ORIGINAL RESEARCH

PUMA – pooled uranium miners analysis: cohort profile

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ABSTRACT

Objectives Epidemiological studies of underground miners have provided clear evidence that inhalation of 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.

Methods The Pooled Uranium Miner Analysis (PUMA) assembles information on cohorts of uranium miners in North America and Europe. 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.

Results The 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 7825 deaths due to lung cancer. Planned research topics include analyses of associations between radon exposure and mortality due to lung cancer, cancers other than lung, non-malignant disease, modifiers of these associations and characterisation of overall relative mortality excesses and lifetime risks.

Conclusion PUMA provides opportunities to evaluate new research questions and to conduct analyses to assess potential health risks associated with uranium mining that have greater statistical power than can be achieved with any single cohort.

Key messages

What is already known about this subject?

- The increased risk of death from lung cancer associated with radon exposure has been clearly demonstrated.
- It is still an open question whether radon increases the risk of cancer other than the lung and of non-cancer diseases.

What are the new findings?

- The Pooled Uranium Miner Analysis study is the largest pooled study of uranium miners to date.
- The substantial increase in the number of cancer deaths compared with prior pooled studies of underground miners provides more precise radon-associated cancer risk estimates.
- Combined exposures and the associated risks will be assessed.
- The substantial increase in the number of cancer deaths compared with prior pooled studies of underground miners increases the ability to investigate associations between radon and diseases other than lung cancer that may be of smaller magnitude than radon-lung cancer associations.

How might this impact on policy or clinical practice in the foreseeable future?

- 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.

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WHY THE COHORT WAS SET UP?

Radon is a naturally occurring, radioactive noble gas produced by the decay of uranium and thorium in soil and rock.[1] The most frequently encountered radioisotope of radon is radon-222, in the radioactive decay chain of uranium-238, but radon-220, in the decay chain of thorium-232, is also present in the environment, usually to a lesser extent (and much less frequently), radon-219 in the decay chain of uranium-235. Radon-222 is formed when radium-226 (with a radioactive half-life of 1600 years) emits an alpha particle. Internationally, radon activity concentration in the atmosphere is usually measured in becquerel per cubic metre (Bq/m^3). In outdoor air, concentrations of radon-222 typically are in the range of 10 to 30 Bq/m^3, while typical indoor domestic exposures average about 50 to 150 Bq/m^3 although concentrations vary substantially and can be well above 150 Bq/m^3.[2,3] Radon-222 has a radioactive half-life of 3.8 days, and its radioactive decay produces a variety of radioactive progeny, including the short-lived alpha-particle emitting radionuclides polonium-218 and polonium-214. Alpha particles are a form of ionising 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 emitted alpha-particles cannot penetrate the outer layers of exposed skin; however, once radon is inhaled, the alpha-particles released during decay of radon progeny can deliver substantial doses to cells in the respiratory tract and to some limited extent also to other organs, such as red bone marrow, kidney and liver through the deposition of radon itself and its progeny.[4 5]

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-related excess lung cancer risk.[6] 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 gas in uranium mines in Utah and Colorado in 1949 to 1950 were approximately 92 000 Bq/m^3.[7] However, subsequent studies of more contemporary uranium miners, employed in settings with mechanical ventilation where average concentrations are typically held below the range 500 to 1500 Bq/m^3, have supported the findings derived from the earlier cohorts of miners and provided further information on low exposure rate settings.[8]

Given 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 world's most important epidemiological cohort studies of uranium miners 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 USA (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 (eg, long-lived radionuclides in the uranium dust) compared with miners, as well as other chemical exposures sustained in the milling processes.

