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Mortality (1950–1999) and Cancer Incidence (1969–1999) in the Cohort of Eldorado Uranium Workers

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This study assessed the relationship between radon decay product (RDP) exposure and mortality and cancer incidence in a cohort of 17,660 Eldorado uranium workers first employed in 1932–1980 and followed up through 1999. The analysis was based on substantially revised identifying information and dosimetry for workers from the Beaverlodge and Port Radium uranium mines and for the first time includes workers from a radium and uranium refinery and processing facility in Port Hope, Canada. Overall, male workers had lower mortality rates of all causes and all cancers and lower incidence rates of all cancers compared with the general Canadian male population, a likely healthy worker effect. Individual cancer rates were also reduced except for lung cancer mortality (SMR = 1.31, $P < 0.001$) and incidence (SIR = 1.23, $P < 0.001$). The excess relative risk per 100 WLM (ERR/100 WLM) of lung cancer mortality ($N = 618$, ERR/100 WLM = 0.55, 95% CI: 0.37, 0.78, $P < 0.01$) and incidence ($N = 626$, ERR/100 WLM = 0.55, 95% CI: 0.37, 0.81, $P < 0.001$) increased linearly with increasing RDP exposure. Adjustment for effect modification by time since exposure, exposure rate and age at risk resulted in comparable estimates of risk of lung cancer for all three uranium worksites. RDP exposures and γ-ray doses were not associated with any other cancer site or other cause of death. The risk estimates are in agreement with the results of the pooled analysis of 11 miner cohorts and more recent studies of uranium workers. The current analysis provides more precise risk estimates and compares the findings from the mortality study with the incidence study. Future follow-up of the cohort and joint analysis with other uranium miners' studies should shed more light on the effects of low RDP exposures as experienced by current workers as well as help to understand and address the health risks associated with residential radon.

INTRODUCTION

Follow-up of the mortality of and cancer incidence in uranium mine, mill and processing workers is essential to improve our understanding of radiation risk and to ensure that radiation protection programs appropriately protect workers' health. Exposure to radon decay products (RDP) is one of the best-studied carcinogenic phenomena in radiation epidemiology (*1*). Epidemiological studies, primarily of underground miners, show increases in lung cancer risk from exposure to RDP but little evidence for an increase in any other disease (*2*). These results are consistent with physiological considerations (i.e., RDP are deposited in the airway structures of the lungs and emit α-particle radiation) and with animal studies (*3*).

The relationship between RDP exposure and lung cancer for former employees at the Eldorado Beaverlodge and Port Radium mines was reported previously based on mortality follow-up from 1950 to 1980 (*4–6*). The risk estimates for workers from the two mines differed by an order of magnitude [excess relative risks per 100 working level month[3] (ERR/100 WLM) of 3.25 (*5*) and 0.27 (*6*), respectively]. These two cohorts were part of a combined analysis of 11 underground mining cohorts (*2, 7*), which found an approximately linear relationship between RDP exposure and lung cancer mortality. The risk per unit RDP exposure decreased with increasing time since exposure, with increasing exposure rate, and with increasing age at risk. The BEIR VI Committee (*2*) adopted this model in 1999, emphasizing the importance of effect modifiers in the RDP exposure and lung cancer risk relationship. Recent

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[3] The concentration of RDP in workplace air is expressed in working levels (WL), where 1 WL is the concentration of RDP per liter of air that would result in the ultimate release of 1.3×10^5 MeV of potential α-particle energy. Occupational exposure to RDP is the product of time in the workplace and the concentration of RDP in the workplace air, measured in working level months (WLM), where 1 WLM is equivalent to one working month (170 h) in a concentration of 1 WL.

updates of the French, German, Czech, Colorado Plateau, and Newfoundland Fluorspar miners studies (*8–16*) have increased statistical power and precision of risk estimates and largely support the BEIR VI Committee model (*2*).

Since the publication of the original Eldorado studies (*4–6*), we made substantial efforts to improve the identifying and dosimetry information in the Beaverlodge and Port Radium studies and added a group of workers from the Port Hope radium and uranium refinery and processing facility to form a cohort of Eldorado uranium workers. We used the data from the Canadian Mortality Database (CMDB) and from the Canadian Cancer Database (CCDB) to analyze and compare mortality (1950–1999) and cancer incidence (1969–1999) in the cohort of Eldorado uranium workers, to evaluate the relationship between workers' lung cancer risk and RDP exposure and its modification by age at risk, time since exposure and exposure rate, and to evaluate other causes of death and cancer in relation to RDP exposures and γ-ray doses.

MATERIALS AND METHODS

The Cohort

Potential study subjects came from the personnel records provided by the mines and processing sites operated by Eldorado Nuclear Ltd. Most workers were uranium miners and mill workers employed at two mine sites (Port Radium, Northwest Territories, and Beaverlodge, northern Saskatchewan) and workers employed at the radium and uranium refining and processing plant (Port Hope, Ontario), with a small number of individuals employed at "other sites" including head office, aviation, research and development, and exploration. The sub-cohort membership was based upon the employment site where a worker spent the longest time working for Eldorado. For inclusion in the study, workers had to be employed during the ages of 15–75 years at one of the facilities of Eldorado sometime between 1932 and 1980, had their last contact after 1940, and had to be alive at start of follow-up in 1950 (mortality analysis) or 1969 (cancer incidence analysis).

The previous analysis of the Port Radium uranium mine workers included all male workers employed at the mine between 1942 and 1960 and known to be alive at the start of follow-up in 1950 (*6*). The original nominal roll included 2,696 workers, many of whom were excluded from linkage and analysis because of missing date of birth information (*6*). After an extensive search and review of original records, the updated nominal roll was expanded to include 4,079 workers.

The previous analyses of the Beaverlodge mine workers were based on 10,945 male workers employed at the mine between 1948 and 1980 (*4, 5*). The current analysis is based on the extended follow-up of that cohort with the addition of 305 workers who joined the Beaverlodge mine between the cutoff of the original study and the final shutdown of the mine in June 1982. Improvements in the quality and quantity of identifying data in the nominal roll and work histories resulted in a final updated nominal roll containing 11,788 workers.

The Port Hope radium and uranium refinery and processing facility became operational in 1932. Initially, radium was the primary product, but uranium became the primary product in 1942, and radium production was phased out by 1954. Port Hope continues to operate today as Cameco Corporation Port Hope Conversion Facility. Workers have been exposed to relatively concentrated forms of uranium with greater solubility than that found in the uranium ore. This sub-cohort has not been presented in epidemiological studies previously. The current Eldorado nominal roll contained 3,338 Port Hope workers.

The updated Eldorado study was conducted in accordance with accepted ethical practices and was approved by Health Canada's Research Ethics Board and Institutional Review Board Services.

Record Linkage

An internal linkage carried out at Statistics Canada identified and eliminated duplicates and invalid records. Further manual unduplication/update work resulted in a final nominal roll file containing 19,855 individuals. The Historic Tax Summary file (1984 to 2000) was used to confirm 8,218 (41.4%) cohort subjects alive at the end of follow-up in 1999. In addition, 1,356 (6.8%) cohort subjects were confirmed alive at some time between 1984 and 1998, and 1,572 (8.0%) cohort subjects were confirmed dead.

The nominal roll file was then linked to the CMDB from 1940 to 1999 via probabilistic record linkage (*17*). The CMDB contains records of all deaths registered in Canada by all provinces and territories and those voluntarily reported deaths of Canadian residents occurring in the United States. The CMDB has cause of death information since 1950, is considered to be complete and accurate, and is routinely used to ascertain mortality in a number of cohort studies (*17*). From 1940 to 1949 the CMDB does not contain cause of death, only fact of death. This information was used for death clearances from 1940 to 1949, and deceased subjects were eliminated from further analysis. Linkage to the CMDB increased the number of confirmed deaths in the cohort to 5,974 (30.1%). An additional 32 deaths confirmed from the Tax file had no death records in the CMDB.

