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PUMA: Pooled Uranium Miners Analysis: Cohort profile

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Abstract

Epidemiological studies of underground miners have provided clear evidence that exposure to radon decay products causes lung cancer. Moreover, these studies have served as a quantitative basis for estimation of radon-associated excess lung cancer risk. However, questions remain regarding the effects of exposure to the low levels of radon decay products typically encountered in contemporary occupational and environmental settings on the risk of lung cancer and other diseases, and on the modifiers of these associations. These issues are of central importance for estimation of risks associated with residential and occupational radon exposures. The Pooled Uranium Miner Analysis (PUMA) study represents the largest study of uranium miners conducted to-date, encompassing 124,507 miners, 4.51 million person-years at risk, and 54,462 deaths, including 7,825 deaths due to lung cancer. 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. Some, but not all, cohorts also have individual information on cigarette smoking, external gamma radiation exposure, and non-radiological occupational exposures. In summary, PUMA provides opportunities to evaluate new research questions and to conduct analyses to assess potential health risks associated

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with uranium mining that have greater statistical power than can be achieved with any single cohort.

Keywords

radon; low-level ionizing radiation; uranium miners; cancer; cardiovascular

Why the cohort was set up?

Radon (Rn-222) is a naturally occurring, radioactive noble gas produced by the decay of uranium in soil and rock [1]. Internationally, radon concentration in the atmosphere is usually measured in becquerel per cubic meter (Bq/m^3). In outdoor air, concentrations of radon typically are in the range of 10–30 Bq/m^3, while typical indoor domestic exposures average about 50–150 Bq/m^3 although concentrations vary substantially and can be well above 150 Bq/m^3 [23]. Rn-22 has a half-life of 3.8 days, and its radioactive decay produces a variety of radioactive progeny, including the alpha-particle emitting radioisotopes polonium-218 and polonium-214. Alpha particles are a form of ionizing radiation that can travel only a short distance through human tissue. Consequently, if alpha-particle emitters remain outside the body, they pose little danger because the radiation emitted from these particles cannot penetrate the outer layers of exposed skin; however, once inhaled, the alpha particles released during decay of radon progeny can deliver substantial doses to cells in the respiratory tract and to some extent also to other organs, such as red bone marrow, kidney and liver through long-lived emitters [45].

As early as the sixteenth century, excess respiratory disease was noted among metal miners and referred to as “mala metallorum” [6]. In the 1950s and 1960s, epidemiological cohorts of miners began to be assembled that would subsequently play a major role in helping to establish that exposure to radon decay products causes lung cancer, as well as providing a quantitative basis for estimates of radon-associated excess lung cancer risk [7]. Concentrations of radon progeny in some of these early underground mines were several orders of magnitude higher than typically encountered today; for example, average concentrations of radon progeny in uranium mines in Utah and Colorado in 1949–1950 were approximately 92,000 Bq/m^3 [8]. However, subsequent studies of more contemporary uranium miners, employed in settings with mechanical ventilation where average concentrations are typically held below the range 500–1,500 Bq/m^3, have supported the findings derived from the earlier cohorts of miners and provided further information on low exposure rate settings [9].

Give the ubiquity of radon decay products in indoor and outdoor air, the burden of disease caused by radon decay products may be substantial. Understanding of the risks of lung cancer and other diseases associated with contemporary occupational and environmental exposures to radon decay products, and the modifiers of these associations, has important implications for public health decision-making. The Pooled Uranium Miner Analysis (PUMA) study draws together information from some of the most major epidemiological cohort studies of uranium miners in the world that are still being actively researched and followed. The PUMA study was undertaken to strengthen the basis for radiation protection, to address novel research questions that might not be feasible to address in any single cohort of uranium miners, and to improve our understanding of radon and radon progeny-related diseases.

Who is in the cohort?

PUMA is a cohort mortality study of 124,507 workers employed in uranium mining, including open pit miners, underground miners and surface workers, assembled by pooling cohorts of uranium miners from Canada, Europe, and the United States (Table 1). People who were ever employed as millers are not included in the PUMA study due to substantial differences in the occupational radiation exposure profile of uranium millers (e.g. long-lived radioncludies in the uranium dust) compared to miners, as well as other chemical exposures sustained in the milling processes.

The PUMA study builds upon a previous pooled study of 60,606 underground miners of uranium and other ores described in reports by the US National Academies of Sciences Biological Effects of Ionizing Radiation (BEIR) VI Committee and the U.S. National Institutes of Health [110]. The findings of that earlier pooled study were highly influential for national and international assessments of radon progeny-related health risks [11]. The PUMA study includes 7 of the cohorts of uranium miners that were included in that earlier pooled study, encompassing uranium miners from Canada (Beaverlodge, Port Radium, and Ontario), the Czech Republic, France, and the United States (Colorado Plateau and New Mexico). PUMA also includes a large uranium miner cohort that was established in Germany in 1999 [12] and that was not available to be included in the BEIR VI study.

