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Miscellaneous

Mortality among uranium miners in North America and Europe: the Pooled Uranium Miners Analysis (PUMA)

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Abstract

Background: The Pooled Uranium Miners Analysis (PUMA) study draws together information from cohorts of uranium miners from Canada, the Czech Republic, France, Germany and the USA.

Methods: Vital status and cause of death were ascertained and compared with expectations based upon national mortality rates by computing standardized mortality ratios (SMRs) overall and by categories of time since first hire, calendar period of first employment and duration of employment as a miner.

Results: There were 51 787 deaths observed among 118 329 male miners [SMR = 1.05; 95% confidence interval (CI): 1.04, 1.06]. The SMR was elevated for all cancers (n = 16 633, SMR = 1.23; 95% CI: 1.21, 1.25), due primarily to excess mortality from cancers of the lung (n = 7756, SMR = 1.90; 95% CI: 1.86, 1.94), liver and gallbladder (n = 549, SMR = 1.15; 95% CI: 1.06, 1.25), larynx (n = 229, SMR = 1.10; 95% CI: 0.97, 1.26), stomach (n = 1058, SMR = 1.08; 95% CI: 1.02, 1.15) and pleura (n = 39, SMR = 1.06; 95% CI: 0.75, 1.44). Lung-cancer SMRs increased with duration of employment, decreased with calendar period and persisted with time since first hire. Among non-malignant causes, the SMR was elevated for external causes (n = 3362, SMR = 1.41; 95% CI: 1.36, 1.46) and respiratory diseases (n = 4508, SMR = 1.32; 95% CI: 1.28, 1.36), most notably silicosis

($n = 814$, SMR = 13.56; 95% CI: 12.64, 14.52), but not chronic obstructive pulmonary disease ($n = 1729$, SMR = 0.98; 95% CI: 0.93, 1.02).

Conclusions: Whereas there are important obstacles to the ability to detect adverse effects of occupational exposures via SMR analyses, PUMA provides evidence of excess mortality among uranium miners due to a range of categories of cause of death. The persistent elevation of SMRs with time since first hire as a uranium miner underscores the importance of long-term follow-up of these workers.

Key words: Radon, cohort studies, uranium miners, mortality study, occupational diseases

Key Messages

- The Pooled Uranium Miner Analysis (PUMA) study draws together data from long-term follow-up of some of the world's most informative cohort studies of uranium miners.
- PUMA provides evidence of excesses of mortality due to cancers of the lung, liver and gallbladder, larynx, stomach and pleura, as well as external causes and non-malignant respiratory diseases, but not chronic obstructive pulmonary disease.
- Long-term follow-up of these cohorts provides evidence of persistently elevated mortality rates for a range of categories of causes of death among uranium miners.

Introduction

Following World War II, the uranium-mining industry grew rapidly in North America and Europe, driven by demand for uranium for the production of nuclear weapons and fuel for nuclear reactors.[1,2] In the immediate post-war period, working conditions in uranium mines were poor; miners often laboured underground in mines lacking mechanical ventilation and motorized ore transport. Over time, working conditions tended to improve due to efforts to increase mine ventilation, which had the primary purpose of lowering concentrations of the noble gas radon and its radioactive-decay products, to reduce drilling dust, using water in addition to compressed air to flush drill cuttings, and to mechanize ore transport. The improved working conditions, particularly ventilation of the mines, were motivated by convincing evidence that radon and its progeny caused lung cancer, reported from the 1950s onwards.[3] Now, exposure to radon and radon progeny is widely recognized as an occupational and environmental cause of lung cancer.[4–6]Hundreds of thousands of workers have been employed in uranium mining worldwide.[7] Uranium miners have the potential for exposure to a wide range of occupational hazards and established carcinogens, including radon and its progeny, gamma radiation from uranium and its decay products in the rock, long-lived radioactive dust containing uranium and its decay products, silica, arsenic and diesel exhaust. Assessments of exposure to some of these occupational hazards, notably radon progeny, have been made based upon expert judgement, historical records of area monitoring and, in some cases, personal-exposure monitoring.[6,8,9] However, there is relatively little information about many of the other occupational hazards encountered in uranium mining. Reports on mortality among uranium miners relative to the general population, quantified as standardized mortality ratios (SMRs), can help to describe the net impact of occupational exposures on specific causes of mortality. Although SMR analyses are seldom sufficient to establish the agent (or agents) responsible for disease excesses, such analyses offer one tool for occupational-health surveillance that provides a summary measure of relative mortality that is efficient, can be informative even when the numbers of events are small and may facilitate examination of a potentially wide range of outcomes.