In total, we were able to ascertain the vital status of 15,580 (78.5%) cohort subjects. The 4,307 (21.8%) individuals who could not be linked to the Historic Tax Summary records or the CMDB had their termination date at work as the last date alive. Further data processing led to the exclusion of 2,195 (11.0%) records [missing information on sex (3), birth year (1,866), no occupational record (42), exposure data (116), age of employment (15 to 75 years) out of range (35), age >100 with no death found (100), last contact before 1940 (24), and recorded exposure after recorded death (9)]. The final cohort for mortality analysis thus consisted of 17,660 subjects (88.9% of the original cohort).

Cancer incidence was also determined through probabilistic record linkage of the nominal roll file to the CCDB from 1969 to 1999. Data in the CCDB are obtained from provincial and territorial cancer registries and are essentially complete for all cases of cancer occurring in Canada (*18*). This database contains records of all cancer cases diagnosed in Canada among people who reside in a province/territory at the time of diagnosis and voluntarily reported cases of Canadian residents diagnosed in the United States since 1969 (www.statcan.gc.ca/). Information on death was used for "death clearance" between 1950 and 1969 ($N = 886$), and four additional subjects were excluded because their RDP exposure occurred after the cancer diagnosis, leaving a cohort of 16,770 subjects for the incidence analysis.

Outcomes

For the mortality and incidence analyses, the underlying causes of death and cancer diagnoses were recoded from the original International Classification of Disease (ICD) code in use at the time of death or diagnosis to ICD-9 (*19*). The majority of analyses were done for lung cancer. Additional mortality and incidence analyses were performed to investigate effects of RDP exposures and γ-ray doses on other causes of death and cancer that yielded 50 or more

cases and leukemia, recently reported to be associated with long-lived radionuclides and γ radiation among uranium workers (*20*).

Exposures

Detailed description of the process of estimation of exposure to radon decay products in Port Radium and Beaverlodge have been published previously (*4, 6*). Briefly, at Port Radium, workplace measurements, initially of radon and later RDP, started in 1945 and were carried out sporadically through the 1940s and 1950s. During the period between 1945 and 1958, a total of 251 samples (9–71 per year) of radon were made. The range of concentrations was 5–300,000 pCi/liter. No personal exposures were calculated. For the original Port Radium study (*6*), individual annual exposures in WLM were estimated using the annual geometric mean RDP concentrations underground and in the mill and time spent in the workplace.

At Beaverlodge, both radon and RDP measurements started in 1954 and continued at increasing frequency throughout the life of the mine. The total number of radon and radon decay product measurements taken per workplace per year during the period 1954–1968 was generally less than 12, with an average of about four measurements per workplace per year. The radon concentration measurements were converted to RDP concentrations by use of equilibrium factors determined in 1954, 1956, 1959 and 1961 through paired measurements of radon concentrations and decay products. Personal exposures were assigned, starting with underground miners in November 1966 and expanding to cover all personnel in the 1970s. For the period before assignment of individual exposures, the exposures were estimated using the same procedures used at Port Radium.

In the current study, the annual individual RDP exposures were recalculated for all Port Radium and Beaverlodge personnel for whom no individual exposure had been recorded during the operation of the mine. The annual mean for workers from Beaverlodge was calculated by summing over the WL measurements 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.[4] For Port Radium, a similar approach was taken, but seasonal averages were determined to account for different winter and summer mine ventilation rates, and the rather scant measurement data were augmented by ventilation modeling.[5] There were no early radon or RDP measurements taken at Port Hope. The RDP estimates were based on quantities of radium present in the plant in ore and at various stages of refinement, measured radon emanation rates from various radium-bearing materials, building air volumes and estimates of air exchange rates.

In addition to RDP exposures, the current study has information on individual γ-ray doses for all cohort subjects. At Port Radium, film badges were used for a few short campaigns of personal and area measurements in the 1950s. At Beaverlodge, similar short campaigns of personal and area monitoring with film badges took place in the 1950s, and starting in 1963 a sampling of workers wore film badges fulltime. This coverage was gradually increased through the 1970s. At Port Hope, film badges were used on some personnel from the late 1940s, coverage was increased in the 1960s, and full external dosimetry was in place by about 1970. In this analysis, personal γ-ray doses were calculated from the average dose rates and time on the job and expressed in millisieverts (mSv) for each individual who had not been wearing a badge.

Finally, many workers' personnel records indicated prior experience in other early Western Canadian mines, and many obtained employment in other mines or other industries with potential radiation exposure after leaving Eldorado. The National Dose Registry (NDR) collects and records radiation exposure and dose data for all exposed workers in Canada from 1951 (with some records going back to 1944) and contains information on γ-ray doses for uranium miners starting in 1981 (*21*). However, the NDR had no early records from Eldorado and no records for any of the other early Western Canadian mines. For workers with mining exposure history in early non-Eldorado Western Canadian mines, we estimated exposure levels based on the Beaverlodge WL data. For all other non-Eldorado radiation exposures from 1951 to 1999, the nominal roll was linked to the NDR records (*22*).

Statistical Analysis

In the mortality analysis, each individual contributed person-years at risk from the later of the date of hire or the start of follow-up, defined as January 1, 1950, to the exit date of December 31, 1999, the date of death, or the last date known alive, whichever occurred earliest. In the cancer incidence analysis, individuals contributed person-years at risk from the later of the date of hire or the start of follow-up, defined as January 1, 1969, to the exit date of December 31, 1999, the date of cancer diagnosis, or the last date known alive, whichever occurred earliest. The summary person-year experience was cross-classified by age at risk (15–19, 20–24… 85–100 years old), calendar year at risk[6], (1950–1954, 1955–1959… 1995–1999), subcohort (Port Hope, Port Radium, Beaverlodge, and "other sites"), total duration of employment (*23*) (<6 months and 6 months+)[7], and age at first exposure, cumulative exposure, and years since first exposure, separately for WLM exposures and γ-ray doses. For all analyses, WLM exposures were lagged by 5 years and γ-ray doses were lagged by 2 years to account for the latent period between exposure and cancer incidence and mortality. The person-year weighted mean dose in each cross-classified cell was used in the regression analysis.

Two types of comparisons were used to conduct mortality and cancer incidence analyses. The first series of analyses was a comparison of the cohort with the general Canadian population. Observed and expected values were used to estimate standardized mortality ratios (SMR) and standardized incidence ratios (SIR) by means of indirect standardization. Expected values were derived from Canadian national population mortality (1950–1999) and cancer incidence (1969–1999) rates.[8] National rather than provincial rates were used, because deaths and cancer cases were spread across Canada and did not appear to be concentrated in specific locations. Expected values were adjusted for sex, age and calendar year at risk. Confidence interval estimates for the SMR and SIR and *P* values testing departures of these values from 1.0 were based on treating the observed numbers of deaths and cancer cases as Poisson variables (*24*).

The second series of comparisons was based upon internal comparisons, i.e., with no reference to an external population. These were conducted by using grouped Poisson regression analyses (*24, 25*). The general model used in this analysis is a simple linear relative risk model where risks may conveniently be modeled as relative risks, which multiply the background risk (i.e., the risk in the absence of

[4] SENES Consultants Limited, An algorithm for estimating radon decay product exposures from underground employment at the Eldorado Beaverlodge Mine. Atomic Energy Control Board of Canada, Richmond Hill, ON, 1996.

[5] SENES Consultants Limited, A re-evaluation of radon decay product exposures to underground workers at the Port Radium mine. Atomic Energy Control Board of Canada, Richmond Hill, ON, 1996.

[6] Calendar year at risk for the cancer incidence analysis was (1969–1970, 1970–1974…1995–1999).