PUMA is restricted to cohorts of uranium miners and therefore does not include three non-uranium cohorts of miners that were included in the BEIR VI study [1314], namely tin miners from China [15], fluorspar miners from Canada [16], and iron miners from Sweden [1718].

PUMA only includes cohorts of uranium miners for which there are quantitative estimates of exposure to radon progeny, and for which there are peer-reviewed published results as well as an ongoing active research program [19–25]. Information on sex, date of birth, date of hire, and date of termination was required; all the miners had to be identified in a non-selective way with respect to outcomes; the start and end date of follow-up had to be clearly defined for every cohort member; and, ascertainment of vital status and cause of death was required to be relatively complete. Based on these criteria, the Radium Hill cohort of Australian miners [26], a uranium miner cohort that had been included in the pooled analyses carried out by the BEIR VI Committee [110], was not included in PUMA because vital status follow-up was relatively incomplete (i.e., 36% of the cohort could not be traced beyond end of employment at Radium Hill); and, research on the cohort is no longer active and efforts had not been made to update or improve vital status follow-up. Finally, while there are some new cohorts of uranium miners for whom epidemiological studies are scheduled or underway, such as in Kazakhstan, work on those studies is not complete enough for data to be included in PUMA.

Participating cohorts:

PUMA includes the following uranium miner cohorts: 1) miners employed by the Eldorado Mining and Refining Company at the Port Radium mine in the Northwest Territories, Canada, where mining began in 1942, and at the Beaverlodge uranium mine in Saskatchewan, Canada, where mining started in 1948 [20]; 2) miners employed in Ontario, Canada enumerated based on government files of annual medical examinations of underground miners in Ontario since 1954 [27]; 3) miners from Western and Central Bohemia, Czech Republic, based on records starting from 1948 [25]; 4) French uranium miners, employed bythe CEA-COGEMA Company, primarily working in the regions of Limousin, Vendee, Forez and Herault, France, since mining started in 1946 [22]; 5) uranium miners employed in Eastern Germany, in the regions of Thuringia and Saxony, in the post-World War II period based on records of the Wismut corporation [12]; 6) miners in the Colorado Plateau region, USA, employed from 1953 and based on records which assembled by the US Public Health Service [24]; and, 7) miners in New Mexico based on company personnel and clinic records since the 1950s [23]. The characteristics of the PUMA cohorts are described in Table 1.

How have people been followed?

Each cohort was followed to collect information on vital status, date of death, and underlying cause of death coded according to the International Classification of Diseases. For the Canadian cohorts, vital status and cause of death information were obtained through linkages with the Canadian Mortality DataBase of Statistics Canada [20]. For the Czech cohort, vital status was initially ascertained from records of the Czech Population Registry at the Ministry of Interior, district death-registry records, and oncologic notification records; information on cause of death was collected from local death registries and, more recently, follow-up is updated every five years with cause of death information obtained from the Czech Institute of Health Information and Statistics. For the French cohort, information on vital status was ascertained from the National Directory for the Identification of Natural Persons and for deceased miners, causes of death were collected from the national Epidemiological Center on medical Causes of Death. For deaths before 1968, causes were supplied by the occupational medicine department of the French General Company of Nuclear Fuel, as well as local physicians and hospitals [28]. For the German Wismut cohort, a mortality follow-up is performed every five years. Information on vital status is obtained primarily from local registries offices and complemented by information from Wismut company records. Causes of death were obtained from copies of death certificates collected from Public Health Administration records and autopsy files from the former Wismut pathology archive [12]. For the US cohorts, vital status was initially ascertained from mining company records, state vital statistics offices, and searches of records of the US Social Security Administration and Internal Revenue Service. More contemporary vital status and cause of death information is obtained from the National Death Index and confirmed via Social Security records through periodic searches. Losses to follow-up in the individual PUMA cohorts are minimal (Table 1).

What has been measured?

Demographic and Employment Information.

Information on demographic characteristics, including sex and date of birth, was obtained from employment records, as was information on periods of work, job titles and mine or facilities of employment.

Radon exposure.

Radiation dose is expressed in terms of energy absorbed per unit mass of tissue. However, because of the complexity and uncertainties of estimation of dose to a target organ which depends upon unmeasured factors such as breathing rate and particle size distribution, for radon decay products it is customary to consider only exposure, the product of time in a workplace and concentration of radon decay products in the workplace air. Radon decay product exposure has been traditionally quantified in working level months (WLM), where 1 WLM is equivalent to 1 working month (170 hours) in a concentration of radon decay products that would result in the ultimate release of 2.08×10^{-5} joules of potential energy per cubic meter of air (J/m^3). 1 WLM is roughly equivalent to 630 Bq h/m^3. All workers included in the study cohorts have individual annual quantitative estimates of exposure, expressed in WLM. Recently, some of the European cohorts have also estimated doses to target organs by using ICRP dosimetric models and information regarding particle size distribution in mines and breathing rate of miners [52930].