The Pooled Uranium Miner Analysis (PUMA) study draws together information from long-term follow-up of cohort studies of uranium miners from North America and Europe.[10] A major motivation for PUMA was to combine information across studies and therefore obtain more informative results regarding cause-specific mortality.[11–13] The PUMA analyses provide an updating to a previous pooled analysis of data from cohorts of underground

miners first reported in 1994, although the cohorts included are not identical.[12,14] The PUMA study encompasses twice as many miners as that previous pooled analysis[12,14] and approximately three times as many lung-cancer deaths. Using these data, we offer descriptions of relative mortality considering cancer and non-cancer causes of death.

Methods

PUMA is a pooled cohort mortality study of workers employed in uranium mining in Canada, the Czech Republic, France, Germany and the USA. To be included, a worker must have been employed in the uranium-mining industry, including open-pit miners, underground miners and surface workers; however, people who were only ever employed as millers are excluded.

PUMA includes the following uranium-miner cohorts: 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[15]; miners employed in Ontario, Canada, where mining started in 1954[16]; miners employed in Western and Central Bohemia in the Czech Republic, based on records starting from 1948[17]; French uranium miners, employed by the CEA-COGEMA Company, primarily working in the regions of Limousin, Vendee, Forez and Herault, France, since mining started in 1946[18]; uranium miners employed in the former East Germany, in the regions of Saxony and Thuringia, in the post-World War II period (starting in 1946) based on records of the Wismut corporation[8]; miners in the Colorado Plateau region, USA, enumerated from 1950 to 1960 and based on records that were assembled by the US Public Health Service[19]; and miners in New Mexico based on company personnel and clinic records since the 1950s.[20] We restrict analyses in the current report to male miners, noting that only the Wismut and Eldorado cohorts contributed female miners to PUMA.[10]

The vital status of cohort members was ascertained through linkages with local or national population registration offices, pathology archives, employer records, Social Security Administration records and searches of local and national death registries.[8,15–20] Mortality information for decedents in the study cohorts, including information on underlying cause of death, was abstracted from death certificates and causes of death were coded according to the International Classification of Diseases (ICD).

The observed mortality in the study cohort was compared with expected mortality based upon external reference mortality rates.[21] For Canada, these were national rates of cause-specific mortality for males by 5-year age and 5-year calendar periods for the entire study period. For the Czech cohort, these were national rates of cause-specific mortality for males by 5-year age and single-year calendar periods for the study period based on Czechoslovakian reference rates because miners in the cohort were of both Czech and Slovak origin and separate rates for the Czech and Slovak populations are available only since the 1990s. For France, these were national rates of cause-specific mortality for males by 5-year age and single-year calendar period since 1968; age- and calendar-year-specific national mortality rates for French males for the period prior to 1968 were imputed based on an assumption that rates were stable.[22] For Germany, these were rates of cause-specific mortality for males in East Germany, the former German Democratic Republic, by 5-year age and single-year calendar period since 1960. For the USA, for White miners, these were rates of cause-specific mortality by 5-year age and 5-year calendar period for White males in Arizona, Colorado, New Mexico and Utah since 1960; and, for non-White males (including American Indian miners), these were rates of cause-specific mortality by 5-year age and 5-year calendar period for non-White males in Arizona and New Mexico since 1960.

The study spans periods during which the 6th, 7th, 8th, 9th and 10th revisions of the ICD were in effect; therefore, we defined categories of cause of death in terms of ranges of codes for each of these revisions of the ICD (Supplementary Table 1, available as Supplementary data at *IJE* online). Categories of cause of death may encompass a range of outcomes defined by more detailed ICD codes; e.g. we refer to the category of cause of death of lung cancer, noting that this category encompasses cancers of the trachea, bronchus and lung. The categories of cause of death that we examined were defined a priori and were informed, in part, by those categories of cause of death for which appropriate reference rates were available for the partner countries.

A worker entered into the analysis on the latest date of: start of employment, start of the follow-up period for the study cohort (which, for some workers, was well after the start of employment), start of available reference rates for the study cohort or at the end of any minimum employment period for that study. A worker exited the study on the earliest date of: death, loss to follow-up or end of study follow-up.

For the SMR analysis, let subscript i index study cohort (considering White and non-White miners in the US cohorts as separate study cohorts, thereby allowing separate reference rates by race), j index attained age category and k index calendar period; let superscript c index

category of cause of death and denote by $O^c_{i,j,k}$, $P_{i,j,k}$ and $R^c_{i,j,k}$, respectively, the observed number of deaths due to cause c, the observed number of person-years at risk and the mortality rate for death due to cause c in the reference population associated with study cohort i, at age category j and calendar period k. The SMR calculation took the form $SMR = \frac{\sum_{i=1}^{I}\sum_{j=1}^{J_i}\sum_{k=1}^{K_i} O^c_{i,j,k}}{\sum_{i=1}^{I}\sum_{j=1}^{J_i}\sum_{k=1}^{K_i} P_{i,j,k}R^c_{i,j,k}}$, where indexing of age and calendar year categories for study cohort i conforms to the categories used to construct the external reference rates associated with study cohort i, and J_i and K_i denote the number of age categories and calendar-period categories observed in study i. A 95% confidence interval (CI) was computed using mid-P exact methods if the number of events was <10 and using Byar's approximate method if the number of events was ≥10.[23]