[7] Total duration of employment was split at 6 months, because risk drops after 6 months but then remains constant. Similar phenomena have been observed previously in other studies (*23*).

[8] R. Semenciw, personal communication, 2006.

TABLE 1
Basic Characteristics of the Eldorado Uranium Workers Cohort

Characteristic	Sub-cohort				
	Beaverlodge	Port Radium	Port Hope	Other sites	Total
Number of subjects, Total	10,050	3,300	3,003	1,307	17,660
Males (%)	9,498 (94.5)	3,047 (92.3)	2,652 (88.3)	1,039 (79.5)	16,236 (91.9)
Females (%)	552 (5.5)	253 (7.7)	351 (11.7)	268 (20.5)	1,424 (8.1)
Mean[a] RDP exposure, WLM (SD)					
Males	84.8 (203.4)	180.1 (349.5)	14.2 (54.1)	14.9 (85.8)	100.2 (254.4)
Females	1.5 (3.1)	5.2 (17.6)	6.7 (11.1)	0.1 (0.3)	4.6 (10.1)
Mean[a] γ-ray dose, mSv (SD)					
Males	25.6 (39.4)	46.8 (82.2)	121.5 (306.8)	23.4 (42.3)	52.2 (152.4)
Females	3.0 (4.4)	49.8 (163.5)	52.0 (78.4)	3.1 (5.4)	34.4 (77.4)

Note. Abbreviations used: RDP, radon decay products; WLM, working level months.
[a] Weighted by person-years.

radiation exposure modeled by using various confounding factors in the background term):

$$\text{Risk} = \text{Background Risk} * \text{Relative Risk}. \quad (1)$$

The relative risk estimated by the latter technique may be expressed as

$$\text{Relative Risk} = 1.0 + (\beta\, X)\ \exp\ (\Sigma_i \gamma_i z_i), \quad (2)$$

where X represents factors such as RDP exposure or γ-ray dose, z_i are potential modifying factors such as time since exposure, and β and γ_i are coefficients estimated using maximum likelihood techniques. The β coefficient is referred to as the excess relative risk per unit of exposure (ERR); by adding 1.0 to the ERR one obtains the relative risk at 100 WLM for RDP exposure and per sievert (Sv) for γ-ray dose.

Dose–response analyses for RDP exposures relied on the time-dependent cumulative WLM exposure expressed as a continuous variable. For lung cancer, we also conducted exploratory analyses using a categorical RDP exposure variable the cutpoints for which were chosen to distribute lung cancer deaths evenly among the seven categories. For comparability, the same cutpoints were used in the incidence analysis.

Regression parameters, confidence intervals around these point estimates, and *P* values were estimated using the method of maximum likelihood in the AMFIT module of the EPICURE software (*25*). Tests of statistical significance were based on the likelihood ratio test comparing the two nested models with and without the variable of interest. All *P* values were two-sided.

Confounders

Age at risk, calendar year at risk, sub-cohort and total duration of employment were evaluated for possible independent effects on the background rate of lung cancer.

When γ-ray dose was investigated as a potential risk factor for lung cancer, it was entered into the model simultaneously with the RDP exposure. Because γ-ray doses were low relative to RDP exposures, this term was included in the background term as a continuous variable, i.e., assuming a log-linear relationship, which approximates a linear relationship at low doses. This may be regarded as a "screening technique," though radiobiological theory would suggest that a radiation dose–response relationship might be expected if any detectable risk occurs.

Effect Modifiers

We investigated modifying effects of various factors from the BEIR VI Committee model and used parameterization from its exposure-age-concentration model (*2*):

$$\text{RR} = 1.0 + \beta * (w_{5-14} + \theta_{15-24} w_{15-24} + \theta_{25+} w_{25+}) * \varphi_{\text{age at risk}} * \gamma_{\text{exposure rate}}, \quad (3)$$

where 5-year lagged RDP exposure is partitioned into time windows (WLM 5–14, 15–24 and 25+ years previously), and φ and γ represent estimates of modifications to the dose response by categories of age at risk (<55, 55–64, 65–74 and 75+ years old) and exposure rate (<0.5, 0.5–0.9, 1.0–2.9, 3.0–4.9, 5.0–14.9, and 15.0+ WL).

RESULTS

Demographic and Exposure Characteristics

Thirty percent of all Eldorado workers (observed = 5,332, N = 17,660) died between 1950 and 1999 and 23% (observed = 2,210, N = 16,770) were diagnosed with cancer between 1969 and 1999. Table 1 presents the basic characteristics of the cohort. Most workers were male (N = 16,236, 91.9% of the cohort) and most women were employed at jobs with low radiation exposures. Thus all further analyses are restricted to male workers, unless indicated otherwise. Most workers worked at Beaverlodge mine (N = 10,050), with smaller numbers at Port Radium mine (N = 3,300), the Port Hope radium and uranium refinery and processing facility (N = 3,003), and a few at "other sites" (N = 1,307). The age of individuals when the update ended in 1999 was between 70 and 79 years of age.

The mode mean RDP exposure (weighted by person-years) for the cohort as a whole (N = 17,660) was 100 WLM (SD = 254) and 117 WLM (SD = 271) among those with non-zero exposures (Table 1). As would be expected, the maximum mean RDP exposure was at

TABLE 2
Relative Risks of Lung Cancer Mortality (1950–1999) and Lung Cancer Incidence (1969–1999) and 95% Confidence Intervals by Categories of Cumulative Radon Exposure in the Eldorado Cohort

Lung cancer mortality					
Cumulative exposure (WLM)	Mean exposure (WLM)	Number of deaths	Person-years	RR[a] and 95% CI	*P* value[b]
0.00–	0	110	175,143	1	<0.001
0.0001–	1.27	83	130,688	0.85 (0.62, 1.17)	
3.58–	8.32	86	70,919	1.30 (0.96, 1.75)	
14.83–	30.76	87	55,349	1.51 (1.12, 2.03)	
53.12–	94.70	83	38,776	1.79 (1.31, 2.43)	
164.51–	300.43	84	27,976	2.50 (1.82, 3.42)	
614.38–2569.00	1084.78	85	9,822	7.34 (5.13, 10.53)	
Total		618	508,673		
Lung cancer incidence					
	Mean exposure (WLM)	Number of cases[c]	Person-years	RR[a] and 95% CI	*P* value[b]
0.00–	0	111	116,822	1	<0.001
0.0001–	1.27	102	109,317	0.89 (0.66, 1.20)	
3.58–	8.29	90	55,306	1.23 (0.91, 1.65)	
14.83–	30.69	95	41,015	1.55 (1.15, 2.07)	
53.12–	94.82	93	27,102	1.98 (1.47, 2.68)	
164.51–	298.90	79	18,255	2.52 (1.82, 3.48)	
614.38–2708.00	1079.41	56	5,070	7.20 (4.84, 10.68)	
Total		626	372,888		

Note. Abbreviations used: WLM, working level months; RR, relative risk; CI, confidence interval.
[a] Adjusted for sub-cohort, age at risk, calendar year at risk and duration of employment by stratification.
[b] *P* value of the test of linear trend based on mean values for exposure categories.
[c] Number of cases in the incidence analysis based on the earliest cancer diagnosis where each subject could contribute at most one cancer.

Port Radium, which had its highest RDP exposures in the 1930s–1940s when there were no radiation protection standards in mines. There was a noticeable drop in the mean RDP value for Beaverlodge, which was primarily mined in the 1950–1970s. RDP exposures at Port Hope and the ''other sites'' were minimal. Members of the ''other sites'' sub-cohort with significant RDP exposure would have acquired this at one of the three production sites. Workers of the Port Hope facility had the highest whole-body penetrating γ-ray doses, with the two mine sites having doses less than half those in Port Hope.