The methods used for radon exposure assessment differ between cohorts included in the PUMA study, and vary within each cohort over calendar time (Table 3). Individual estimates of exposure to radon progeny were based on expert judgment, historical records of area monitoring, and in some cases personal exposure monitoring.

Eldorado-Beaverlodge.—Area measurements of both radon and radon decay products started in 1954 and continued throughout operations of the mine. Assignment of individual exposure estimates started in November 1966; for the period before assignment of individual exposure estimates, exposures were estimated using the geometric mean radon decay product concentrations over the working level meaurements available for each type of workplace, the proportion of employees in each occupation, and the proportion of time spent in each type of workplace by employees in each occupation.

Eldorado-Port Radium.—Workplace measurements, initially of radon and later of radon decay products, were made starting in 1945 and carried out sporadically through the 1940s and 1950s. Individual annual exposures were estimated using the geometric mean radon decay product concentrations over the working level meaurements available for each type of workplace, the proportion of employees in each occupation, and the proportion of time spent in each type of workplace by employees in each occupation. The scant measurement data was augmented by ventilation modeling. Seasonal averages were used to account for different winter and summer mine ventilation rates [20].

Ontario.—In the early years of mining (1954–1957), annual mine-specific radon progeny levels were estimated retrospectively by mine engineers using stationary area sampling. Starting in 1958, measurements of radon decay products were conducted by mine operators on a quarterly basis with stationary measurements made in different mine areas, including heading, stopes, raises, and travelways. Individual annual estimates of exposure in WLM were computed based on length of employment and percentage of time spent in these different work areas and travelways. From 1968, detailed work histories were collected for each individual on duration of task in specific locations and these were combined with extensive area sampling to assign individual exposure estimates [21].

Czech.—Area monitoring based on radon gas measurements, conducted in nearly all mine shafts, had commenced prior to the start of enrolment into the cohort in 1949. From 1949–1960, estimates of exposure to radon progeny are based on extensive measurements of concentrations of radon gas (more than 200 per year and shaft), converted to estimates of concentrations of progeny using measures of equilibrium factors in the mines. Starting in 1961, area measurements of concentrations of radon progeny were collected. An estimate of each worker’s exposure in each month was calculated from the time spent in each mine shaft and the year- and shaft-specific working-level estimates. Beginning in 1968 individual exposure estimates were based on personal exposure records derived from large numbers of radon-progeny measurements in ambient air and and detailed employment information about duration of underground work in specific shafts and job categories [31].

France.—For the period 1946 to 1955, individual annual radon exposures were estimated retrospectively by a group of experts. For the period 1956 to 1982, annual exposures were estimated based on ambient measurements performed at different working places in the mines per year; and from 1983 onwards, personal portable alpha-particle dosimeters were used [32].

Wismut.—Ambient air measurements of radon gas started 1955 in the different mines, while regular measurements of radon decay products were introduced in 1966 by the Wismut company in facilities in Saxony and in 1975 in Thuringia. For each mining facility, place of work (underground, open pit or surface) and calendar year (1946–1989) an expert group evaluated the exposure to radon progeny and developed a comprehensive job-exposure matrix (JEM) [12]. For the time period without measurements of radon or radon progeny (1946–1954), exposure to radon was reconstructed based on the first available ambient measurements of radon gas in 1955 taking into account uranium deposit and delivery, ventilation and mine architecture. For years where only radon gas measurements were available (1955–1965), the mean annual concentrations of radon gas in the different shafts were converted into WLM using equilibrium factors of 0.2 to 0.6 depending on the level of ventilation. For each worker a detailed working history was derived from the payrolls of the Wismut company and linked to the JEM. The annual radon progeny values of the JEM were then multiplied by a weighting factor for the number of exposed working days of each worker and a job-specific weighting factor (0 to 1). This factor takes into account the proportion of time spent in contact with radiating ore and the ventilation rate compared to a hewer. In total, about 900 different jobs were evaluated by the expert group and were included in the JEM [12,33].

Colorado Plateau.—Prior to 1950 estimates of radon progeny concentration are based on knowledge of ore bodies, ventilation practices and early measurements. After 1950, estimates of the working levels of radon progeny in a given mine in a given year were based on either actual measurements in that mine in that year, interpolation or extrapolation over time of measurements made in that mine in other periods, or geographic area estimation (i.e., using information from other mines that were proximate to that mine) [34].

New Mexico.—Individual annual exposure estimates are based on numerous area measurements and detailed personal work records. During the period 1957–1967 estimates of radon progeny concentration are based on knowledge of ore bodies, ventilation practices and about 20,000 measurements that were made previously by the state of New Mexico. From 1968 to 1985, exposure estimates came from mining company records for individual miners [23]. For employment outside of New Mexico, the database developed for the Colorado Plateau miners was used.

External radiation exposure and long-lived radionuclides.