The PUMA study builds on a previous pooled study of 60 606 underground miners of uranium and other ores coming from 11 cohorts (China, Czechoslovakia, Colorado Plateau (USA), Ontario (Canada), Newfoundland (Canada), Sweden, New Mexico (USA), Beaverlodge (Canada), Port Radium (Canada), Radium Hill (Australia) and France) described in reports by the US National Academies of Sciences Biological Effects of Ionizing Radiation (BEIR) VI Committee and the US National Institutes of Health.[1 9] The findings of that earlier pooled study were highly influential for national and international assessments of radon progeny-related health risks.[10] The PUMA study includes seven of the eight cohorts of uranium miners that were included in that earlier pooled study, encompassing uranium miners from Canada (Beaverlodge, Port Radium, Ontario), the Czech Republic, France and the USA (Colorado Plateau, New Mexico). PUMA also includes a large uranium miner cohort that was established in Germany in 1999[11] and that was not available to be included in the BEIR VI study.

PUMA is restricted to cohorts of uranium miners, because it aims to consider next to radon also the effect of other ionising radiation emitted in uranium mines. Consequently, PUMA does not include three non-uranium miner cohorts that were included in the BEIR VI study,[12 13] namely tin miners from China,[14] fluorspar miners from Canada[15] and iron miners from Sweden.[16 17]

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.[18–24] Information on sex,

Table 1 PUMA study: numbers of miners, period of follow-up, employment 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)	P-yrs (10^6)
Men										
Eldorado*[19]	Canada*	13 574	1950–1999	1942–1980	<12†	None	29	2	31	0.42
Ontario[26]	Canada	28 546	1954–2007	1954–1996	n.a.†	1 week	29	5	33	1.00
Czech[24]	Czech Republic	9978	1952–2014	1948–1995	4.0	1 year‡	28	8	32	0.32
France[21]	France	5086	1946–2007	1946–1990	0.8	1 year	28	17	35	0.18
Wismut[11]	Germany	54 919	1946–2013	1946–1989	3.4	6 months	24	14	39	2.16
Colorado Plateau[23]	USA	4137	1960–2005	1953–1968	0.3	1 month	32	4	30	0.12
New Mexico[22]	USA	3469	1957–2012	1956–1982	0.0	1 year	28	9	38	0.13
Women										
Eldorado*[19]	Canada*	1073	1950–1999	1948–1980	<12†	None	26	2	31	0.03
Wismut[11]	Germany	3725	1951–2013	1946–1989	6.2	6 months	32	10	39	0.15
PUMA		124 507								4.51

*Includes Port Radium, Beaverlodge and Other facilities. 'Other' was defined as workers who worked in more than one facility.
†Canadian data were probabilistically matched to national death records; probabilistic linkage is quite accurate and misses less than 2% of deaths (Howe 1998); n.a., not applicable.
‡4 years for early members of study.
PUMA, Pooled Uranium Miner Analysis; P-yrs, person-years.

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 dates of follow-up had to be clearly defined for every cohort member and ascertainment of vital status and cause of death was required in the most exhaustive way possible. Based on these criteria, the Radium Hill cohort of Australian miners,[25] a uranium miner cohort that had been included in the pooled analyses carried out by the BEIR VI Committee,[1 9] was not included in PUMA because vital status follow-up was relatively incomplete (ie, 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 have not been made to update or improve vital status follow-up. Finally, while there are some new cohorts of uranium miners for which epidemiological studies are scheduled or underway, such as in Kazakhstan, work on those studies is not sufficiently complete 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;[19] (2) miners employed in Ontario, Canada, enumerated based on government files of annual medical examinations of underground miners in Ontario since 1954;[26] (3) miners from Western and Central Bohemia, Czech Republic, based on records starting from 1948;[24] (4) French uranium miners, employed by the CEA-COGEMA Company, primarily working in the regions of Limousin, Vendée, Forez and Hérault, France, since mining started in 1946;[21] (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;[11] (6) miners in the Colorado Plateau region, USA, enumerated from 1950 and based on records which assembled by the US Public Health Service[23] and (7) miners in New Mexico based on company personnel and clinic records since the 1950s.[22] 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. Losses to follow-up in the individual PUMA cohorts are minimal (table 1).

WHAT HAS BEEN CONSIDERED AND 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

The methods used for radon exposure assessment differ between cohorts included in the PUMA study, and vary within each cohort over calendar time (table 2). Individual estimates of exposure to radon were based on expert judgement, historical records of area monitoring and in some cases personal exposure monitoring.