Comparison of the Cohort with the General Canadian Population

Mortality. Overall, male Eldorado workers had a very slight deficit in the number of deaths from all causes (observed = 5,148, expected = 5,284.17, SMR = 0.97, 95% CI: 0.95, 1.00), and all cancers (observed = 1,406, expected = 1,442.64, SMR = 0.97, 95% CI: 0.92, 1.03) compared with the general Canadian male population, although it was not statistically significant (Supplementary Table S1). Lung cancer was the only cancer site with a significantly elevated death rate (observed = 618, expected = 470.29, SMR = 1.31, 95% CI: 1.21, 1.42). There was a statistically significant excess of lung cancer deaths among both Port Radium (SMR = 1.61, 95% CI: 1.41, 1.83, $P < 0.001$) and Beaverlodge (SMR = 1.28, 95% CI: 1.14, 1.44, $P < 0.001$) workers but not for Port Hope workers (SMR = 1.10, 95% CI: 0.89, 1.33, $P = 0.38$), not shown. For females (not shown), only the lung cancer death rate was elevated compared to the general Canadian female population (SMR = 1.46, 95% CI: 0.90, 2.23, $P = 0.12$) but was not statistically significant.

Cancer incidence. For all males in the cohort there was a deficit in the incidence of all cancers (SIR = 0.83, 95% CI: 0.80, 0.87) (Supplementary Table S2). The only exception was lung cancer, where overall there was an elevated SIR of 1.23 (95% CI: 1.14, 1.33). Workers at Port Radium and Beaverlodge had significantly elevated SIRs for lung cancer of 1.31 (95% CI: 1.14, 1.50, $P < 0.001$, not shown) and 1.30 (95% CI: 1.16, 1.44, $P < 0.001$, not shown). Port Hope workers' cancer incidence was very similar to that in the general Canadian male population (not shown). Lung cancer among females was elevated (SIR = 1.49, 95% CI: 0.99, 2.16, $P = 0.054$), although all cancers showed a deficit (SIR = 0.85, 95% CI: 0.71, 1.00, $P = 0.044$, not shown) compared with the general Canadian female population.

Dose–Response Analysis of RDP Exposure-Associated Lung Cancer Risks

Mortality. There were 618 lung cancer deaths and 508,673 person-years at risk in the male Eldorado cohort

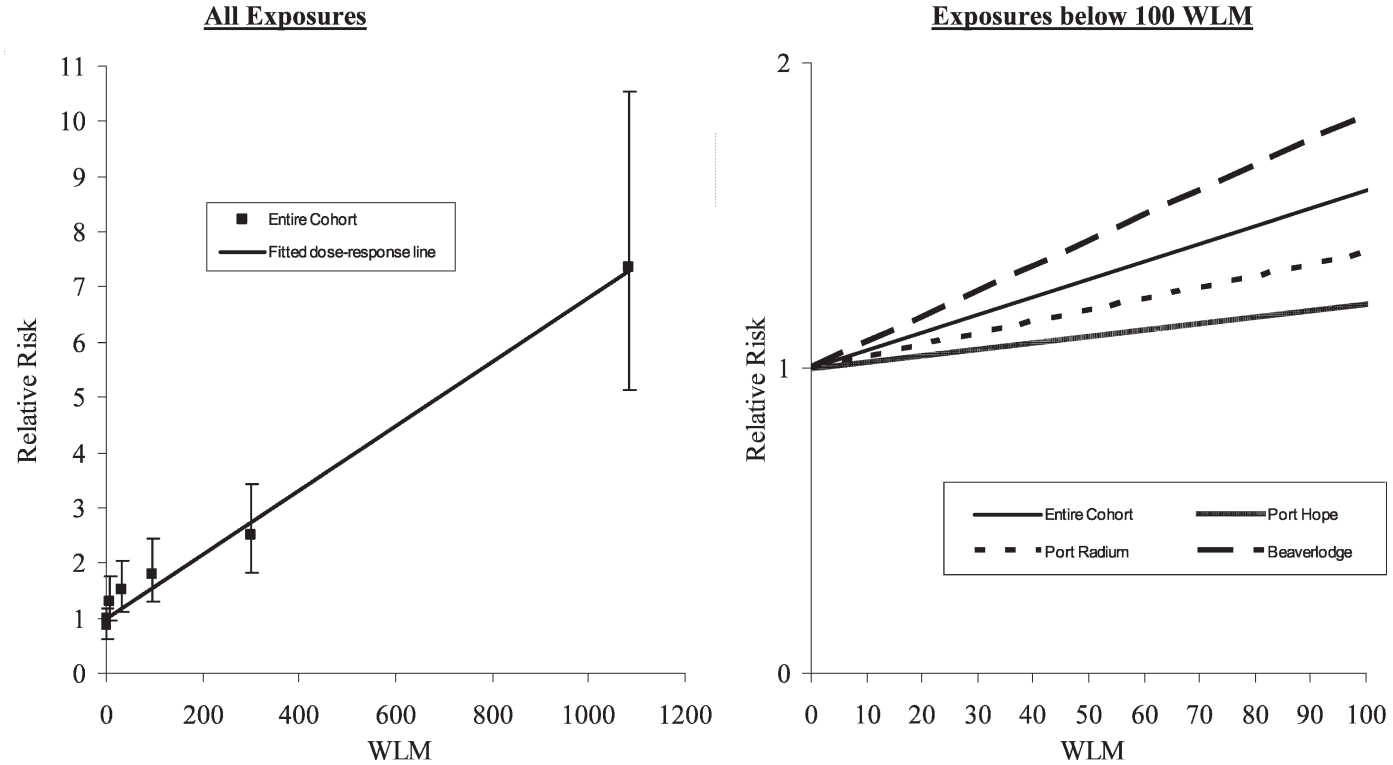

FIG. 1. Plot of the relative risk estimates of lung cancer mortality and 95% CI from the categorical analysis presented in Table 2 and a fitted dose–response line for males. Relative risk estimates were plotted as a function of person-year-weighted means in WLM exposure categories.

(Table 2). The entire cohort and the Port Radium and Beaverlodge sub-cohorts separately all yielded highly statistically significant ($P < 0.001$) linear positive increases in the risk of lung cancer death with increased cumulative RDP exposures. The highest risks were seen in the highest exposure category, with risks increased more than sevenfold compared to the lowest exposure category for the combined cohort (RR = 7.34, 95% CI: 5.13, 10.53). The risks were generally lower and the relationship was not significant for Port Hope workers (Supplementary Table S3, $P = 0.10$). Figure 1 plots the relative risks estimates for lung cancer mortality as a function of the category-specific person-year weighted mean RDP exposure for the entire male cohort. There was little evidence to suggest any departure from linearity, other than that which might be due to statistical fluctuations. The relatively small relative risk of lung cancer mortality for cumulative exposures below 100 WLM (right panel of Fig. 1) reflects the risk observed for about three-quarters of all Eldorado employees.

Among those with similar RDP exposures, those who worked less than 6 months ($N = 172$ cases) had a 1.31 times higher risk of lung cancer than those who worked more than 6 months (95% CI: 1.07, 1.60, $P = 0.009$). In addition, background risks of lung cancer differed by sub-cohort, age at risk, and calendar year at risk. All subsequent models were adjusted for these variables by stratification. Whole-body γ-ray dose did not statistically significantly add to the fit of the model ($P = 0.88$) and was not included in subsequent analyses.

The relationship between RDP exposure and lung cancer mortality in a simple linear model was highly significant, with an ERR/100 WLM = 0.55 (95% CI: 0.37, 0.78, Table 3). There was no evidence of any curvature with the addition of a quadratic term to the model ($P = 0.66$, not shown). The ERR/100 WLM for Port Radium and Beaverlodge was 0.37 (95% CI: 0.23, 0.59) and 0.96 (95% CI: 0.56, 1.56), respectively. There was no evidence of any curvature with the addition of a quadratic term to the model ($P = 0.66$ for the entire male sub-cohort). We observed marked heterogeneity of the excess relative risks by sub-cohort (including the sub-cohort of "other sites") (P test for heterogeneity <0.001, not shown).