Gamma radiation, a penetrating form of radiation, was present in each of the uranium mines in PUMA, and was a source of low-level exposures to external penetrating forms of ionizing radiation. Some workers have individual annual quantitative estimates of occupational external ionizing radiation exposure, expressed in millirem or millisievert, based on a job-exposure matrix, area measurements, or personal radiation dosimeters. Measurement methods of external ionizing radiation exposure are described for each cohort in Appendix Table A1. Where available, the PUMA study includes individual annual quantitative estimates of external exposure to ionizing radiation. The doses from external radiation exposures tend to be quite low, and prior work suggests little evidence of confounding by external radiation on estimation of the excess relative rate of lung cancer per WLM[20,30,35]. The PUMA cohort, however, gives the opportunity to evaluate the impact of external ionizing radiation exposure on disease risk, and its effect on the radon-related lung cancer risk among a large population of miners. Potential for exposure to ionizing radiation from internal deposition of long-lived radionuclides (i.e., inhalation or ingestion of long-lived radionuclides) also was present in each of uranium mines in PUMA. Some workers in the study cohorts have individual annual quantitative estimates of occupational exposure to long-lived radionuclides based on a job-exposure matrix or individual measurements [12,36]; where available, the PUMA study has compiled these individual estimates of doses from intakes of these radionuclides.

Cigarette smoking.

The prevalence of cigarette smoking was quite high in all of the uranium miner cohorts included in PUMA (Table 4). Individual smoking history information was not collected for the Canadian cohorts, but in a case-control study of Beaverlodge lung cancers [37] and in a recent sensitivity analysis of the Beaverlodge cohort [38], the potential confounding effect of smoking and its ability to influence the radon–lung cancer mortality risk estimates were was considered to be small. Limited information on smoking is available for the European cohorts, although in a case-control combined study of Czech [39], German [40], and French [41] miners there was little evidence of positive confounding of radon-lung cancer associations by smoking [42]. In contrast, relatively complete smoking history information, based on self-report and medical record information, was assembled for the US New Mexico and Colorado Plateau cohorts of uranium miners (Table 4). While insufficient for direct control of confounding of radon-mortality associations by smoking in the full PUMA cohort, the available information does allow us to assess if smoking is a confounder and to characterize the magnitude of smoking in each cohort and its likely correlation with cumulative WLM, and offers an empirical basis for assessment of sensitivity of findings to confounding by smoking.

Diesel exhaust.

Exposure to disesel exhaust was present in some, but not all, of uranium mines in PUMA; and, diesel exhaust, as as a known pulmonary carcinogen in humans, is a potential cause of lung cancer[43]. Diesel equipment was not used underground at Port Radium [44]. Diesel engine powered equipment was used infrequently in the Beaverlodge mines in Canada because the vehicles were primarily powered by electricity [1]. In contrast, diesel engines were used in the Ontario uraium mines. Diesel engine powered equipment was not used in the Czech mines because most ore transport was done manually in the Jachymov mines, and electric locomotives were used in the Pribram mines. Diesel engines were used in the French and German uranium mines, and in some of the mines in the North American cohorts from the Colorado Plateau and New Mexico. No workers in the study cohorts have individual estimates of diesel exhaust exposure; therefore, the PUMA study does not include individual level information regarding diesel exposures. However, stratified analyses can be conducted because PUMA includes workers with no history of occupational diesel exposure, as well as workers employed at mines in which there was a history of using diesel equipment.

Silica.

Silica dust (respirable, crystalline fraction, in the form of quartz) exposure was common in all mines; and, silica exposure is a potential cause of lung cancer. Silica exposures for Beaverlodge miners were not estimated and generally considered very low [45]. Silica exposures were not measured in the New Mexico and French mines, however both cohorts report on the occurrence of silicosis disease as an indirect assessment of potential impacts of silica exposures [4647]. In the Ontario, Canada mines silica ore content varied by region, being about 5–15% in Bancroftt and 60%−70% in Elliot Lake [48]. In the Czech mines, silica ore content also varied by region, being about 15% average free crystalline silica content in ore dust in Pribram and Jachymov mines [49]. Silica exposures were characterized for US Colorado Plateau miners by Archer et al. [50]. In the Wismut study, individual quantitative estimates of exposure to silica dust are available based on a comprehensive job-exposure-matrix [12]; and, adjustment for silica exposure was found to have only minor confounding influence on the estimated ERR per WLM for lung cancer [51]. Since only in one study silica data are available, the PUMA study does not include individual level information regarding silica exposures.

Arsenic.

Arsenic exposure was common in some of the mines; and, arsenic exposure is a potential cause of lung cancer. Estimates of arsenic levels in mines are available based on process, mine characteristics, and some records of area sampling. In Canada, Port Radium ore had relatively high arsenic content, while Beaverlodge ore had a low arsenic content[20]. Some Ontario mines also had relatively high arsenic content. In the Czech Pribram mines, average arsenic content was very low, while in Czech Jachymov mines arsenic content was relatively high [52]. In the German Wismut study; only miners in Saxony had some arsenic exposure (31% of the cohort members). In the Ontario study and in the Wismut study, estimates of arsenic exposure in dust-years were estimated from a job-exposure matrix; however, the PUMA study does not include individual level information regarding arsenic exposures. Quantitative data on arsenic exposure for the Ontario cohort and for the Wismut cohort were used in prior analyses to investigate confounding of estimates of excess relative risk per WLM by comparison of esitmates obtained with and without adjustment for arsenic exposure; this did not have a large impact on radon-related lung cancer risk estimates [35].