Given long-term follow-up, we examined relative mortality among more recently employed uranium miners as well as among those employed in earlier years by classifying miners according to the calendar period of first hire; thus, we could examine the mortality experience of more recently employed miners whose exposures were much closer to those encountered in underground mining today. We also examined whether SMRs for some leading causes of death varied over time since first hire and duration employed by further classifying person-time at risk and observed deaths according to these time-related factors.[24]

Results

The current analysis includes 118 329 men (Table 1). The average duration of follow-up in the individual cohorts ranges from 30 years for the Colorado Plateau cohort to 41 years for the Wismut study. Overall, 51 787 (44%) of the miners were deceased; the Ontario cohort has the lowest percentage of the cohort deceased (30%), reflecting the inclusion of more recently employed miners, whereas the Colorado Plateau cohort has the highest percentage of deceased miners (72%). Loss to follow-up was relatively low for the US (<0.5%), French (0.8%), German (1.6%) and Czech (4.0%) cohorts and highest for the Canadian Eldorado cohort (12%). The US and Canadian cohorts had very low percentages (<2%) of deaths with missing cause-of-death information, whereas 3%, 3% and 5% of deaths in the Czech, French and German cohorts had missing causes, respectively.

All-cause mortality was elevated (SMR = 1.05; 95% CI: 1.04, 1.06) among men in the PUMA cohorts (Table 2). Whereas the SMR for all causes other than cancer was 0.98 (95% CI: 0.97, 0.99), the SMR for all cancer mortality was elevated (SMR = 1.23; 95% CI: 1.21, 1.25) due to elevated SMRs for cancers of the lung (SMR = 1.90; 95% CI: 1.86, 1.94), liver and gallbladder (SMR = 1.15; 95% CI: 1.06, 1.25), larynx (SMR = 1.10; 95% CI: 0.97, 1.26), stomach (SMR = 1.08; 95% CI: 1.02, 1.15) and pleura (SMR = 1.06; 95% CI: 0.75, 1.44). The SMR for all cancers excluding lung was below unity (SMR = 0.94; 95% CI: 0.92, 0.96), as were SMRs for some cancers other than lung that are strongly related to cigarette smoking, including cancers of the oral cavity (SMR = 0.77; 95% CI: 0.66, 0.90), pharynx (SMR = 0.83; 95% CI: 0.71, 0.96), oesophagus (SMR = 0.92; 95% CI: 0.83, 1.03), pancreas (SMR = 0.96; 95% CI: 0.89, 1.04), kidney (SMR = 0.96; 95% CI: 0.87, 1.06) and bladder (SMR = 0.85; 95% CI: 0.77, 0.94).

Lung cancer was elevated in all of the PUMA cohorts (Supplementary Table 2, available as Supplementary data at *IJE* online). The relative excess of lung cancer was highest among the US Colorado Plateau (SMR = 4.69; 95% CI: 4.32, 5.08) and Czech miners (SMR = 2.93; 95% CI: 2.76, 3.10), intermediate for the US New Mexico (SMR = 2.68; 95% CI: 2.36, 3.04) and German Wismut (SMR = 1.94; 95% CI: 1.88, 2.00) miners and lowest among the Canadian Eldorado (SMR = 1.39; 95% CI: 1.28, 1.52), French (SMR = 1.35; 95% CI: 1.17, 1.54) and Canadian Ontario (SMR = 1.25; 95% CI: 1.18, 1.32) miners.

Excesses of mortality due to liver and gallbladder cancer were observed for all PUMA cohorts except the New

Table 1 Information on male uranium miners in the Pooled Uranium Miners Analysis (PUMA) study

Study	Location	Miners	Follow-up	Period of first hire	Deaths	Person-years
Eldorado[15]	Canada	13 574	1950–1999	1942–1980	4044	424 549
Ontario[16]	Canada	28 546	1954–2007	1954–1996	8572	1 002 851
Czech[17]	Czech Republic	9978	1952–2010	1948–1995	5564	323 806
CEA-COGEMA[18]	France	5086	1946–2007	1946–1990	1924	180 122
Wismut[8,25]	Germany	53 654[a]	1960–2013	1946–1989	27 143	1 943 231[a]
Colorado Plateau[19]	USA	4022[a]	1960–2005	1953–1968	2964	120 437
New Mexico[20]	USA	3469	1958–2012	1956–1982	1576	130 537
PUMA	–	118 329	1946–2013	1942–1996	51 787	4 125 533

[a]Males alive and on study from 1 January 1960.