Cancer incidence. Like mortality, we observed a monotonic increase in risk for lung cancer incidence (Fig. 2), with the highest risks seen in the highest exposure category and the risk for the highest exposure having a value more than sevenfold higher than that for the combined male cohort (Table 2, RR = 7.20, 95% CI: 4.84, 10.68). The linear trend test was highly statistically significant ($P < 0.001$).

The relationship between continuous RDP exposure and lung cancer incidence was also highly statistically significant (ERR/100 WLM = 0.55 (95% CI: 0.37, 0.81; Table 3). Similar to the mortality analysis, there was an apparent heterogeneity of effect by sub-cohort when

TABLE 3
Excess Relative Risk Estimates and 95% Confidence Intervals of Lung Cancer Mortality (1950–1999) and Lung Cancer Incidence (1969–1999) From the Simple Linear Model

	Lung cancer mortality			
	Number of deaths	Mean exposure (WLM)	ERR/100 WLM and 95% CI[a]	*P* value[b]
Total[c]	618	100.21	0.55 (0.37, 0.78)	<0.001
By sub-cohort				
Port Hope	101	14.23	0.18 (−0.10, 1.49)	0.59
Port Radium	230	180.08	0.37 (0.23, 0.59)	<0.001
Beaverlodge	279	84.80	0.96 (0.56, 1.56)	<0.001
	Lung cancer incidence			
	Number of cases[d]	Mean exposure (WLM)	ERR/100 WLM and 95% CI[a]	*P* value[b]
Total[e]	626	88.57	0.55 (0.37, 0.81)	<0.001
By sub-cohort				
Port Hope	110	10.42	0.68 (−0.23, 3.07)	0.17
Port Radium	196	198.74	0.40 (0.23, 0.68)	<0.001
Beaverlodge	311	60.61	0.70 (0.38, 1.17)	<0.001

Note. Abbreviations used: WLM, working level months; ERR/100 WLM, excess relative risk per 100 WLM; CI, confidence interval.
[a] Adjusted for sub-cohort, age at risk, calendar year at risk and duration of employment by stratification.
[b] *P* values from the likelihood ratio test comparing models with and without exposure variable.
[c] Includes lung cancer deaths among workers from "other sites."
[d] Number of cases based on the earliest cancer diagnosis where each subject could contribute at most one cancer.
[e] Includes lung cancer cases among workers from "other sites."

using a simple excess relative risk model (*P* for heterogeneity = 0.017, not shown). The estimated risk for Port Hope workers was higher than in the mortality analysis (ERR/100 WLM = 0.68 and 0.18, respectively).

To further investigate the shape of the dose response, we included γ-ray dose and quadratic term in WLM in the model and observed no evidence of an improvement in fit ($P = 0.84$ and 0.93, respectively). Exclusion of the various subgroups of the cohort, e.g., those with some recorded non-Eldorado experience, those with incomplete Eldorado dates of employment, and those with zero exposure, essentially made little difference to the results (results not shown).

Comparison with the BEIR VI Interaction Model for Lung Cancer

Mortality. When potential effect modifiers were investigated (Table 4), the variables selected by the BEIR VI Committee (*2*), i.e. time since exposure, exposure rate and age at risk, were the only variables that suggested some evidence of effect modification. For the lung cancer mortality analysis, splitting total WLM exposure into three time windows since exposure significantly improved the fit ($P < 0.001$). The excess relative risk decreased monotonically with increasing time since exposure. Adding exposure rate using the six exposure rates defined by the Committee further significantly improved the fit ($P = 0.001$), with the excess relative risks decreasing monotonically with increasing exposure rate. Adding the age at risk also improved the fit but not significantly ($P = 0.06$). Using BEIR VI parameterization, we estimated an ERR/100 WLM of 6.11 for time since exposure 5–14 years, exposure rate <0.5 WL and attained age <55 years. Sub-cohort-specific risk estimates were no longer significantly different in this model (*P* for heterogeneity of exposure effect by sub-cohort = 0.46, not shown).

Cancer incidence. For lung cancer incidence (Table 4), time since exposure significantly improved the fit of the model ($P < 0.001$). Inclusion of exposure rate in the model did not lead to a statistically significant improvement ($P = 0.13$), though the corresponding estimates for the exposure-rate effect showed decreasing effects per exposure unit with increasing exposure rate. Finally, adding terms in age at risk to the model led to a *P* value of 0.21 with somewhat wide confidence intervals. Those over age 75 years appeared to have a decreased risk per unit of exposure compared to those developing lung cancers at younger ages. Risk estimates from the full interaction model were comparable across sub-cohorts of male Eldorado employees (*P* for heterogeneity = 0.21, i.e., no longer significant).

Dose–Response Analysis for RDP Exposures and γ-Ray Doses and Other Causes of Death and Cancers Other Than Lung

There was no meaningful evidence of an association between RDP exposure and increased risk of any other cancer deaths or causes of cancer (Table 5). Additional exploratory analyses of γ-ray doses and CLL and non-

TABLE 4
Excess Relative Risk Estimates of Lung Cancer Mortality (1950–1999) and Lung Cancer Incidence (1969–1999) From the Full Interaction Model and Comparison with BEIR VI Model Estimates

	Lung cancer mortality			Lung cancer incidence			
Parameter	Number of deaths	Parameter estimate and 95% CI[a, b]	*P* value[c]	Number of cases[d]	Parameter estimate and 95% CI[a, b]	*P* value[c]	Parameter estimate for BEIR VI[e]
Total WLM exposure							
ERR/100 WLM[f]	618	6.11 (1.51, 17.82)	<0.001	626	7.85 (2.00, 24.70)	<0.001	7.68
Time-since-exposure window (years)							
WLM 5–14 previously		1			1		1
WLM 15–24 previously		0.47	<0.001		0.37	<0.001	0.78
WLM 25+ previously		0.29	<0.001		0.16	<0.001	0.51
Exposure rate (WL)							
0.0–0.5	209	1	0.001	233	1	0.10	1
0.5–1.0	47	1.05 (0.40, 2.80)		50	0.70 (0.28, 1.75)		0.49
1.0–3.0	123	0.47 (0.19, 1.18)		130	0.41 (0.18, 0.91)		0.37
3.0–5.0	38	0.34 (0.11, 1.01)		36	0.28 (0.09, 0.86)		0.32
5.0–15.0	88	0.31 (0.12, 0.81)		88	0.36 (0.14, 0.91)		0.17
15+	113	0.16 (0.06, 0.43)		89	0.23 (0.09, 0.61)		0.11
Attained age (years)							
<55	111	1	0.06	95	1	0.21	1
55–64	239	1.62 (0.57, 4.59)		240	1.97 (0.62, 6.20)		0.57
65–74	208	0.82 (0.27, 2.52)		229	1.13 (0.34, 3.81)		0.29
75+	60	0.19 (0.01, 2.38)		62	0.44 (0.06, 3.08)		0.09

Note. Abbreviations used: WL, working levels; WLM, working level months; ERR/100 WLM, excess relative risk per 100 WLM; CI, confidence interval.

[a] ERR/100 WLM for total WLM exposure and relative risks for time since exposure, exposure rate and attained age variables.

[b] Adjusted for sub-cohort, age at risk, calendar year at risk and duration of employment by stratification.

[c] *P* value of the test of heterogeneity of category-specific relative risks.

[d] Number of cases in the incidence analysis based on the earliest cancer diagnosis where each subject could contribute at most one cancer.

[e] BEIR VI exposure-age-concentration model with radon exposures lagged by 5 years (*2*).

[f] ERR/100 WLM for time since exposure window 5–14 years, exposure rate <0.5 WL, and attained age <55 years.

