Project Title: Combined analysis of lung cancer among uranium miners

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List of terms and abbreviations

PUMA- Pooled Uranium Miner Analysis

WL- working level

Abstract

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The objective of this project was to conduct a pooled analysis of major cohorts of uranium miners selected based on cohort size, availability of demographic and employment information, and completeness of radon exposure data. It has been over two decades since the US National Cancer Institute reported on a highly-influential pooled analysis of underground miners. Since that time, epidemiological cohorts of underground miners have been substantially updated and expanded, and important developments have occurred in the methods for statistical analyses of longitudinal data. This combined study of uranium miners was undertaken to strengthen the basis for protection of contemporary workers from the carcinogenic effects of radon progeny, and to improve understanding of the risks faced by workers who were exposed in the past. The pooling has permitted us to address questions regarding variation in mortality risks with exposure, risks associated with lower level exposures more typical of contemporary settings, as well as variation in risks by type of cancer. Because a causal interpretation of epidemiological findings is strengthened by evidence of reproducibility and consistency, we assessed the consistency of results derived from analysis of US underground miner cohorts with associations observed in other international cohorts. The international combined analysis, called PUMA, was undertaken and these data yield the most statistically powerful analysis of radon risks among miners reported to-date.

Section One

Significant Findings

A pooled analysis of 124,507 miners has been undertaken; and, a series of presentations have been made at professional conferences, and a series of papers describing the methods and findings from this project are in process, under review, or published.

A report describing the pooled international cohort, called the Pooled Uranium Miner Analysis (PUMA) study, has been prepared. A report describing the updated methods for the PUMA study cohort has been prepared and is ready for submission for publication. A report on empirical data analyses describing relative mortality rates in each cohort and in each country, as well as trends and comparability of cause-specific mortality ratios has been prepared as well. Reports on lung cancer mortality and on analyses of other cancer and non-cancer outcomes are being prepared. Following the project's proposed aims, papers and scientific presentations describing outcome specific excesses of mortality as well as methodological innovations, are being prepared, or have been presented, (see list of publications and presentations) based on the pooled data.

Translation of findings

The work has led to developments for addressing uncertainties between cohorts in exposure information that may influence modeling of exposure-cancer associations, as well as insights into heterogeneity in the excess relative risk of cancer following occupational exposure to radon. A major advance in terms of translation of findings from earlier occupational cohort studies to contemporary settings relates to the ability to focus our analyses on more recently hired miners with exposures more similar to those experienced by contemporary miners. Analyses focused on radon progeny-associated risks for more recently-hired miners, who tend to have lower radon progeny exposure rates (more similar to those encountered in contemporary work settings) and tend to have better quality exposure estimates have been undertaken in order to facilitate direct translation of historical cohort mortality study findings to contemporary occupational health and safety settings.

Research outcomes/impacts

These findings illustrate how useful insights into associations between occupational radon exposure and mortality may be obtained via pooled analysis of cohort data. Analyses of mortality relative to external reference rates as well as regression modeling of the data to derive internal comparisons of rate ratios provides risk estimates for cause-specific mortality and address questions remain regarding the magnitude of risk of lung cancer associated with the low levels of exposure typical of contemporary occupational settings, and the radon-associated risk of diseases other than lung cancer.

The findings of PUMA have already been communicated to, and discussed in the context of, the ongoing United Nations Work Group on Lung Cancer from Exposure to Radon, Scientific Committee on the Effects of Atomic Radiation, United Nations, (Geneva, Switzerland, 2018-2019). The findings of PUMA are expected to play a substantial role nationally and internationally in radon protection policy discussions.

Section Two

Scientific Report

Epidemiological studies of underground miners have provided definitive evidence that exposure to radon decay products cause lung cancer. As early as the sixteenth century, excess respiratory disease was noted among workers in metal mines (1). Studies of cohorts of uranium and other miners assembled in the 1950s and 1960s established the causal association between occupational radon exposure and lung cancer mortality (2), following earlier evidence from Eastern European miners. These studies also have served as a quantitative basis for estimation of radon-associated excess lung cancer risk. However, questions remain regarding the magnitude of risk of lung cancer associated with the low levels of exposure typical of contemporary occupational settings.

We conducted a pooled analysis of cohort data for miners from major cohorts in the US and internationally. The Pooled Uranium Miner Analysis (PUMA) study builds upon a previous pooled study of 60,606 underground miners, including miners of uranium and other ores, assembled from 11 cohorts described in detail in reports by the US National Academies of Sciences Biological Effects of Ionizing Radiation VI Committee report and the U.S. National Institutes of Health (3, 4). The findings of that earlier pooled study were highly influential for national and international assessments of radon progeny-related health risks (5).

