we proposed to empirically assess the consistency of results derived from US nuclear worker data with results derived from UK and French nuclear worker cohorts, two nations that also developed large nuclear programs. An international combined study, called INWORKS, was undertaken. The international combined data yields the most statistically powerful analysis of radiation risk among nuclear workers reported to-date.

Section One

Significant Findings

A pooled analysis of US worker data for employees of 5 major facilities (Oak Ridge National Laboratory, Savannah River Site, Hanford site, Idaho National Laboratory, and Portsmouth Naval Shipyard) was undertaken; and, a paper describing the findings from this pooled analysis is published(Schubauer-Berigan, Daniels et al. 2015).

In addition, we have successfully completed an international collaborative study of nuclear industry workers that involves combined data for US, UK and French nuclear workers. A report describing the pooled international cohort, called INWORKS, has been prepared(Hamra, Richardson et al. 2015). A report describing the updated methods for dosimetry and estimation of organ-specific radiation doses for the INWORKS cohort has been published(Thierry-Chef, Richardson et al. 2015). A report on empirical data analyses for leukemia mortality has been published(Leuraud, Richardson et al. 2015), and a report on analyses of cancer outcomes has been published(Richardson, Cardis et al. 2015). Following the project's proposed aims of developing innovative methods for analysis of these data, a paper describing hierarchical regression models for joint analysis of outcome data has been accepted for publication (Richardson, Hamra et al. 2015) and provides the basis for methods for cause-specific analysis of the pooled data.

Translation of findings

The work has led to developments for joint modeling of exposure-cancer data using a hierarchical model for studies of cancer among workers exposed to occupational hazards, as well as insights into heterogeneity in the excess relative risk of cancer following occupational exposure to ionizing radiation.

Usefulness of Findings

These findings illustrate how useful insights into the association between radiation exposure and cancer mortality may be obtained via pooled analysis of cohort data. Modeling of the data via the hierarchical regression model can provide further stabilization of radiation risk estimates when attention is focused on cause-specific mortality. The work has led to developments that simplify

fitting of the hierarchical model as well as insights into heterogeneity of occupational radiation-cancer risk associations.

<u>Section Two</u>

<u>Scientific Report</u>

Background. Epidemiological studies of workers in the nuclear industry have been ongoing for over 40 years. Given the magnitudes of the doses received by US nuclear workers, some authors suggested that epidemiological studies of nuclear workers were expected to have extremely low statistical power to detect real associations between radiation and cancer. Recent studies have encompassed larger numbers of nuclear workers than earlier cohort studies and have pooled cohort data across facilities; and, the numbers of cancer deaths ascertained in these cohorts has increased nearly exponentially as follow-up of the early hire cohorts has continued. Moreover, previously, it was often assumed that the carcinogenic effectiveness of low dose rate exposures was approximately half that of higher dose rate exposures, implying the need for approximately twice the study size in a low setting compared to a high dose setting to achieve comparable statistical power. Recent findings have led some investigators to change their assumptions regarding the carcinogenic risk following chronic low dose-rate exposures.

We conducted a pooled analysis of US nuclear worker data for employees of 5 major facilities selected based on cohort size, availability of demographic and employment history information, and completeness of radiation monitoring data: Oak Ridge National Laboratory, Savannah River Site, Hanford site, Idaho National Laboratory, and Portsmouth Naval Shipyard. An update of vital status follow-up of each cohort has been conducted recently, and analytical files for each cohort are available for the proposed study purposes from NIOSH collaborators, making the proposed combined analysis feasible. Pooling of US nuclear worker data is important because it provides direct epidemiological evidence regarding associations between radiation exposure and mortality among US workers; and, the data for many of these workers is similar in terms of the quality and completeness of exposure assessment and mortality follow-up. Reproducibility of findings is an important consideration in the interpretation of epidemiological findings, and evidence of consistency of results may strengthen interpretation of findings considerably. We

addressed reproducibility of findings by conducting joint analyses of US, UK, and French nuclear worker cohorts.