What has been found?

PUMA includes a total of 124,507 uranium miners, hired between 1942 and 1996 and followed-up between 1946 and 2013. PUMA encompasses a total of 4.51 million person-years at risk. Most miners were male (Table 1). 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 (Table 1); therefore, quantitative results reported from PUMA pertain primarily to men. The average duration of follow-up in the individual cohorts ranges from 30 years for the Colorado Plateau cohort to 39 years for the Wismut study.

Estimated radon progeny exposures differ markedly between cohorts, and vary within cohort over time. A major factor leading to changes in radon progency 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 (Table 3).

PUMA includes 54,462 deceased miners among the 124,507 workers in the pooled cohort (Table 2). 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 (Table 2).

Excesses of lung cancer mortality relative to national or regional reference rates are observed in all cohorts included in the PUMA study; however, the magnitudes of the lung cancer excesses differ markedly between cohorts, as summarized in Table 5, mainly due differences in the level of radon exposure. All individual studies provide strong evidence of a positive association between cumulative radon exposure (quantified in WLM) and lung cancer. In addition, the majority of large-sized previous individual or pooled studies suggested effect modification by time since exposure, age, and exposure rate [1313853].

In contrast, it is still an open question whether cancers other than lung are associated with radon exposure. Given that absorbed doses from inhaled radon progeny to organs other than lung tend to be substantially lower than absorbed doses to the lung, it is expected that if there is an excess, the excess is small and large studies, such as PUMA, will be needed to detect such associations. Currently, findings from individual cohort studies are inconsistent. In analyses of standardized mortality ratios, some cohorts have reported excesses of cancer of larynx[205455], brain [22], kidney [29], stomach[56], and leukemia [1957], as well as excesses of non-cancer diseases such as circulatory system diseases [58], whereas other cohorts have reported no excesses, or even relative deficits, in mortality due to these cancer in comparison to the general population [59]. Analyses of exposure-response associations between radon progeny and cancers other than lung are rare, some cohorts have reported positive but imprecise estimates of association with individual cancer sites including the extrathoracic airways and leukemia [195460]. In the large Wismut cohort study, a statistically significant ERR/WLM of 0.014% (95% CI: 0.006–0.023%) for all cancers other than lung cancer was observed [60].

What are the main strengths and weaknesses?

The PUMA study includes a large number of miners with individual quantitative radon and radon-progeny exposure estimates and long-term follow-up. While a study of uranium miners, the findings may have broader relevance because the potential for occupational exposure to radon and radon progeny occurs in many types of underground mines, including phosphate, fluorspar, iron, tin, talc, and slate mines, where concentrations of airborne radon progeny can reach or exceed the levels typically encountered in contemporary uranium mines. Potential for occupational exposure to radon and radon progeny also occurs in occupational settings other than underground mining. For example, substantial potential for occupational exposure to radon and radon progeny may occur in subway and utility tunnels, caves, phosphate fertilizer plants, natural gas and oil piping facilities, oil refineries, and water treatment plants. Moreover, levels of radon progeny in indoor air that approach or exceed the levels typically encountered in contemporary mines (e.g., >1000 Bq/m3) have been observed in homes built on soils with a high uranium content, as well as in public buildings including schools, hospitals, and prisons [61].

The PUMA study assembles a population of uranium miners who worked under different conditions, in different countries and at different time periods; this is a notable strength of the study as it allows for assessment of associations over a large range of exposure conditions. The study increases the amount of information that can be used in quantitative analyses of associations between radon exposure and mortality, particularly at the lower range of exposure compared to the one covered in the prior analysis. As compared to the previous pooled study of 11 underground miner cohorts, PUMA includes information from longer term follow-up of workers employed in later periods of mine operation for whom we have better exposure information and for whom exposures tended to be accrued at lower intensities that are more comparable to contemporary occupational settings. The PUMA cohorts encompass twice as many miners as the BEIR VI pooled analysis, and approximately three times as many lung cancer deaths [1]. This increase in available information should improve the statistical precision of estimates of association derived from the PUMA study, and also strengthen the ability to investigate modifiers of radon progeny- mortality associations such as time since exposure, age-at-exposure, attained age, and exposure rate. These modifiers are potentially important for a calculation of lifetime excess absolute risk. Through pooling and joint analyses of these data, the PUMA study also will enhance understanding of potential radon-associated excesses of diseases other than lung cancer, such as other cancer sites and circulatory system diseases.