Aims. The PUMA study was undertaken to strengthen the basis for radiation protection and to improve our understanding of radon and radon progeny-related diseases. Pooling of data is important because it provides direct epidemiological evidence regarding associations between radon exposure and mortality among 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. The project has the following analytical aims: Time since exposure – we characterize radiation risks over time with attention to the persistence of excess risks; Age – we assess variation in radon-mortality associations with age; radon and smoking- using available information we examine radon-associated mortality risks among non-smokers and smokers; Reproducibility and heterogeneity- undertaken using international pooled data. 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 cohorts.

Methods. The PUMA study includes 7 of the cohorts of uranium miners that were included in that earlier pooled study, encompassing miners from Canada (Port Radium, Beaverlodge, Ontario), the Czech Republic, France, and the United States (Colorado Plateau and New Mexico). Efforts have been undertaken to update each of these major epidemiological studies of uranium miners. In addition, PUMA includes a large new uranium miner cohort that was established in Germany in 1999 (6) that was not included in the prior pooled study. The PUMA study represents the largest study of uranium miners conducted to-date.

Results. The Pooled Uranium Miner Analysis (PUMA) study represents the largest study of uranium miners conducted to-date, encompassing 124,507 miners and 4.51 million person-years at risk. PUMA includes workers employed in uranium mining, open pit miners, underground miners and surface workers, assembled by pooling cohorts of uranium miners from Canada, Europe, and the United States. Most miners were male. The Czech, French, and US cohorts do not include women by design. The German and Canadian cohorts include women but the percentages of female miners were small in these cohorts; only 4,798 women were included for a total of 178,266 person-years; therefore, quantitative results reported from PUMA pertain primarily to men.

PUMA includes 54,462 deceased miners among the 124,507 workers in the pooled cohort. The Ontario and Eldorado cohorts have the lowest percentage of the cohort deceased (30%), reflecting the inclusion of more contemporary miners, while the Colorado Plateau cohort has the highest percentage of deceased miners (72%). The pooled cohort includes 17,085 deaths due to cancer of which 7,825 are lung cancer deaths.

Data available include individual annual estimates of exposure to radon decay products, demographic and employment history information on each worker, and information on vital status, date of death, and cause of death. The US cohorts include individual level information on smoking histories for most miners while the other cohorts in PUMA do not. Radon progeny is the primary exposure of interest and estimates were available for miners in each of uranium mines in PUMA. In the mining industry, radon exposure has been traditionally quantified in working level (WL), where 1 WL is equivalent to $2.08 \times 10{-}5$ joules per cubic meter of air (J/m^3). Estimated radon progeny exposures differ markedly between cohorts, and vary within cohort over time. A major factor leading to changes in radon progeny exposure rate was the introduction of mechanical ventilation, as opposed to relying solely on natural ventilation for air exchange. In Canada, at the Beaverlodge and Ontario mines, large-scale mining operations began around 1953 and radon monitoring and mechanical ventilation were introduced within the first few years of operations. In France, the introduction of mechanical ventilation in 1956 led to a prompt decline in radon progeny concentrations. In contrast, in the Czech Republic and German Wismut cohorts, as ventilation of the mines improved with the introduction of ventilation measures, in 1953 in the Czech mines and in 1955 in the German Wismut mines, exposure rates gradually declined. In the US, effective forced air ventilation became widespread around 1961. Cohorts that include operation in the immediate post-war period tend to have higher cumulative radon exposures than cohorts based in uranium mines that started operations in more recent periods.

Excesses of lung cancer mortality relative to national or regional reference rates were observed in all cohorts included in the PUMA study; however, the magnitudes of the lung cancer excesses differ between cohorts. Regarding cancers other than lung, there is little consistency in findings across the cohorts included in PUMA. In analyses of standardized mortality ratios, some cohorts have excesses of cancer of larynx, brain cancer, kidney cancer, stomach cancer, and leukemia, as well as excesses of non-cancer diseases such as circulatory system diseases, but other cohorts have reported no excesses, or even relative deficits, in mortality due to these cancer in comparison to the general population. In analyses of exposure-response associations between radon progeny and cancers other than lung, some cohorts have positive but imprecise estimates of association with sites including larynx, nasal passages, and leukemia.

A set of manuscripts reporting the findings of these analyses is in preparation and/or under review; and, we published a SAS software program for fitting linear excess relative rate regression models for outcome-specific associations in occupational case-cohort data, a design applied to an update of the Czech uranium miner cohort data. A series of scientific presentations have been made on the PUMA project (see publications and presentations list below). Manuscripts published or in preparation include the following: 1) a paper that describes statistical methods for analyses of linear excess relative rates in case cohort data; 2) a paper that present the study materials, methods and design of the PUMA project; 3) a paper that reports the results of standardized mortality ratio analyses of the PUMA data; 4) empirical data analyses of the pooled data for lung cancer; 5) a paper that describes empirical data analyses of time-since-exposure and age-at-exposure; 6) a paper that examines radon-smoking joint effects in the combined updated US cohorts of uranium miners.