External radiation exposure and long-lived radionuclides

Gamma radiation, a penetrating form of radiation, was present in each of the uranium mines in PUMA. Some workers have individual annual quantitative estimates of occupational external ionising radiation exposure. Measurement methods of external ionising radiation exposure are described for each cohort in online supplementary table A1. Sensitivity analyses could be conducted to consider long-lived radionuclides exposure among European cohorts which have available data.

Cigarette smoking

The prevalence of cigarette smoking was quite high in all of the uranium miner cohorts included in PUMA (table 3). Individual smoking history information was not collected for the Canadian cohorts;[27] and, limited information on smoking is available for the European cohorts.[28] In contrast, relatively complete smoking history information, based on self-report and medical record information, was assembled for the USA New Mexico[22] and Colorado Plateau[23] cohorts of uranium miners (table 3).

Other occupational hazards

Exposure to diesel exhaust was present in some, but not all, of uranium mines in PUMA. Diesel engine powered equipment was used in some but not all mines because in some mines vehicles

Table 2 Radon progeny exposure assessment methods and distribution of exposure, by cohort in the PUMA study

Study	Assessment methods	Mean cumulative exposure (WLM)	Mean annual exposure rate (WLM/year)
Eldorado	Port Radium: Area monitoring (1945–1960); Beaverlodge: Area monitoring (1954–1966), personal estimates (1966–1980)	121.7	8.3
Eldorado - Port Radium	Area monitoring (1945–1960)	180.1	15.1
Eldorado - Beaverlodge	Area monitoring (1954–1966), personal estimates (1966–1980)	84.8	3.7
Ontario	Expert rating (1954–57), area monitoring (1958–1967), personal estimates (1968–1999)	31*	0.9*
Czech	Area monitoring (1948–67), personal estimates (1968–1999)	73	0.8
France	Expert rating (1946–55), area monitoring (1956–82), personal monitoring (1983–99)	37†	0.8†
Wismut	Expert rating (1946–54), area monitoring (1955–89)	304‡	1.9‡
Colorado Plateau	Expert rating (1946–49), area monitoring (1950–89)	579	11.7
New Mexico	Area monitoring (1953–89)	90.4§	9.6§

*Among 26 473 miners with cumulative exposure greater than 0 WLM.
†Among 4133 miners with cumulative exposure greater than 0 WLM.
‡Among 50 746 male miners with cumulative exposure greater than 0 WLM.
§Among 3455 miners with cumulative exposure greater than 0 WLM.
PUMA, Pooled Uranium Miner Analysis; WLM, working level month.

Table 3 Smoking exposure assessment methods and distribution, by cohort in the PUMA study

Study (reference)	Assessment methods	Prevalence of smoking
Eldorado*[27]	Nested case-control data derived from interview	96% (cases)/88% (controls)
Ontario[46]	Medical records, interview, and mail survey	~80%
Czech Republic[47]	Nested case-control data derived from medical files and interview	92% (cases)/72% (controls)
France[48]	Nested case-control data derived from medical files and a questionnaire	90% (cases)/73% (controls)
Wismut[49]	Nested case-control data derived from medical files and interview	95% (cases)/75% (controls)
Colorado Plateau[23]	Cigarette use: duration, rate, cessation from surveys in the 1950s, 1960s and 1985	77%
New Mexico[22]	Cigarette use: duration, rate, cessation (at last exam) from medical files	79%

*Beaverlodge miners.
PUMA, Pooled Uranium Miner Analysis.

were primarily powered by electricity[1] . Silica dust (respirable, crystalline fraction, in the form of quartz) and arsenic exposure were common in the study mines. The PUMA study does not include individual level information regarding silica exposures or arsenic exposures.

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 4798 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 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 USA, 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 2).