Table 2 Standardized mortality ratios among male uranium miners in the Pooled Uranium Miners Analysis (PUMA) study

Cause (ICD-9 codes)	Observed	SMR	95% CI	
All causes (all)	51 787	1.05	1.04	1.06
Tuberculosis (010–018)[b]	75	1.02	0.80	1.28
All cancers (140–208)	16 633	1.23	1.21	1.25
Oral (140–145)	161	0.77	0.66	0.90
Pharynx (146–149)	175	0.83	0.71	0.96
Oesophagus (150)	351	0.92	0.83	1.03
Stomach (151)	1058	1.08	1.02	1.15
Intestine and colon (152–153)	919	0.89	0.83	0.95
Rectum (154)	554	0.96	0.89	1.05
Liver and gallbladder (155–156)	549	1.15	1.06	1.25
Pancreas (157)	641	0.96	0.89	1.04
Larynx (161)	229	1.10	0.97	1.26
Trachea, bronchus, lung (162)	7756	1.90	1.86	1.94
Pleura (163)	39	1.06	0.75	1.44
Prostate (185)	857	0.84	0.79	0.90
Kidney (189.0–189.2)	392	0.96	0.87	1.06
Bladder and other urinary (188, 189.3–189.9)	421	0.85	0.77	0.94
Melanoma and skin (172–173)	133	0.86	0.72	1.02
Brain and other nervous system (191–192)	298	0.87	0.77	0.97
Hodgkin's disease (201.0, 201.2, 201.9)	65	0.90	0.70	1.15
Non-Hodgkin's lymphoma ([a])	321	0.92	0.83	1.03
Multiple myeloma (203)	161	0.88	0.75	1.03
Leukaemia (204–208)	396	0.93	0.84	1.03
Circulatory diseases (390–459)	16 921	0.88	0.86	0.89
Ischaemic heart disease (410–414, 429.2)	9457	0.92	0.91	0.94
Non-cancer diseases of the respiratory system (460–519)	4508	1.32	1.28	1.36
Chronic obstructive pulmonary disease (490–492, 496)	1729	0.98	0.93	1.02
Silicosis (502)	814	13.56	12.64	14.52
Non-cancer diseases of the digestive system (520–579, 997.4)	2480	0.93	0.89	0.96
Cirrhosis (571)	1415	0.99	0.94	1.05
External causes (E800–E999)[b]	3362	1.41	1.36	1.46

SMR, standardized mortality ratio; CI, confidence interval.

[a]200.0, 200.1, 200.2, 200.8, 202.0, 202.1 202.3, 202.4, 202.8, 202.9, 273.

[b]External reference mortality rates for this category of cause of death were not available for the Wismut cohort; therefore, the reported results for this category of cause of death pertain to the PUMA study excluding the Wismut cohort.

Mexico and Ontario cohorts (Supplementary Table 2, available as Supplementary data at *IJE* online). Excesses of mortality from laryngeal cancer were observed in all PUMA cohorts except the Eldorado cohort; and stomach-cancer excesses were observed in all PUMA cohorts except the Czech, Eldorado and Ontario cohorts.

The SMR for lung cancer was above unity for all periods of time since first hire examined (Table 3), was largest for the period 10 to <30 years after hire (SMR = 2.23; 95% CI: 2.14, 2.31), but also was in excess in the period <10 years after hire (SMR = 1.66; 95% CI: 1.39, 1.97) and remained in excess even in the period 30+ years after hire (SMR = 1.77; 95% CI: 1.72, 1.82). The SMR for liver and gallbladder cancer was above unity for the period 10 to <30 years after hire (SMR = 1.15; 95% CI: 0.94, 1.39) and persisted in excess in the period 30+ years after hire (SMR = 1.16; 95% CI: 1.05, 1.27). The SMR for laryngeal cancer was modestly elevated in the period 10 to <30 years after first hire (SMR = 1.09; 95% CI: 0.86, 1.35) and 30+ years after hire (SMR = 1.14; 95% CI: 0.96, 1.33). The SMR for pleural cancer was elevated in the period 10 to <30 years after hire, albeit based on small numbers of deaths (SMR = 1.09; 95% CI: 0.54, 1.95).