CLL leukemia and other causes of death and cancer, which were not adjusted for RDP exposures, showed that γ-ray doses did not increase the risk of any other cancer deaths or any other causes of cancer (Table 5). Although there was a positive risk estimate for bladder cancer incidence of 2.83 per Sv, it was not statistically significant ($P = 0.147$). While CLL incidence showed a positive association, with an ERR/Sv of 7.28, incidence of non-CLL leukemia gave a negative estimate. However, neither of these observations was statistically significant.

DISCUSSION

This report presents the analysis of 50 years of mortality (1950–1999) and 31 years of cancer incidence (1969–1999) in a cohort of uranium workers known to have worked for Eldorado Nuclear Ltd. and its predecessor companies sometime between 1932 and 1980. Workers had lower rates of all cancer together and separately, except for lung cancer, compared to the age- and calendar year-adjusted rates for the general Canadian male population, a likely healthy worker effect. A highly statistically significant linear dose–response relationship was found between RDP exposure and lung cancer mortality and incidence (ERR/100 WLM = 0.55, 95% CI: 0.37, 0.78 and ERR/100 WLM = 0.55, 95% CI: 0.37, 0.81, respectively). Risks were significantly different between the three principal sub-cohorts in the simple linear model, but after adjustment for effect modification by time since exposure, exposure rate and age at risk using BEIR VI report parameterization, they became more similar. The overall ERR/100 WLM of mortality and incidence in the entire cohort were 6.11 and 7.85, respectively. In the low-exposure range (lifetime cumulative exposures less than 100 WLM), risk of lung cancer was also significantly higher compared to zero exposure (right panels of Figs. 1 and 2). No other cancer site and no other cause of death were associated with RDP exposure or γ-ray doses.

One of the strongest advantages of this study is its long-term follow-up with essentially complete ascertainment for cancer incidence and mortality. The North American Association of Central Cancer Registries estimates that completeness of case ascertainment for Canadian provincial cancer registries is consistently in the range 90–95% (www.naaccr.org/). Similarly, since the registration of deaths is a legal requirement in each

TABLE 5
Excess Relative Risk Estimates and 95% Confidence Intervals for RDP Exposures and γ-Ray Dose for Various Causes of Death (1950–1999) and Cancer Incidences (1969–1999)

		RDP exposures		Gamma-ray dose	
		Mortality			
Cause of death	Number of deaths	ERR/100 WLM[a]	*P* value[b]	ERR/Sv[c]	*P* value[b]
Stomach cancer	75	−0.04	0.16	0.28	0.78
Colon cancer	82	0	0.99	0.82	0.58
Pancreatic cancer	67	−0.01	0.84	−0.29	0.44
Prostate cancer	98	−0.03	0.52	0.19	0.8
Leukemia	34	0.02	0.81	−0.29	0.82
Other cancers	113	0.06	0.51	−0.07	0.94
Diabetes mellitus	64	0	0.98	0.29	0.86
Endocrine cancer	61	−0.04	0.29	0.26	0.79
Ischaemic heart disease	1235	−0.01	0.18	0.15	0.36
Stroke	244	−0.04	0.012	−0.29	0.21
Other cardiovascular diseases	317	−0.02	0.49	0.07	0.78
Pneumonia	134	−0.01	0.61	0.68	0.25
Respiratory diseases	158	0.02	0.59	0.12	0.86
Cirrhosis of liver	60	0.03	0.77	−0.1	0.89
Digestive diseases	179	−0.03	0.33	−0.29	0.45
		Cancer incidence			
Cancer site	Number of cases[d]	ERR/100 WLM[a]	*P* value[b]	ERR/Sv[c]	*P* value[b]
Buccal cavity	50	−0.04	0.68	−0.34	0.62
Stomach cancer	69	−0.04	0.25	−0.34	0.45
Colon cancer	118	−0.04	0.4	0.31	0.59
Rectum cancer	95	0.03	0.54	−0.34	0.72
Pancreatic cancer	59	−0.03	0.74	−0.34	0.51
Prostate cancer	350	−0.01	0.77	−0.34	0.21
Bladder cancer	89	−0.04	0.55	2.83	0.15
Non-Hodgkin's lymphoma	78	0.04	0.68	−0.34	0.7
Chronic lymphocytic leukemia	22	−0.04	0.58	7.28	0.38
Leukemia, excluding CLL	31	−0.04	0.49	−0.34[e]	0.73

Note. Abbreviations used: RDP, radon decay products; ERR/100 WLM, excess relative risk per 100 WLM; CI, confidence interval; ERR/Sv, excess relative risk per sievert; CLL, chronic lymphocytic leukemia.

[a] Model adjusted for sub-cohort, age at risk, calendar year at risk and duration of employment by stratification. Gamma-ray doses were not included in the model.

[b] *P* values from the likelihood ratio test comparing nested model with and without the exposure term.

[c] Model adjusted for sub-cohort, age at risk, calendar year at risk and duration of employment by stratification. RDP exposures were not included in the model.

[d] Number of cases based on the earliest cancer diagnosis where each subject could contribute at most one cancer.

[e] Estimate may not be a maximum likelihood estimate.

Canadian province and territory, reporting of deaths is virtually complete and undercoverage is thought to be minimal. Thus underascertainment of cancer cases and deaths is unlikely and cannot account for the observed healthy worker effect. Another advantage is comparatively high rates of follow-up (*12, 26*), which were achieved by multiple internal linkages and the manual resolution of potential computer links.

Incidence and mortality data provided a complementary view of the effects of RDP exposures and γ-ray doses on the risk of cancers. While some have shown that death certificates were sufficiently accurate when evaluating lung cancer mortality (*27*), others have reported misclassification of lung cancer on death certificates to be quite prevalent and possibly related to smoking status, with lung cancer diagnosis frequently being omitted from death certificates of nonsmokers (*28*). In our study, the total number of lung cancer cases ($N = 626$) was numerically similar to the mortality analysis ($N = 618$), with 490 individuals contributing to both analyses. There were relatively few lung cancer cases and deaths among Eldorado workers before 1969 ($N = 83$), with the majority of cases and deaths occurring during the period 1969 to 1999. There were 58 cases of lung cancer for which as yet there is no death record and 78 cases with cause of death other than lung cancer; thus these represent a contribution to the incidence analysis that is independent of the mortality analysis.

Due to high fatality of lung cancer, relative risk estimates from mortality and incidence analyses should closely approximate each other. Some differences