PUMA includes 54 462 deceased miners among the 124 507 workers in the pooled cohort (table 4). 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 7825 are lung cancer deaths (table 4). 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 summarised in table 5, mainly due to differences in the level of radon exposure. All individual studies provide strong evidence of a positive association between cumulative radon exposure (quantified in workinglevel month) 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.[1 29–31]

Current and planned research topics within PUMA address questions about associations between radon and cancer other

Table 4 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	Non-malignant respiratory disease
Men						
Eldorado*	4044	0	1134	517	1331	295
Ontario	8572	0	2734	1246	2804	639
Czech	5572	169	2071	1176	1874	288
France	1984	59	730	213	464	114
Wismut	27 738	1497	8503	3759	9806	2569
Colorado Plateau	2964	22	961	612	797	448
New Mexico	1576	5	470	251	379	161
Women						
Eldorado*	105	0	48	14	25	6
Wismut	1907	102	434	37	936	101
PUMA	54 462		17 085	7825	18 416	4621

The categories of cause of death correspond to the following ranges of the International Classification of Diseases, ninth revision: all cancers (140 to 208); lung cancer (162), circulatory disease (390 to 459) and non-malignant respiratory disease (460 to 519).
*Includes Port Radium, Beaverlodge and Other facilities. 'Other' was defined as workers who worked in more than one facility.
PUMA, Pooled Uranium Miner Analysis.

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]	9498	279	1.28 (1.13 to 1.43)	0.96 (0.56 to 1.56)
Eldorado, Port Radium*[20]	3047	230	1.63 (1.42 to 1.84)	0.37 (0.23 to 0.59)
Ontario[21]	28 546	1230	1.34 (1.27 to 1.42)	0.64 (0.43 to 0.85)
Czech[25]	9978	1141	3.47 (3.27 to 3.67)	0.97 (0.74 to 1.27)†
France[22]	5086	211	1.34 (1.16 to 1.53)	0.71 (0.31 to 1.30)
Wismut	58 987	3942	1.95 (1.90 to 2.01)	0.19 (0.16 to 0.22)
Colorado Plateau (White)[24]	3255‡	549	4.96 (4.55 to 5.39)	N.E.
Colorado Plateau (American Indian)[24]	767‡	63	3.18 (2.45 to 4.07)	
New Mexico[23]	3469	68	4.00 (3.1 to 5.1)	1.8 (0.7 to 5.4)

*From CNSC report RSP-0205.[50]
†ERR (CI 90%).
‡Number of miners alive at the start of follow-up in January 1960.
ERR, Excess Relative Risk; N.E., Not Estimated; SMR, Standardized Mortality Ratio.

than lung cancer and non-cancer diseases, particularly non-malignant respiratory system diseases and circulatory system diseases. Given that absorbed doses from inhaled radon and 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. In analyses of standardised mortality ratios, some cohorts have reported excesses of cancer of larynx,[19 32 33] brain,[21] kidney,[34] stomach,[24 35] leukaemia[18 36] and multiple myeloma[24] and of all cancers combined other than lung,[24] as well as excesses of non-cancer diseases such as circulatory system diseases,[37] whereas other cohorts have reported no excesses, or even relative deficits, in mortality due to these cancers in comparison to the general population.[38] Analyses of exposure-response associations between radon and 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 leukaemia.[18 32 39] A summary of the major current and planned research topics in PUMA is provided in online supplementary table A2.

WHAT ARE THE MAIN STRENGTHS AND WEAKNESSES?

The PUMA study includes a large number of miners with individual quantitative radon exposure estimates and long-term follow-up. While a study of uranium miners, the findings expected from the analyses of cancer and non-cancer risks among the PUMA cohort may have broader relevance because the potential for occupational exposure to radon occurs in many types of underground mines, including phosphate, fluorspar, iron, tin, talc, gold 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 also occurs in occupational settings other than underground mining.

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 with the one covered in the prior analysis. As compared with 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 and residential 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, as well as the form of interaction between radon and smoking. Due to the specificity of cohorts and periods of exposure, the effect of radon on lung cancer risk will be assessed for several windows of 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 will enhance understanding of potential radon-associated excesses of diseases other than lung cancer, such as other cancer sites and circulatory system diseases.