The SMR for lung cancer was largest for miners first hired in the calendar period <1955 (SMR = 2.48; 95% CI: 2.41, 2.55) and was smallest for those hired in the period 1965+ (SMR = 1.34; 95% CI: 1.26, 1.44). SMRs for laryngeal cancer and for liver and gallbladder cancer were above unity for those hired <1955 (SMR = 1.16; 95% CI: 0.94, 1.42; and SMR = 1.29; 95% CI: 1.15, 1.45, respectively) and for those hired 1955 to <1965 (SMR = 1.15; 95% CI: 0.93, 1.41; and SMR = 2.43; 95% CI: 2.19, 2.68,

Table 3. Standardized mortality ratios among male uranium miners in the Pooled Uranium Miners Analysis (PUMA) study by time since first hire, calendar period of hire and duration of employment

	Time since first hire (years)											
	<10				10 to <30				30+			
	Obs	SMR	95% CI		Obs	SMR	95% CI		Obs	SMR	95% CI	
All causes	2419	1.08	1.04	1.12	15 840	1.10	1.09	1.12	33 528	1.03	1.02	1.04
Lung cancer	129	1.66	1.39	1.97	2617	2.23	2.14	2.31	5010	1.77	1.72	1.82
Pleural cancer	<6	0.00	0.00	3.94	11	1.09	0.54	1.95	25	0.97	0.62	1.43
Larynx cancer	<6	0.57	0.14	1.55	79	1.09	0.86	1.35	147	1.14	0.96	1.33
Liver cancer	6	0.92	0.37	1.92	105	1.15	0.94	1.39	422	1.16	1.05	1.27
Stomach cancer	27	0.88	0.58	1.28	381	1.16	1.04	1.28	650	1.05	0.97	1.13
Leukaemia	21	0.95	0.59	1.46	111	0.92	0.76	1.11	264	0.93	0.82	1.05
	Period of hire											
	<1955				955–1964				1965+			
	Obs	SMR	95% CI		Obs	SMR	95% CI		Obs	SMR	95% CI	
All causes	23 562	1.14	1.12	1.15	19 917	0.96	0.95	0.98	8308	1.06	1.04	1.09
Lung cancer	4368	2.48	2.41	2.55	2532	1.50	1.44	1.56	856	1.34	1.26	1.44
Pleural cancer	18	1.09	0.65	1.73	11	0.72	0.36	1.29	7	1.39	0.61	2.75
Larynx cancer	94	1.16	0.94	1.42	95	1.15	0.93	1.41	40	0.91	0.65	1.24
Liver cancer	288	1.29	1.15	1.45	382	2.43	2.19	2.68	62	0.82	0.63	1.05
Stomach cancer	585	1.11	1.02	1.20	340	1.05	0.94	1.17	133	1.03	0.86	1.22
Leukaemia	173	1.00	0.85	1.16	158	0.89	0.75	1.04	65	0.89	0.68	1.13
	Duration of employment (years)											
	<1				1 to <10				10+			
	Obs	SMR	95% CI		Obs	SMR	95% CI		Obs	SMR	95% CI	
All causes	5211	0.99	0.96	1.01	24 610	1.02	1.00	1.03	21 966	1.11	1.10	1.13
Lung cancer	581	1.24	1.15	1.35	3187	1.60	1.54	1.65	3988	2.45	2.38	2.53
Pleural cancer	<6	0.33	0.02	1.61	18	1.05	0.62	1.66	17	1.02	0.59	1.63
Larynx cancer	22	1.07	0.67	1.62	119	1.16	0.96	1.39	88	1.04	0.84	1.29
Liver cancer	35	1.04	0.73	1.45	227	1.13	0.99	1.28	271	1.23	1.08	1.38
Stomach cancer	86	1.07	0.86	1.32	471	1.03	0.94	1.13	501	1.13	1.03	1.23
Leukaemia	39	0.81	0.58	1.11	188	0.88	0.76	1.02	169	1.03	0.88	1.19

Obs, observed deaths; SMR, standardized mortality ratio; CI, confidence interval.

respectively), but not for those hired in the period 1965+ (SMR = 0.91; 95% CI: 0.65, 1.24; and SMR = 0.82; 95% CI: 0.63, 1.05, respectively). The SMR for stomach cancer was largest for miners first hired in the calendar period <1955 (SMR = 1.11; 95% CI: 1.02, 1.20). Leukaemia SMRs were at, or below, unity among those in each hire cohort examined. The SMR for pleural cancer was elevated, albeit imprecisely estimated, for miners first hired <1955 and for miners first hired in the period 1965+.

SMRs for lung cancer increased in a monotonic fashion with duration of employment (Table 3), with the SMR for lung cancer being largest for those employed 10+ years (SMR = 2.45; 95% CI: 2.38, 2.53). SMRs for liver and gallbladder cancer also increased in a monotonic fashion with duration of employment; SMRs for stomach cancer did not increase in a monotonic fashion with duration of employment but, among those with the longest duration of employment (10+ years) the SMR for stomach cancer was elevated (SMR = 1.13; 95% CI: 1.03, 1.23). The SMR for leukaemia was below unity among those employed <1 year and among those employed 1 to <10 years, and was slightly above unity among those employed 10+ years (SMR = 1.03; 95% CI: 0.88, 1.19). The SMR for pleural cancer was not elevated among those with the shortest

duration of employment (<1 year), but was slightly elevated among those employed 1 to <10 and 10+ years (Table 3).