Specific Aims.   We proposed four specific aims:

1. Time-since-exposure. We will characterize the evolution of radiation risks over time with particular attention to relative risks under long latencies, and the persistence of excess risks many decades after exposure. State-of-the-art regression modeling of latency will be employed.

2. Age-at-exposure. We will assess variation in radiation-mortality associations with age-at-exposure. The combined analysis will allow us to better characterize this temporal modifier of radiation effects.

3. Variation in radiation risks by type of cancer. Pooled analysis will offer large numbers of cancers for radiation risk estimation; a novel hierarchical regression modeling approach will be used to derive stabilized estimates of radiation risk for rare cancer types.

4. Reproducibility and heterogeneity. Random effects models will be used to assess heterogeneity in risk estimates by country. If appropriate, an international pooled analysis will be conducted, complementing the pooled US data analysis by addressing aims 1-3 using international combined nuclear worker data

Results. INWORKS includes workers employed by the Atomic Energy Commission (CEA), AREVA NC (formerly COGEMA), and the National Electricity Company (EDF) in France; the Departments of Energy and Defense in the USA, and, in the UK, by nuclear industry employers included in the National Registry for Radiation Workers (NRRW). Workers who were employed in the nuclear industry for less than 1 year were excluded from INWORKS.   INWORKS includes 308,297 workers contributing 8.2 million person-years of observation. In all 3 countries, workers were followed to ascertain vital status from the time that they started employment at a participating nuclear facility until loss-to-follow-up, death, or end of study, whichever came first. The French, UK, and USA cohorts were followed until the end of 2004, 2001, and, 2005 respectively. The number of deaths in INWORKS is 66,632.

Dr. Richardson and collaborators have prepared a series of manuscripts reporting the findings of these analyses, as well as published a simple SAS software program for fitting a hierarchical regression model for outcome-specific associations in occupational cohort data. Manuscripts include the following: 1) a paper that present the results of empirical data analyses of the pooled US data; 2) describe the INWORKS international combined occupational cohort data; 3) describe the dosimetry methods used to derive organ-specific radiation dose estimates in INWORKS; 4) a paper that present the results of empirical data analyses of leukemia mortality in the combined international data; 5) a paper that describes empirical data analyses of solid cancer mortality in the combined international data; 6) currently in internal review is a paper that describes empirical data analyses of time-since-exposure and age-at-exposure; 7) a paper that describes empirical data analyses of site specific cancer mortality; 8) a paper that describes a hierarchical regression approach for outcome data.

Aim 1 involved time since exposure; results were addressed for the US data in {Schubauer-Berigan, 2015 #5839} and in the international data in {Leuraud, 2015 #5852;Richardson, 2015 #5896}. In the US data, we found that the excess relative risk was greatest for solid cancers between 20 and 30 years following exposure, for leukemia risks were greatest 7-10 years following exposure and for lymphoma risk was greatest 30 years or more after exposure{Schubauer-Berigan, 2015 #5839}. In the international combined study we found that leukemia associations for leukemia excluding CLL were somewhat better described by effects 10 or more years after exposure than 2 or more years after exposure; there was relatively little association with lymphoma under the lags examined {Leuraud, 2015 #5852}. Aim 2 involved age at exposure; results are addressed in the forthcoming international data in (Daniels et al. forthcoming). Aim 3 involved cause specific associations described in {Leuraud, 2015 #5852;Richardson, 2015 #5896} and in forthcoming publication (Richardson, forthcoming). The development of methods for this aim in paper {Richardson, 2015 #5895} also address this aim and analysis of data as applied to international cohorts. In the international combined study, we examined the associations between cumulative red bone marrow dose and subtypes of leukaemia: estimated associations were positive for chronic myeloid, acute myeloid, and acute lymphatic leukaemia; the estimated association was largest for chronic myeloid leukaemia (ERR per Gy=10•5 [90% CI 4•48–19•7]), and lower in magnitude for acute lymphoblastic leukaemia