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. 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.[11]

Exposure misclassification in underground miner studies is a well-known limitation that has been addressed in some cohorts.[1] Generally, miners who worked in the 1940s and 1950s were exposed to higher radon concentrations than those employed in later years; with the introduction of mechanical ventilation in underground mines, radon concentrations declined. As indicated in table 3, 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. General principles and simulation works suggest that radon exposure measurement errors may lead to attenuation of estimates of exposure-disease trends as well as loss of precision in these estimates.[40] 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.[41] 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.[29 30] 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. 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.[40–42]

In PUMA we have not attempted to combine every available cohort of underground miners, but rather have focussed 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.

Prior work suggests that external radiation exposure does not substantially confound associations between radon and cancer in the Czech,[36] German[43] and Canadian cohorts;[38] this is perhaps not surprising since mechanical ventilation, a strong determinant of exposure to radon, does not affect external radiation dose. Prior work also suggests that arsenic is not a strong confounder;[44] this may in part be due to the relatively weak association between inhalation of inorganic arsenic and lung cancer. 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 exposures in the pooled cohort is reduced by the presence of cohorts of miners in which diesel engines were never used. Confounding of the cumulative radon-lung cancer association by silica exposure has been assessed in some cohorts, where there was evidence of modest, or minimal, confounding.[23 44 45] Some of the uranium miners probably worked in other types of mining prior, or subsequent, to their employment in the uranium mines under study. Information on exposure to radon and other hazard encountered outside of employment in the uranium mines under study is not available for most cohorts, nor is information on exposures to radon at home. Besides occupational hazards, one of the most important individual confounding factor for lung cancer is smoking. Although individual data on smoking habits are not available for the whole PUMA cohort, they will be considered for a subgroup of the cohort for which smoking data are available.

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 Radiological Protection and Nuclear Safety (Paris, France); it is not possible to send the individual data outside of the Institute. Data cannot 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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Data availability statement No data are available. 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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REFERENCES

1 National Research Council. *Committee on health risks of exposure to radon. Health effects of exposure to radon (BEIR VI*. Washington DC: National Academy Press, 1999.
2 Agency USEP. *Radiation protection*. Radon, 2007.
3 Gaskin J, Coyle D, Whyte J, *et al*. Global estimate of lung cancer mortality attributable to residential radon. *Environ Health Perspect* 2018;126:057009.
4 Marsh JW, Blanchardon E, Gregoratto D, *et al*. Dosimetric calculations for uranium miners for epidemiological studies. *Radiat Prot Dosimetry* 2012;149:371–83.