The PUMA study focuses on mortality outcomes. The reliance on information on cause of death will not have a significant impact on the assessment of the risk of lung cancer, since its prognosis is unfortunately poor; but, information on disease incidence derived from registries often has advantages. Ascertainment of outcomes based on cause of death information, for example, may have low sensitivity when used to study diseases with a better prognosis than lung cancer, such as leukaemia. It is well recognized that classifications of outcomes based on death certificate information suffer from the imperfect sensitivity and specificity of cause of death information. In international pooling of data, attention also needs to be given to the potential differences between cohorts, and within cohorts over time, in death certificate-based outcome classifications. In the early years of follow-up, in particular, attention needs to be given to deaths for which cause of death information is missing. In the German and French cohort, for example, cause of death information of decedents prior to 1969 was difficult to obtain, however, few deaths occurred in the early years [12].

Exposure misclassification in underground miner studies is a well-known limitation that has been addressed in some cohorts [1]. Often, the available exposure information for historical mines is of relatively poor quality, particularly in the early years of mine operations. Generally, miners who worked in the 1940s and 1950s were exposed to higher radon decay product concentrations than those employed in later years; with the introduction of mechanical ventilation in underground mines, radon concentrations declined. As indicated in Table 4, methods for exposure assessment differed between the cohorts included in the PUMA study. Exposure assessments tended to improve over time and in recent years have included direct measures of individual exposure. Exposure measurement error is a concern as a potential source of bias in regression estimates of cumulative exposure-disease trends; general principles and simulation works suggest that radon progeny exposure measurement errors may lead to attenuation of estimates of exposure-disease trends as well as loss of precision in these estimates [62]. Moreover, time-dependent exposure measurement error may distort evidence of modification of exposure-disease associations by temporal factors such as time-since- exposure and exposure rate because measurement error likely diminished with calendar time in each of the PUMA cohorts, and more recently hired miners were likely to have lower average errors (and lower exposure rates) than those who started working in the more distant past [32]. One way to limit potential bias in analyses that include information from periods with poorer quality of exposure assessments, and to more clearly investigate potential effect modification by time-since-exposure is by restricting the analyses to more contemporary workers with higher quality exposure assessments [3153]. This is much more feasible in PUMA than in earlier pooled analyses [1] because the PUMA study encompasses relatively long-term follow-up of workers employed in more recent periods of mine operation for whom we have a more accurate exposure assessment. It is not as easy to disentangle temporal trends in exposure rates from trends in exposure measurement error since lower measurement errors tend to be coincident with lower intensity exposures. Again, however, PUMA affords opportunities to examine information across cohorts that had somewhat different exposure intensities even in more recent periods of mining. Of course, restriction is not the only approach to dealing with potential bias due to exposure measurement error; we also can leverage insights from recent methodological work on impacts and potential corrections for exposures measurement errors that make use of all available data[6263].

Pooling epidemiological cohort data offers the possibility of obtaining more precise estimates of an association of interest than can be obtained from a single cohort; and, unlike a meta-analysis, pooling epidemiological data allows for statistical analyses of the pooled data which were not conducted on the original data. However, a large sample size afforded by pooling data is no protection against bias, and differences between cohorts in confounding, selection bias, or measurement error are potential sources of heterogeneity in estimates of association between cohorts. We have attempted to address some concerns regarding bias and data quality through decisions in PUMA study design. For example, in PUMA we have not attempted to combine every available cohort of underground miners, but rather have focused on assembling information from the most informative uranium miner cohort studies, with attention to quality and completeness of exposure and follow-up data. We have included some, but not all, of the cohorts of underground miners that were included in the BEIR VI report[1], while distinctively in PUMA the German cohort of uranium miners makes a large contribution to the statistical information in the pooled study. Attention to heterogeneity in radon-mortality associations between cohorts, and the impact of each cohort’s data on the magnitude of pooled summary estimates of association, will be important considerations.