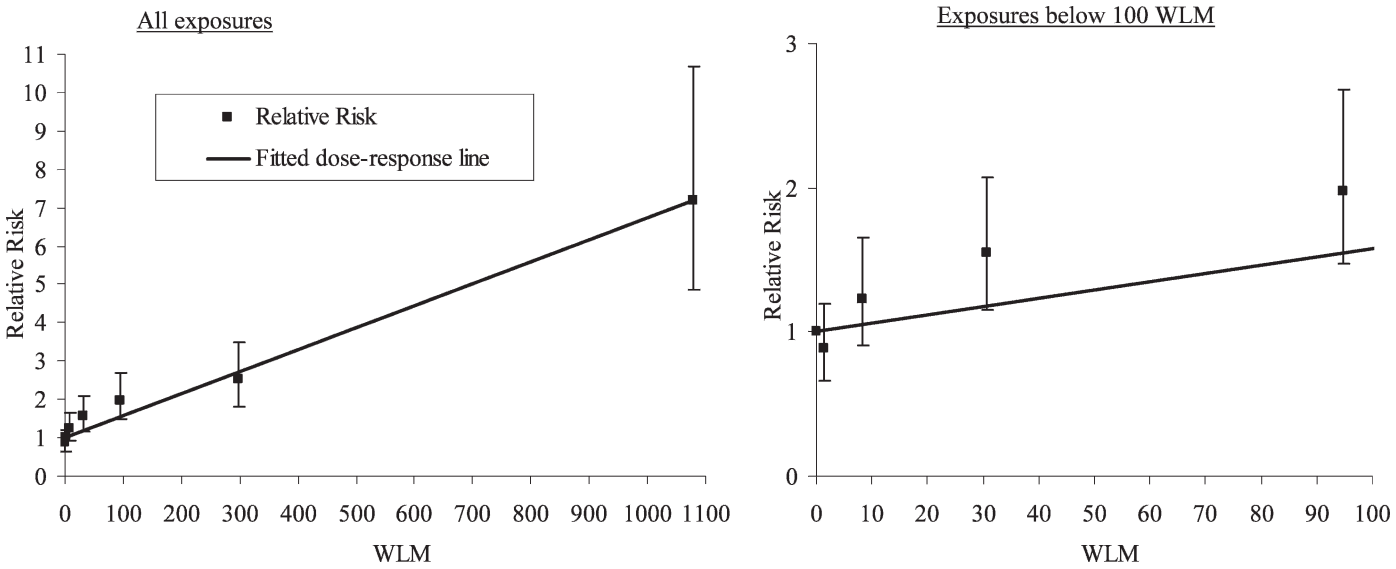

FIG. 2. Plot of the relative risk estimates of lung cancer incidence and 95% CI from the categorical analysis in Table 2 and a fitted dose–response line for males. Relative risk estimates were plotted as a function of person-year-weighted means in WLM exposure categories.

between estimates of risk based on the incidence and mortality may have a contribution from chance or are possibly due to the effects of time-dependent effect modifiers representing a different time pattern occurring in the mortality and incidence analyses, i.e., various time windows of RDP exposure while the other modifying effects have the same value.

Improvements in identifying data for Beaverlodge and Port Radium and inclusion of workers from the Port Hope refinery and processing facility and "other sites" in the analysis improved statistical power and precision of risk estimates compared with the original studies (*4, 6*). In the current study, the annual individual RDP exposures were recalculated for all Port Radium personnel and for all Beaverlodge personnel for whom no individual exposure assignments had been made during the mines' operation. Although the basis for the new calculations is sounder than that used in the earlier studies and provided far more accurate exposure estimates than the original Eldorado analyses, it must be recognized that the methods used yield good annual average results for a work group, but individual exposures could vary from the average by as much as an order of magnitude. RDP exposures from the Eldorado sites were supplemented with exposure information from early non-Eldorado Western Canadian mines and NDR data on Eldorado exposures received since 1980 and all other non-Eldorado exposures. In addition to RDP exposure, this analysis also investigated the effects of γ-ray doses on cancer mortality and incidence.

Several limitations should be borne in mind when considering the above results. Tobacco smoking is the primary cause of lung cancer, with a 10- to 20-fold relative risk for current smokers (*29–31*). For smoking to modify RDP-related risks of lung cancer it should be correlated with RDP exposure. A case-control study of the Beaverlodge cohort (*32*) suggested that smoking was not correlated with radon exposure, and, in general, occupational studies frequently show a lack of any strong correlation between occupational exposure and smoking. Even though smoking was banned at the Port Hope facility in the 1940s and 1950s and was allowed on a very limited basis thereafter and was banned in the workplace at Beaverlodge in 1975, people still smoked outside the workplace. Although smoking data were not available, we observed that smoking-related cancers other than lung cancer generally were not elevated in the cohort, suggesting that smoking was not substantially elevated relative to the general Canadian male population. A recent study of German uranium miners reported that smoking was not a major independent risk factor of lung cancer and that RDP risk estimates with and without adjustment for smoking were similar (*33*).

Other sources of ionizing radiation and other carcinogenic occupational exposures received at Eldorado or other workplaces also require consideration. Beaverlodge ore was relatively clean with minimal amounts of other carcinogens. Port Radium ore contained many elements, including arsenic and cobalt, but no useful exposure data were available. Arsenic, a known human carcinogen (*34*), was recently shown to increase lung cancer among uranium miners (*35*). However, the correlation between arsenic and RDP is unknown. In addition to ore, Port Hope workers were exposed to processing chemicals and a variety of uranium compounds at higher concentration and of greater solubility than that found in the ore. Some Port Hope workers were also exposed to radium compounds, uranium metal

and some enriched uranium. Duport (*36*) estimated that γ radiation contributed 25% of the miners' effective dose and so may play a role in lung cancer risk. However, there was no meaningful relationship between risk of lung cancer death and γ-ray dose in our analysis. No data were available for the cohort members on any other potential risk factors and, again, the interpretation for such factors would have the same considerations as those given for smoking.

Measurement errors in exposure estimation almost certainly decreased with calendar time; thus the Port Radium cohort had greater measurement errors than the Beaverlodge cohort, and recent workers had lower mean errors than earlier workers. Some potential RDP exposures in other mines or workplaces may have been underascertained. A further consideration is that residential radon exposure likely had a greater relative contribution to total exposure in recent times when occupational exposures were lower. The impact of such measurement error depends on a number of factors, in particular, the quantitative nature of the error and the risk function that has been considered. However, if there is no correlation between domestic exposure and total occupational exposure, the risk estimates would be unbiased.

Our risk estimates were similar in magnitude to the estimates of the BEIR VI report based on the pooled analysis of 11 underground miners studies (*2*) and to more recent studies of uranium miners (*11, 37*). The present analysis provides further evidence of the importance of effect modifiers in the relationship between RDP exposure and lung cancer risk and suggests that the BEIR VI exposure-age-concentration model performs well in an essentially independent data set. While the estimates for time since exposure and for exposure rate are similar between the present study and the BEIR VI estimates for both lung cancer mortality and incidence, the estimates of risk by age at risk in the lung cancer incidence analysis differed somewhat from the BEIR VI estimates and from the mortality analysis. These differences could be due to comparatively small number of lung cancer cases below age 55 years ($N = 95$) or to differences in age effect in incidence and mortality analyses. When a reference category was changed to include all those below age 60 years, we observed a more gradual decrease in risk of lung cancer incidence with estimated relative risks for those aged 60–65, 65–69 and 70+ years at 0.99, 0.98 and 0.32, respectively.

The original analysis of workers of the Beaverlodge uranium mine was based on 65 deaths from lung cancer (*5*) with an ERR/100 WLM = 3.25. The current study is based on 279 deaths in Beaverlodge miners with an estimated ERR/100 WLM = 0.96 in the simple linear model and 7.55 (95% CI: 1.58, 29.60) from the model adjusted for effect modification by time since exposure, exposure rate and age at risk using BEIR VI report parameterization (ERR/100 WLM = 6.87, 95% CI: 1.46, 24.84 for lung cancer incidence). The decrease in the magnitude of risk compared to Howe *et al.* (*5*) most likely reflects the higher and more accurate mean exposure (195 and 81 WLM, respectively, among those with non-zero exposures).

Port Radium workers were exposed to significantly higher levels of RDPs than the Beaverlodge workers. Compared to the original analysis where an estimated ERR/100 WLM based on 57 deaths was 0.27 (*6*), we observed a somewhat higher risk in the current analysis of 230 deaths with an estimate of 0.37. In previous analyses, risk estimates for Beaverlodge and Port Radium differed by an order of magnitude (*5, 6*), but in the current analysis, the estimates for the two cohorts were closer together, had narrower 95% confidence intervals, and moved closer to the mid-range of the estimate from the pooled analysis of the 11 miner cohorts (ERR/100 WLM = 0.49, 95% CI: 0.2, 1.0) (*2, 7*). These differences likely reflect the large improvements in the data quality and radiation exposure estimates.

Workers in the Port Hope sub-cohort had significantly lower RDP exposures and consequently experienced lower risks of lung cancer (increased but non-significant for both incidence and mortality).