Together these manuscripts and presentations address the set of specific aims outlined for this RO3 project, addressing the roles of time since exposure and age at exposure in paper 5, the joint effects of radon and smoking in paper 6, and we address consistency of findings in the international cohorts (reproducibility and heterogeneity) in papers 3 and 4.

Conclusion. 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 radon-cancer associations to-date based on direct analysis of epidemiological data for occupational cohorts.

<u>Publications and Presentations (accepted, under review, and in preparation)</u>

Journal Articles

Published

1. Richardson DB, Langholz B, Kelly-Reif K: [2018] General relative rate models for the analysis of case-cohort designs. *American Journal of Epidemiology*: 1-24 doi.org/10.1093/aje/kwy223.

Under Review

2. E. Rage, DB. Richardson, PA. Demers, M. Do, N. Fenske, M. Kreuzer, J. Samet, C. Wiggins, MK. Schubauer-Berigan, K. Kelly-Reif, L. Tomasek, LB. Zablotska, D. Laurier: [2019] Cohort Profile: Pooled Uranium Miners Analysis (PUMA). *Occupational and Environmental Medicine* (under review).

In preparation

3. DB. Richardson, E. Rage, PA. Demers, M. Do, N. Fenske, M. Kreuzer, J. Samet, C. Wiggins, MK. Schubauer-Berigan, K. Kelly-Reif, L. Tomasek, LB. Zablotska, D. Laurier [2019] Relative mortality among uranium miners: Findings from the Pooled Uranium Miners Analysis (PUMA). *Radiation Research* (in preparation).

4. DB. Richardson, E. Rage, PA. Demers, M. Do, N. Fenske, M. Kreuzer, J. Samet, C. Wiggins, MK. Schubauer-Berigan, K. Kelly-Reif, L. Tomasek, LB. Zablotska, D. Laurier: [2019] Radon and lung cancer mortality among uranium miners: Findings from the Pooled Uranium Miners Analysis (PUMA). *Radiation Research* (in prepartion).

5. K. Kelly-Reif, DB. Richardson, E. Rage, PA. Demers, M. Do, N. Fenske, M. Kreuzer, J. Samet, C. Wiggins, MK. Schubauer-Berigan, L. Tomasek, LB. Zablotska, D. Laurier: [2019] Time-since-exposure and age-at-exposure the PUMA study of uranium miners (in preparation).

6. LB. Tomasek, DB. Richardson, E. Rage, PA. Demers, M. Do, N. Fenske, M. Kreuzer, J. Samet, C. Wiggins, MK. Schubauer-Berigan, K. Kelly-Reif, L., Zablotska, D. Laurier:

[2020] Radon-smoking joint effects in the PUMA study of uranium miners (in preparation)

Presentations

1. Richardson DB, Laurier D, Rage E, Demers P, Tomasek L, Zablotska L, Samet J, Kreuzer M. Mortality among workers in the Pooled Uranium Miners Analysis (PUMA). International Society for Environmental Epidemiology, Utrecht, Netherlands, 2019.

2. Kelly-Reif K, Richardson DB: [2018] Cancer incidence and mortality among uranium miners in the Pribram region of the Czech Republic. 12th International Conference on the Health Effects of Incorporated Radionuclides, Fontenay-aux-Roses, France.

3. Richardson DB, Arrandale V, Demers P. Innovations in applied decision theory for miner health and safety. International Society for Environmental Epidemiology, Ottawa, Canada, 2018.

4. Richardson DB: [2017] Pooled Uranium Miners Analysis (PUMA): Goals and Challenges. EPICOH, Edinburgh, Scotland.

5. Richardson DB: [2016] Symposium: International studies of uranium miners: Country-specific research and collaborative research efforts. EPICOH, Barcelona, Spain.

Enrollment Table

Inclusion of women and minorities

The US study cohort includes male workers. The international combined study further includes men and women in some international cohorts. In the US cohorts, white males constitute approximately 90% of the cohort, and nonwhite males constitute another 10% of the cohort; there are no females included. In the international cohorts, information is not recorded on race; these cohorts are primarily constituted by male workers, while approximately 5% of all workers are female.

Inclusion of children

This is an occupational cohort study. The minimum age of persons hired is usually 16 years although some international cohorts include workers who started work at age 14 years.

Materials available for other investigators

Software

A simple SAS software program (SAS Institute, Inc., Cary, North Carolina) was developed for fitting linear excess relative rate models to case-cohort data for the purposes of radon-lung cancer mortality analyses among uranium miners. This program was published as an appendix to paper 1.

Literature cited

1. Mala metallorum. *Br Med J* 1966; **1:5. doi: https://doi.org/10.1136/bmj.1.5478.5**.

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5. International Agency for Research on Cancer. *Man-made mineral fibers and radon*. Lyon, France: IARC; 1988.

6. Kreuzer M, Grosche B, Schnelzer M, Tschense A, Dufey F, Walsh L. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: follow-up 1946-2003. *Radiation and environmental biophysics* 2010; **49**: 177-85.