Among the categories of cause of death other than malignancy (Table 2), respiratory-disease mortality was elevated in the PUMA cohort (SMR = 1.32; 95% CI: 1.28, 1.36), due in part to a substantial excess of silicosis (SMR = 13.56; 95% CI: 12.64, 14.52). The SMR for respiratory disease excluding silicosis was 1.10 (95% CI: 1.06, 1.14). Elevated SMRs for non-malignant respiratory-disease mortality were observed in all PUMA cohorts except the Eldorado and Ontario cohorts, and elevated SMRs for silicosis were observed in all PUMA cohorts. The SMR for chronic obstructive pulmonary disease—a category of cause of death that encompasses chronic bronchitis and emphysema and is strongly related to tobacco smoking—was 0.98 (95% CI: 0.93, 1.02). A deficit in circulatory-disease mortality (SMR = 0.88; 95% CI: 0.86, 0.89) was observed overall and deficits were observed in all PUMA cohorts except the Colorado Plateau cohort. SMRs below unity were observed for ischaemic heart disease (which includes acute myocardial infarction)—a category of circulatory-disease mortality related to tobacco smoking (SMR = 0.92; 95% CI: 0.91, 0.94). An SMR below unity also was observed for digestive-disease mortality (SMR = 0.93; 95% CI: 0.89, 0.96). In contrast, an elevated SMR for mortality due to external causes was observed (SMR = 1.41; 95% CI: 1.36, 1.46) based on data for most, but not all, cohorts in PUMA due to limitations on the availability of reference mortality rates for this category of cause of death (Supplementary Table 2, available as Supplementary data at *IJE* online).

Discussion

Lung-cancer mortality was elevated overall in the PUMA study in comparison to reference mortality rates and was elevated in each of the constituent cohorts in the PUMA study. The lung-cancer SMR suggests that the lung-cancer rate among miners in the PUMA study is approximately twice that expected based on population reference mortality rates (SMR = 1.90; 95% CI: 1.86, 1.94). Excesses of lung cancer have been noted among underground hard-rock miners for centuries[5,26] and radon has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer.[4,5,26]

Cancer of the larynx was elevated overall in the PUMA study. Excesses of cancer of the larynx were observed in all of the constituent cohorts included in the PUMA collaboration except for the Eldorado cohort. Cancer of the larynx is plausibly related to inhalation of radon and radon progeny because tissues of the upper respiratory tract (e.g. the nose, pharynx and larynx) are among the most highly exposed to alpha radiation after the lung,[27–29] although the SMRs for cancers of the pharynx and oral cavity were not elevated in the PUMA study. In a prior report on relative risks of cancer mortality in pooled cohorts of underground miners (which included results based on earlier follow-up of six of the seven PUMA cohorts), Darby *et al.* (1995) noted an increase in mortality for cancer of the larynx (SMR = 1.32; 95% CI: 0.94, 1.82).[12]

Liver and gallbladder cancer and stomach cancer also were elevated in PUMA. Doses to the liver from inhalation or ingestion of radon and radon progeny are relatively small.[28,30] In a prior pooled analysis, Darby *et al.* (1995) also noted a relative excess of mortality due to liver cancer and stomach cancer[12] and excess stomach cancer also has been observed in prior analyses of the Colorado Plateau cohort[19] and of the Wismut cohort.[31] Ingestion of dust containing uranium and its decay products could contribute to radiation exposure to the digestive tract, although these elements have very long half-lives; and silica exposure, common in the study mines,[10] has been linked to gastric cancer.[32]

Pleural-cancer cases, many of which are likely to be pleural mesothelioma, were in slight excess in the PUMA study. The epidemiological characteristics of mesothelioma are well established; most cases are caused by inhalation of asbestos, which may have occurred for some miners. This cancer also has been associated with high-dose external exposure to ionizing radiation and injection with Thorotrast.[33–35]

Overall, SMRs were not elevated for cancer sites other than the lung, larynx, liver and gallbladder, stomach and pleura. Some prior analyses of uranium miners have suggested excesses at other cancer sites. Kidney cancer has been reported as increased relative to expectations based on national reference rates in prior analyses of the French miners[22] and is of interest given the potential exposure of the kidney to uranium through ingestion or clearance of inhaled uranium, but a kidney-cancer excess was not observed in PUMA. Leukaemia mortality was reported to be in excess relative to expectations in a prior pooled analysis of underground miners (primarily in the period <10 years since starting work),[12] as well as in studies of mortality among Wismut miners[36] and nuclear workers where leukaemia (excluding chronic lymphocytic leukaemia) mortality has been associated with estimated bone-marrow dose.[37] Leukaemia is of interest, as uranium miners may accrue small bone-marrow doses of ionizing radiation from the circulatory transportation of inhaled and absorbed radon gas, as well as from exposure to external penetrating forms of radiation emitted from uranium and its decay products in the rocks (which is likely to be the

primary source of red bone-marrow dose) and long-lived radionuclides.[30] No excess of leukaemia mortality was observed overall in PUMA (Table 2).