Potential for confounding by other occupational hazards is a concern in studies of radon-mortality associations among miners. In PUMA, information on some occupational hazards (such as external radiation exposure, diesel, silica and arsenic) is available for some cohorts and can provide a basis for sensitivity analyses and qualitative assessments of the possible direction and magnitude of bias due to confounding by these factors. Prior work suggests that external radiation exposure does not substantially confound associations between radon progeny and cancer in the Czech [57], German [64], and Canadian cohorts [59]; this is perhaps not surprising since mechanical ventilation, a strong determinant of exposure to radon progeny, does not affect external radiation dose. However, some analyses also suggest correlation between radon and gamma exposures [3659]. Prior work also suggests that arsenic is not a strong confounder [51]; this may in part be due to the relatively weak association between inhalation of inorganic arsenic and lung cancer. Potential for confounding by arsenic may be assessed in the pooled cohort data, since some of the cohorts had relatively high arsenic levels and some had relatively low arsenic levels, thereby allowing us the possibility to undertake sensitivity analyses where minerss with high arsenic are excluded. Similar arguments hold for diesel exposure, a hazard which is present in some, but not all, PUMA cohorts. Diesel exhaust is a relatively weak carcinogen, and correlation between cumulative diesel exhaust exposure and cumulative radon progeny exposures in the pooled cohort is reduced by the presence of cohorts of miners in which diesel engines were never used, thereby reducing the potential for confounding of radon-cancer associations in the PUMA study. Confounding of the cumulative radon progeny-lung cancer association by silica exposure has been directly assessed in the German cohort, where there was evidence of modest confounding[51]; indirect assessment of confounding by silica has been reported in the Colorado Plateau cohort by examination of the association between cumulative radon progeny exposure and silicosis[2446]. The effect of exposure to silica in the New Mexico cohort examined whether the presence of silicosis was associated with lung cancer risk; no such association was found [46]. In the German cohort, a positive association was observed between the risk of lung cancer and silica exposure [51]. In France, no silica measures were available but the potential confounding effect of silica was evaluated from the silicotic status of the miners, noting that the radon-lung cancer association remained after adjustement for silicotic status [47]. Dust levels in mines tended to decline over time, along with radon progeny levels. Confounding also may arise in occupational cohort studies through ongoing processes related to healthy worker survivor bias. Methods for analysis of cohort data that permit adjustment for time-varying confounders affected by prior exposure offer a potential way to address this bias. Confounding by exposures to radon at home have not been examined.

Can I obtain the data? Where can I find out more?

For reasons of ethics and permissions from different agencies, the data are maintained at the Institute for Radiation Protection and Nuclear Safety (Paris, France); it is not possible to send the individual data outside of the Institute. Data can not be exchanged between study participants under an individual format, but are exchanged under a tabulated format defined according to variable categories homogenised among cohorts. Proposals for possible collaborations in further analyses of the data should be addressed to Dr. Dominique Laurier and will be reviewed by the PUMA consortium.

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Appendix

Appendix Table A1:

Exposure assessments for external gamma radiation

Study	Gamma exposure assessment
Eldorado-Beaverlodge	Film badges used sporadically in the 1950s; and starting in 1963 a sample of workers work film badges fulltime. Estimates derived based on average dose rates and time on the job.
Eldorado-Port Radium	Film badges used sporadically in the 1950s; estimates derived based on average dose rates and time on the job.
Ontario	No data (before 1980), Personal dosimeter (1981-)
Czech	Estimated (<1960). Film (1960–69) TLD (1970–99)
France	No data (1946–55), Film (1956–85) TLD (1986–99)
Wismut	Expert rating (1946–54), Area measurements (1955–89)
Colorado Plateau	Not available
New Mexico	Not available

TLD: personal ThermoLuminescence Dosimeter

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Key Messages

- The PUMA study will be the most informative and largest pooled study of uranium miners to-date.
- Substantial increase in the number of cancer deaths compared to prior pooled studies of underground miners provides more accurate cancer risk estimates as well as increases ability to investigate associations of smaller magnitude.
- The findings will strengthen our understanding of disease risks associated with contemporary occupational radon exposures, and provide evidence for assessment of risks of indoor radon exposures and calculations of lifetime risk.
- Excess risk for cancers other than lung and for non-cancer diseases will be assessed.
- Combined exposures and the risks associated with joint exposures will be assessed.

Table 1

PUMA study: Numbers of miners, period of follow-up, eemployment periods, duration of employment, deaths due to all causes, and loss to follow-up.

Study (reference number)	Location	Miners	Period of Follow-up	Period of first hire	Loss to follow-up (%)	Minimum duration of employment	Average age at first exposure (in years)	Average duration of employment (in years)	Average duration of follow-up (in years)	PYRS (10^6)
Men										
Eldorado (20)[c]	Canada[c]	13,574	1950–1999	1942–1980	~2.0[a]	none	29	2	31	0.42
Ontario (27)	Canada	28,546	1954–2007	1954–1996	~2.0[a]	1 week	29	5	33	1.00
Czech (25)	Czech Republic	9,978	1952–2014	1948–1995	4.0	1 year[b]	28	8	32	0.32
France (22)	France	5,086	1946–2007	1946–1990	0.8	1 year	28	17	35	0.18
Wismut (12)	Germany	54,919	1946–2013	1946–1989	3.4	6 months	24	14	39	2.16
Colorado Plateau (24)	USA	4,137	1960–2005	1953–1968	0.3	1 month	32	4	30	0.12
New Mexico (23)	USA	3,469	1957–2012	1956–1982	0.0	1 year	28	9	38	0.13
Women										
Eldorado (20)[c]	Canada[c]	1,073	1950–1999	1948–1980	~2.0[a]	none	26	2	31	0.03
Wismut (12)	Germany	3,725	1951–2013	1946–1989	6.2	6 months	32	10	39	0.15
PUMA		124,507								4.51

[a] Canadian data were probabilistically matched to national death records; approximate sensitivity of the linkage algorithm was reported in Howe (1998).

[b] 4 years for early members of study

[c] Includes Port Radium, Beaverlodge and Other facilities. “Other” was defined as workers who worked in more than one facility

Table 2.