5 Marsh JW, Bessa Y, Birchall A, *et al*. Dosimetric models used in the Alpha-Risk project to quantify exposure of uranium miners to radon gas and its progeny. *Radiat Prot Dosimetry* 2008;130:101–6.
6 Tirmarche M, Harrison JD, Laurier D, *et al*. ICRP publication 115. Lung cancer risk from radon and progeny and statement on radon. *Ann ICRP* 2010;40:1–64.
7 Holaday DA, Doyle HN. *Environmental studies in the uranium mines. p.9-20 in radiological health and safety in mining and milling of nuclear materials, vol.1*. Vienna: IAEA, 1964.
8 Akerblom G. *Radon legislation and national guidelines: department of environmental monitoring and dosimetry*, 1999.
9 Lubin JH, J.D. B, Edling C, *et al*. *Radon and lung cancer risk: a joint analysis of 11 underground miners studies*. Washington,DC: NIH Publication N°94-3644, 1994.
10 International Agency for Research on Cancer. *Man-made mineral fibers and radon*. Lyon, France: IARC, 1988.
11 Kreuzer M, Schnelzer M, Tschense A, *et al*. Cohort profile: the German uranium miners cohort study (WISMUT cohort), 1946-2003. *Int J Epidemiol* 2010;39:980–7.
12 National Research Council,. *Committee on the biological effects of ionizing radiation (BEIR IV). Health risks of radon and other internally deposited Alpha-emitters*. Washington, DC: National Academy Press, 1988.
13 Lubin JH, Boice JD, Edling C, *et al*. *Radon and lung-cancer risk: a joint analysis of 11 underground miners studies*. Washington, D.C: National Institutes of Health, National Cancer Institute, 1994.
14 Xuan XZ, Lubin JH, Li JY, *et al*. A cohort study in southern China of tin miners exposed to radon and radon decay products. *Health Phys* 1993;64:120–31.
15 Villeneuve PJ, Morrison HI, Lane R. Radon and lung cancer risk: an extension of the mortality follow-up of the Newfoundland fluorspar cohort. *Health Phys* 2007;92:157–69.
16 Björ O, Damber L, Jonsson H, *et al*. A comparison between standard methods and structural nested modelling when bias from a healthy worker survivor effect is suspected: an iron-ore mining cohort study. *Occup Environ Med* 2015;72:536–42.
17 Björ O, Jonsson H, Damber L, *et al*. Reduced mortality rates in a cohort of long-term underground iron-ore miners. *Am J Ind Med* 2013;56:531–40.
18 Kreuzer M, Sobotzki C, Fenske N, *et al*. Leukaemia mortality and low-dose ionising radiation in the WISMUT uranium miner cohort (1946–2013). *Occup Environ Med* 2017;74:252–8.
19 Lane RSD, Frost SE, Howe GR, *et al*. Mortality (1950-1999) and cancer incidence (1969-1999) in the cohort of Eldorado uranium workers. *Radiat Res* 2010;174:773–85.
20 Navaranjan G, Berriault C, Do M, *et al*. Cancer incidence and mortality from exposure to radon progeny among Ontario uranium miners. *Occup Environ Med* 2016;73:838–45.
21 Rage E, Caër-Lorho S, Drubay D, *et al*. Mortality analyses in the updated French cohort of uranium miners (1946–2007). *Int Arch Occup Environ Health* 2015;88:717–30.
22 Samet JM, Pathak DR, Morgan MV, *et al*. Lung cancer mortality and exposure to radon progeny in a cohort of new Mexico underground uranium miners. *Health Phys* 1991;61:745–52.
23 Schubauer-Berigan MK, Daniels RD, Pinkerton LE. Radon exposure and mortality among white and American Indian uranium miners: an update of the Colorado Plateau cohort. *Am J Epidemiol* 2009;169:718–30.
24 Tomasek L. Lung cancer mortality among Czech uranium miners-60 years since exposure. *J Radiol Prot* 2012;32:301–14.
25 Woodward A, Roder D, McMichael AJ, *et al*. Radon daughter exposures at the radium Hill uranium mine and lung cancer rates among former workers, 1952-87. *Cancer Causes Control* 1991;2:213–20.
26 Navaranjan G, Berriault C, Demers PA, *et al*. *Ontario uranium miners cohort study report*. Toronto: Occupational Cancer Research Centre, 2015.
27 L'Abbe KA, Howe GR, Burch JD, *et al*. Radon exposure, cigarette smoking, and other mining experience in the beaverlodge uranium miners cohort. *Health Phys* 1991;60:489–95.
28 Leuraud K, Schnelzer M, Tomasek L, *et al*. Radon, smoking and lung cancer risk: results of a joint analysis of three European case-control studies among uranium miners. *Radiat Res* 2011;176:375–87.