Non-malignant respiratory-disease-mortality excesses were observed in the PUMA study. This likely underscores the non-radiological hazards encountered in underground mining, in particular silica dust and its association with the observed excess of mortality due to silicosis.[38] However, underground uranium miners also appear to be at risk for non-malignant respiratory disease that is distinct from silicosis[6]; in PUMA, excess respiratory-disease mortality was not entirely due to deaths attributed to silicosis (the SMR for respiratory disease excluding silicosis was 1.10; 95% CI: 1.06, 1.14) and was observed despite no excess in deaths due to chronic obstructive pulmonary disease (the SMR for respiratory disease excluding silicosis and chronic obstructive pulmonary disease was 1.24; 95% CI: 1.18, 1.29). Whereas this excess could represent misclassification of silicosis deaths to other categories of non-malignant respiratory disease, it could also reflect other types of occupational lung disease that have been documented in uranium miners.[6]

Long-term follow-up of the cohorts included in PUMA allows us to investigate the temporal evolution of excess risk and thus characterize when excess risks appear and how long they persist. We reported results for several cancer outcomes in analyses that stratified person-time and events by categories of time since first hire as a uranium miner (Table 3). One reason for expecting variation in the occurrence of an occupationally associated cancer with time since first hire relates to an assumption that the effect of exposure to a carcinogen may be observed only after a delay because of an induction and latency interval between exposure and observed excess mortality.[3] Another reason for expecting variation in SMRs with time since first hire relates to the potential effects of health-related selection into employment.[39] If relatively good health is necessary for initial employment, then an occupational cohort may have lower mortality rates than the general population in the early years of follow-up.[40] For lung cancer in the PUMA study, the SMR was elevated for person-time and events that were observed <10 years after first hire, was largest in the period 10 to <30 years after first hire and remained elevated >30 years after first hire. Whereas uranium miners may have had previous employment in other types of mines, contributing to lung-cancer excess observed in the first decade after hire as a uranium miner, this pattern is generally consistent with empirical descriptions of radon-progeny exposure–lung cancer associations among miners in which the excess relative rate of lung cancer per unit exposure increased, after a lag, to a maximal value between 10 and 15 years after exposure and then diminished.[41–44] The SMR for cancer of the larynx tended to increase with time since first hire. The SMR for leukaemia did not exceed unity in any of the periods of time since first hire, whereas the SMRs for liver and stomach cancers only exceeded unity in the periods 10+ years after first hire. Prior analyses of the earlier pooled cohort data showed that lung-cancer risk varies with several time-related variables, including time since exposure, rate of exposure accrual and attained age.[14] Future analyses of PUMA will address variation in risk by time-related dimensions of exposure to radon progeny including age at exposure, time since exposure, attained age and exposure rate. In the PUMA study, miners have been followed for an average of nearly 40 years since first hire, which is much greater than the average duration of employment; therefore, trends in SMRs with time since first hire also may be informative about the persistence of mortality excesses after cessation of exposure.

We also examined variation in SMRs by categories of duration of employment. In principle, duration of employment can serve as a proxy for cumulative exposure to occupational hazards; however, this only holds if the average exposure intensities are similar over time. This condition clearly does not always hold in the PUMA study; airborne exposures tended to be high in the early periods of mine operations and tended to diminish markedly until the 1960s. Consequently, duration of exposure is a weak proxy for cumulative exposure in these cohorts and this should be kept in mind when considering trends in SMRs (or the absence of such trends) by duration of employment.

We noted that lung-cancer SMRs were largest for miners first hired prior to 1955 and smallest for those hired in the more recent period (1965+), consistently with the historical evolution of improvements in ventilation (and decreases in average radon-progeny concentrations) over calendar time. SMRs for laryngeal cancer, liver cancer and leukaemia were not elevated among miners hired in the most recent period (1965+). There also is notable variation in the magnitudes of occupational exposures between the cohorts in PUMA. Average concentrations of radon progeny differ markedly among the cohorts, with the highest cumulative exposure in the Colorado Plateau and Wismut cohorts and the lowest cumulative exposure in the French and Ontario cohorts. Lung-cancer SMRs were above unity in each cohort included in the PUMA study (Supplementary Table 2, available as Supplementary data at *IJE* online), with the lowest magnitudes of the cohort-specific lung-cancer SMRs among the Ontario and French cohorts of uranium miners.