Distribution of deaths due to all causes, missing cause of death information, and for selected categories of cause of death by cohort.

Study	**All causes**	**Missing cause of death**	**All cancer**	**Lung cancer**	**Circulatory disease**	**Respiratory disease**
Men						
Eldorado[a]	4,044	0	1,134	517	1,331	295
Ontario	8,572	0	2734	1,246	2,804	639
Czech	5,572	169	2,071	1,176	1,874	288
France	1,984	59	730	213	464	114
Wismut	27,738	1,497	8,503	3,759	9,806	2,569
Colorado Plateau	2,964	22	961	612	797	448
New Mexico	1,576	5	470	251	379	161
Women						
Eldorado[a]	105	0	48	14	25	6
Wismut	1,907	102	434	37	936	101
PUMA	54,462		17,085	7,825	18,416	4,621

The categories of cause of death correspond to the following ranges of the International Classification of Diseases, ninth revision: all cancers (140–208); lung cancer (162), circulatory disease (390–459), and respiratory disease (460–519).

[a] Includes Port Radium, Beaverlodge and Other facilities. “Other” was defined as workers who worked in more than one facility.

Table 3.

Radon progeny exposure assessment methods and distribution of exposure, by cohort in the PUMA study.

Study	Assessment methods	Mean cumulative exposure (WLM)	Mean exposure rate (WL)
Eldorado[†]	Port Radium: Area monitoring (1945–1960), Beaverlodge: Area monitoring (1954– 1966), personal estimates (1966–1980)	121.7	8.3
Ontario	Expert rating (1954–57), area monitoring (1958–1967), personal estimates (1968–1999)	31[a]	0.9[a]
Czech	Area monitoring (1948–67), personal estimates (1968–1999)	73	
France	Expert rating (1946–55), area monitoring (1956–82), personal monitoring (1983–99)	37[b]	0.8[b]
Wismut	Expert rating (1946–54), area monitoring (1955–89)	304[c]	1.9[c]
Colorado Plateau	Expert rating (1946–49), area monitoring (1950–89)	579	11.7
New Mexico	Area monitoring (1953–89)	90.4[d]	9.6[d]

[†] Includes Port Radium, Beaverlodge and Other facilities. “Other” was defined as workers who worked in more than one facility. Among 14,647 miners with cumulative exposure greater than 0 WLM.

[a] Among 26,473 miners with cumulative exposure greater than 0 WLM.

[b] Among 4,133 miners with cumulative exposure greater than 0 WLM.

[c] Among 50,746 male miners with cumulative exposure greater than 0 WLM

[d] Among 3,455 miners with cumulative exposure greater than 0 WLM

Table 4:

Smoking exposure assessment methods and distribution, by cohort in the PUMA study.

Study (reference)	Assessment methods	Prevalence of smoking
Eldorado[a] (37)	Nested case-control data derived from interview	96% (cases)/88% (controls)
Ontario (65)	Medical records, interview, and mail survey	~80%
Czech Republic (39)	Nested case-control data derived from medical files and interview	92% (cases)/72% (controls)
France (41)	Nested case-control data derived from medical files and a questionnaire	90% (cases)/73% (controls)
Wismut (66)	Nested case-control data derived from medical files and interview	95% (cases)/75% (controls)
Colorado Plateau (24)	Cigarette use: duration, rate, cessation from surveys in the 1950s, 1960s, and 1985	77%
New Mexico (23)	Cigarette use: duration, rate, cessation (at last exam) from medical files	79%

[a] Beaverlodge miners

Table 5:

Description of the results previously published in the PUMA uranium miner cohorts for lung cancer risks

Study (reference number)	Workers	Lung cancer deaths	SMR [95%CI]	ERR/100 WLM (95%CI)
Eldorado, Beaverlodge (20)	9,498	279	1.28 [1.13–1.43]	0.96 [0.56, 1.56]
Eldorado, Port Radium (20)	3,047	230	1.63 [1.42–1.84]	0.37 [0.23, 0.59]
Ontario (21)	28,546	1,230	1.34 [1.27–1.42]	0.64 [0.43–0.85]
Czech (25)	9,978	1141	3.47 [3.27, 3.67]	0.97 [0.74–1.27][a]
France (22)	5,086	211	1.34 [1.16–1.53]	0.71 [0.31–1.30]
Wismut (53)	58,987	3,942	1.95 [1.90–2.01]	0.19 [0.16–0.22]
Colorado Plateau (24)	4,137	549	4.96 [4.55–5.39]	N.E.[b]
New Mexico (23)	3,469	68	4.00 [3.1–5.1]	1.8 [0.7–5.4]

[a] ERR [CI 90%]

[b] N.E.: not estimated, but trend tests with cumulative radon exposure categories were positive and significant

[c] All data include workers of the Port Hope radium and uranium refinery and processing facility, which would be excluded from the PUMA analysis.

[d] From CNSC report 67.