29 Kreuzer M, Sobotzki C, Schnelzer M, *et al*. Factors modifying the Radon-Related lung cancer risk at low exposures and exposure rates among German uranium miners. *Radiat Res* 2018;189:165–76.
30 Tomasek L, Rogel A, Tirmarche M, *et al*. Lung cancer in French and Czech uranium miners: radon-associated risk at low exposure rates and modifying effects of time since exposure and age at exposure. *Radiat Res* 2008;169:125–37.
31 Lane RSD, Tomášek L, Zablotska LB, *et al*. Low radon exposures and lung cancer risk: joint analysis of the Czech, French, and Beaverlodge cohorts of uranium miners. *Int Arch Occup Environ Health* 2019;92:747–62.
32 Kreuzer M, Dufey F, Marsh JW, *et al*. Mortality from cancers of the extra-thoracic airways in relation to radon progeny in the Wismut cohort, 1946–2008. *Int J Radiat Biol* 2014;90:1030–5.
33 Tomásek L, Darby SC, Swerdlow AJ, *et al*. Radon exposure and cancers other than lung cancer among uranium miners in West Bohemia. *Lancet* 1993;341:919–23.
34 Drubay D, Ancelet S, Acker A, *et al*. Kidney cancer mortality and ionizing radiation among French and German uranium miners. *Radiat Environ Biophys* 2014;53:505–13.
35 Kreuzer M, Straif K, Marsh JW, *et al*. Occupational dust and radiation exposure and mortality from stomach cancer among German uranium miners, 1946–2003. *Occup Environ Med* 2012;69:217–23.
36 Tomasek L, Malatova I. Leukaemia and lymphoma among Czech uranium miners. *Medical Radiology and Radiation Safety* 2006;51:74–9.
37 Drubay D, Caër-Lorho S, Laroche P, *et al*. Mortality from circulatory system diseases among French uranium miners: a nested case-control study. *Radiat Res* 2015;183:550–62.
38 Lane RSD, Frost SE, Howe GR, *et al*. Mortality (1950–1999) and cancer incidence (1969–1999) in the cohort of Eldorado uranium workers. *Radiat Res* 2010;174:773–85.
39 Kreuzer M, Walsh L, Schnelzer M, *et al*. Radon and risk of extrapulmonary cancers: results of the German uranium miners' cohort study, 1960–2003. *Br J Cancer* 2008;99:1946–53.
40 Hoffmann S, Rage E, Laurier D, *et al*. Accounting for Berkson and classical measurement error in radon exposure using a Bayesian structural approach in the analysis of lung cancer mortality in the French cohort of uranium miners. *Radiat Res* 2017;187:196–209.
41 Allodji RS, Leuraud K, Bernhard S, *et al*. Assessment of uncertainty associated with measuring exposure to radon and decay products in the French uranium miners cohort. *J Radiol Prot* 2012;32:85–100.
42 Hoffmann S, Laurier D, Rage E, *et al*. Shared and unshared exposure measurement error in occupational cohort studies and their effects on statistical inference in proportional hazards models. *PLoS One* 2018;13:e0190792.
43 Walsh L, Dufey F, Tschense A, *et al*. Radon and the risk of cancer MORTALITY—INTERNAL Poisson models for the German uranium miners cohort. *Health Phys* 2010;99:292–300.
44 Sogl M, Taeger D, Pallapies D, *et al*. Quantitative relationship between silica exposure and lung cancer mortality in German uranium miners, 1946–2003. *Br J Cancer* 2012;107:1188–94.
45 Samet JM, Pathak DR, Morgan MV, *et al*. Silicosis and lung cancer risk in underground uranium miners. *Health Phys* 1994;66:450–3.
46 Kusiak RA, Springer J, Ritchie AC, *et al*. Carcinoma of the lung in Ontario gold miners: possible aetiological factors. *Occup Environ Med* 1991;48:808–17.
47 Tomasek L. Interaction of radon and smoking among Czech uranium miners. *Radiat Prot Dosimetry* 2011;145:238–42.
48 Leuraud K, Billon S, Bergot D, *et al*. Lung cancer risk associated to exposure to radon and smoking in a case-control study of French uranium miners. *Health Phys* 2007;92:371–8.
49 Schnelzer M, Hammer GP, Kreuzer M, *et al*. Accounting for smoking in the radon-related lung cancer risk among German uranium miners: results of a nested case-control study. *Health Phys* 2010;98:20–8.
50 Canadian Nuclear Safety Commission (CNSC). Updated analysis of the Eldorado uranium miners' cohort: Part I of the Saskatchewan Uranium Miners' Cohort Study (RSP-0205), 2006. Available: https://protect2.fireeye.com/url?k=b8b931c4-e4f904fa-b8b916d9-0cc47ad9c120-c8bd1ff41ad986c0&u=http://www.nuclearsafety.gc.ca/eng/resources/health/health-studies/eldorado/index.cfm