There are a number of challenges to the ability to detect adverse effects of occupational exposures via SMR

analyses. Often, in occupational cohort mortality studies, low death rates relative to national reference rates are observed due to the exclusion from employment of people too sick to work and due to socio-economic and lifestyle differences between full-time workers and the unemployed (such as alcohol use and cigarette smoking).[40,45,46] In PUMA, the SMR for deaths due to all causes other than cancer was less than unity and the SMR for deaths due to all cancers other than lung cancer also was less than unity. Such findings suggest that uranium miners tended to be healthier than the general population. Contrary to the pattern expected if the prevalence of smoking was markedly higher among miners in PUMA than in the general population, the SMR for chronic obstructive pulmonary disease was near unity and the SMRs for circulatory disease, ischaemic heart disease and cancers of the oral cavity, pharynx, oesophagus, pancreas, kidney and bladder are in deficit. These are causes of death positively associated with smoking.[47,48] Similarly, contrary to the pattern expected in populations with relatively heavy alcohol consumption, in PUMA, deaths due to cirrhosis and oral and pharynx cancers are not in excess (Table 2). Such observations, of course, only offer indirect evidence regarding potential confounding of the SMR, as a measure of effect of occupational exposure on mortality, by cigarette smoking and alcohol consumption. Additional information, or assumptions,[49] are necessary to more fully address potential bias due to unmeasured factors; and, whereas the SMR may be interpretable as a ratio of marginal rates,[50] assessment of interaction between occupational exposures and factors, such as cigarette smoking, also requires direct assessment of those factors.[51,52]

Another challenge in the use of SMRs to detect adverse effects of occupational exposures arises from the imperfect sensitivity and specificity of death certificates for assessing cause-specific mortality; moreover, missing information on cause of death is a potential source of bias in SMR analyses if the mechanisms leading to missing information affect decedents in the study cohort and in the reference population differentially. Methods have been proposed to handle missing outcome information but were not employed in the current analysis.[53] Finally, in some prior analyses of US cohorts, SMRs have been adjusted for Hispanic ethnicity to account for baseline differences in mortality rates by Hispanic ethnicity[20]; however, standard US reference-rate files are not tabulated by ethnicity and consequently the current analysis did not adjust for ethnicity. Despite these limitations, several malignant and non-malignant causes of death were in excess in PUMA (Table 2), including elevated SMRs for a number of cancer sites that have long been associated with uranium-mining work.

Conclusion

Work in underground uranium mines entails the potential for exposure to radon and its progeny as well as other occupational hazards. This study provides strong evidence of excess mortality due to lung cancer, as well as suggestive evidence of excess mortality due to cancers of the liver and gallbladder, larynx, stomach and pleura. Consequently, the PUMA study findings suggest that uranium-mining exposures are associated with excess cancers other than lung. Excess mortality from non-malignant respiratory disease (particularly silicosis) and external causes also was found, but no excess of deaths from chronic obstructive pulmonary disease was observed and a deficit of deaths from circulatory disease was observed, consistent with a 'healthy worker effect'.[46] The findings of this study underscore the importance of long-term follow-up of occupational cohorts to identify occupational exposure–disease associations only observed after long induction and latency periods, and to characterize enduring occupational-exposure effects. Long-term updates of these cohorts allow the evaluation of persistent effects of exposures in the past, and contrasts between miners employed in earlier historical periods and miners employed more recently so as to assess the effects of improved occupational safety standards. The findings therefore have relevance for workers employed in underground mines worldwide.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

D.B.R. and D.L. conceived the study. D.B.R., E.R., D.L., J.S., P.A.D., L.T., L.B.Z., M.D., K.K.R., M.S.B. and M.K. developed the research questions and designed the study. E.R. and D.L. worked on provision of the French data; M.S.B. and K.K.R. worked on provision of the US Colorado Plateau data; J.S. and C.W. worked on provision of the US New Mexico data; L.B.Z. worked on provision of the Canadian Eldorado data; M.T.D. and N.D. worked on provision of the Canadian Ontario data; and V.D. and N.F. worked on provision of the Wismut data. E.R. and D.B.R. were responsible for data management and processing as well as some analyses. D.B.R. produced the initial draft of the manuscript, which was revised and approved by all authors.

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Conflict of interest

All authors have completed the ICMJE uniform disclosure form. D.B.R., P.A.D., M.T.D., N.D., N.F., V.D., M.K., J.S., C.W., M.S.B., K.K.-R., L.T. and L.B.Z. declare no relationships or activities that could appear to have influenced the submitted work. D.L. and E.R. report other support from ORANO during the conduct of the study.

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