and acute myeloid leukaemia. Estimated associations also were positive but highly imprecise for Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma with associated confidence intervals that spanned the null. The estimated association between radiation dose and CLL mortality was negative (ERR=-1•06 [90% CI <0–1•81]). In the international combined study, we found that for all cancers the excess relative rate was 0.51 per Gy (90% CI: 0.23, 0.82), for all cancers other than leukemia, the excess relative rate was 0.48 per Gy (90% CI: 0.20, 0.79), for solid cancers the excess relative rate was 0.47 per Gy (90% CI: 0.18, 0.79), for solid cancers other than lung cancer (excess relative rate=0.46 per Gy; 90%CI: 0.11, 0.85), and for solid cancers other than lung and pleural cancer (excess relative rate=0.43 per Gy; 90%CI: 0.08, 0.82). Aim 4 addresses consistency of findings in the international cohort; {Richardson, 2015 #5896} addresses consistency of findings between cohorts in radiation-cancer mortality associations. To evaluate the impact of data from each country on the summary estimate for the international pooled data, we excluded countries from the combined cohort one-at-a-time. The estimate for the association between cumulative dose under a 10 year lag and all cancer mortality other than leukemia was 0.48 per Gy (90%CI: 0.19, 0.80) upon excluding France, 0.39 per Gy (90%CI: -0.03, 0.85) upon excluding the United Kingdom, and 0.56 per Gy (90% CI: 0.19, 0.97) upon excluding the United States from INWORKS. There was no evidence of heterogeneity in the estimated associations by country based on a statistical test (LRT=0.24, 2 d.f., p=0.89) and visual examination of country-specific estimates of association further supports such a conclusion.

Conclusions. This work has directly contributed radiation research and occupational cancer research, through both development of novel methods and empirical data analyses that provide the most precise radiation-cancer associations to-date based on direct analysis of epidemiological data for occupational cohorts.

Outcomes and outputs

The primary outcomes of this RO3 effort are publications (listed below). In addition, the work has led to increased awareness of occupational radiation safety and health issues; the work has been reported in the media. External organizations helped to disseminate outputs including a widespread media communication from the International Agency for Research on Cancer, and media communications from both the Lancet and the British Medical Journal.

Additional outputs include use of this research as knowledge for additional research and in discussions of radiation protection. The INWORKS project was discussed at recent meeting of the International Commission on Radiological Protection and will be presented at multiple sessions at the 2015 meeting of the Multidisciplinary European Low Dose Initiative (MELODI).

Publications (accepted, under review, and in preparation)

Hamra, G. B., D. B. Richardson, et al. (2015). "Cohort Profile: The International Nuclear Workers Study (INWORKS)." Int J Epidemiol. doi:10.1093/ije/dyv122. PMID: 26150557

Leuraud, K., D. B. Richardson, et al. (2015). "Ionizing radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study." Lancet Heaematology 2(7): e276-e281. PMID: 26436129

Richardson, D. B., E. Cardis, et al. (2015). "Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS)." BMJ 351: h5359.   PMID: 26487649

Richardson, D. B., G. B. Hamra, et al. (2015). "Hierarchical Regression for Analyses of Multiple Outcomes." Am J Epidemiol 182(5): 459-467. doi: 10.1093/aje/kwv047

Schubauer-Berigan, M. K., R. D. Daniels, et al. (2015). "Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation." Radiat Res. 183(6): 620-631. PMID: 26010709

Thierry-Chef, I., D. B. Richardson, et al. (2015). "Dose Estimation for a Study of Nuclear Workers in France, the United Kingdom and the United States of America: Methods for the International Nuclear Workers Study (INWORKS)." Radiat Res 183(6): 632-642. PMID: 26010707

Materials

Software

A simple SAS software program (SAS Institute, Inc., Cary, North Carolina) was developed for fitting hierarchical outcome Poisson regression models. This program was published as an appendix to paper {Richardson, 2015 #5895}.