The lack of correlation of RDP exposure with the risk of other cancer deaths in the Eldorado cohort is consistent with the BEIR VI report (*38*) and recent miner updates (*20, 39–41*). Likewise, the absence of any correlation of RDP exposure with non-cancer causes of death in the Eldorado cohort is consistent with other studies (*2, 40, 42–44*). More recent studies showed some evidence of radon-associated increases in risk of extrapulmonary cancers (*44, 45*) and cerebrovascular diseases (*46*), but cautious interpretation is warranted due to lack of control of possible confounding by cardiovascular risk factors.

This cohort presented a unique opportunity to investigate the effects of RDP exposure and γ-ray doses in the same subjects. In our cohort, RDP exposures and γ-ray doses generally were not correlated (Pearson's $r = 0.18$) except for the Port Hope site, where they were strongly correlated (Pearson's $r = 0.93$). The internal analysis to assess the relationship between whole-body γ-ray dose and lung cancer mortality and incidence detected no effect. Similarly, there was no meaningful evidence of any association between whole-body γ-ray dose and risk of any other cancers or any other causes of death, which was consistent with other studies (*20, 26, 39–41*). Comparatively high doses of γ rays can increase the risk of a number of cancers (*47*), with leukemia being particularly sensitive to such exposure. However, in the present context, the mean γ-ray dose of subjects in the Eldorado uranium workers cohort was fairly low (dose = 52.2 mSv for male subjects), so it is certainly possible that the study lacked statistical power to detect an effect

of γ-ray dose. The risk models published by the ICRP (*48*) and UNSCEAR (*47, 49*) would be appropriate for predicting risk of whole-body γ-ray dose and are not contradicted by the results of the present study.

Conclusions

This study reported a deficit in all causes of death and all cancers (deaths and cases) but a statistically significant excess of lung cancer compared to the general Canadian male population. We found a statistically significant increased risk of lung cancer with RDP exposure but no evidence of an increase in any other cancers or other causes of death. The risk of lung cancer in the low-dose range (lifetime cumulative exposures less than 100 WLM) was significantly higher compared to zero exposure in both the mortality and incidence analyses. The evidence from this study on the effects of low exposures and exposure rates is important to understand the long-term health effects of exposures experienced by current workers as well as to understand and address the health risks of exposures to residential radon. About 30% of the Eldorado cohort had died by the end of the current follow-up. Future mortality and cancer incidence updates and joint analysis with other uranium miner cohorts should improve the statistical power of analyses and expand our knowledge of the effects of uranium mining, milling and processing on the health of those employed in these occupations. This update is consistent with our existing understanding of RDP risk and supports current radiation protection programs.

SUPPLEMENTARY INFORMATION

Supplementary Table S1. Standardized mortality ratios (SMR) for various causes of death and 95% confidence intervals compared to Canadian national mortality rates for males (1950–1999). **Supplementary Table S2.** Standardized incidence ratios (SIR) for various cancers and 95% confidence intervals compared to Canadian national incidence rates for males (1969–1999). **Supplementary Table S3.** Relative risks of lung cancer mortality (1950–1999) and 95% confidence intervals by categories of cumulative exposure (WLM), separately for sub-cohorts of the Eldorado cohort. http://dx.doi.org/RR2237.1.S1

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REFERENCES

1. M. Al-Zoughool and D. Krewski, Health effects of radon: A review of the literature. *Int. J. Radiat. Biol.* **85**, 57–69 (2009).
2. National Research Council, Committee on Health Risks of Exposure to Radon, *Health Effects of Exposure to Radon (BEIR VI)*. National Academy Press, Washington, DC, 1999.
3. C. G. Collier, J. C. Strong, J. A. Humphreys, N. Timpson, S. T. Baker, T. Eldred, L. Cobb, D. Papworth and R. Haylock, Carcinogenicity of radon/radon decay product inhalation in rats—effect of dose, dose rate and unattached fraction. *Int. J. Radiat. Biol.* **81**, 631–647 (2005).
4. G. R. Howe, R. C. Nair, H. B. Newcombe, A. B. Miller and J. D. Abbatt, Lung cancer mortality (1950–80) in relation to radon daughter exposure in a cohort of workers at the Eldorado Beaverlodge uranium mine. *J. Natl. Cancer Inst.* **77**, 357–362 (1986).
5. G. R. Howe and R. H. Stager, Risk of lung cancer mortality after exposure to radon decay products in the Beaverlodge cohort based on revised exposure estimates. *Radiat. Res.* **146**, 37–42 (1996).
6. G. R. Howe, R. C. Nair, H. B. Newcombe, A. B. Miller, J. D. Burch and J. D. Abbatt, Lung cancer mortality (1950–80) in relation to radon daughter exposure in a cohort of workers at the Eldorado Port Radium uranium mine: possible modification of risk by exposure rate. *J. Natl. Cancer Inst.* **79**, 1255–1260 (1987).
7. J. H. Lubin, J. D. Boice, Jr., C. Edling, R. W. Hornung, G. R. Howe, E. Kunz, R. A. Kusiak, H. I. Morrison and E. P. Radford, Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J. Natl. Cancer Inst.* **87**, 817–827 (1995).
8. D. Laurier, M. Tirmarche, N. Mitton, M. Valenty, P. Richard, S. Poveda, J. M. Gelas and B. Quesne, An update of cancer mortality among the French cohort of uranium miners: extended follow-up and new source of data for causes of death. *Eur. J. Epidemiol.* **19**, 139–146 (2004).
9. A. Rogel, D. Laurier, M. Tirmarche and B. Quesne, Lung cancer risk in the French cohort of uranium miners. *J. Radiol. Prot.* **22**, A101–A106 (2002).
10. I. Bruske-Hohlfeld, A. S. Rosario, G. Wolke, J. Heinrich, M. Kreuzer, L. Kreienbrock and H. E. Wichmann, Lung cancer risk among former uranium miners of the WISMUT Company in Germany. *Health Phys.* **90**, 208–216 (2006).
11. L. Walsh, A. Tschense, M. Schnelzer, F. Dufey, B. Grosche and M. Kreuzer, The influence of radon exposures on lung cancer mortality in German uranium miners, 1946–2003. *Radiat. Res.* **173**, 79–90 (2010).
12. B. Grosche, M. Kreuzer, M. Kreisheimer, M. Schnelzer and A. Tschense, Lung cancer risk among German male uranium

miners: a cohort study, 1946–1998. *Br. J. Cancer* **95**, 1280–1287 (2006).

13. L. Tomasek, Czech miner studies of lung cancer risk from radon. *J. Radiol. Prot.* **22**, A107–A112 (2002).
14. L. Tomasek and H. Zarska, Lung cancer risk among Czech tin and uranium miners—comparison of lifetime detriment. *Neoplasma* **51**, 255–260 (2004).
15. M. K. Schubauer-Berigan, R. D. Daniels and L. E. Pinkerton, Radon exposure and mortality among white and American Indian uranium miners: an update of the Colorado Plateau cohort. *Am. J. Epidemiol.* **169**, 718–730 (2009).
16. P. J. Villeneuve, H. I. Morrison and R. Lane, Radon and lung cancer risk: An extension of the mortality follow-up of the Newfoundland fluorspar cohort. *Health Phys.* **92**, 157–169 (2007).
17. G. R. Howe, Use of computerized record linkage in cohort studies. *Epidemiol. Rev.* **20**, 112–121 (1998).
18. M. Westland, Summary Report of the Eldorado Nuclear Cohort Study: Internal Linkage, "Alive" Follow-up, 1950–2000 Mortality Linkage, 1969–2000 Cancer Incidence Linkage. RSP-0188, Canadian Nuclear Safety Commission, Ottawa, 2004. [Available online at http://www.cnsc-ccsn.gc.ca/eng/about/researchsupport/reportabstracts/]
19. WHO, *International Classification of Diseases, Ninth Revision (ICD-9)*. World Health Organization, Geneva, 1998.
20. M. Mohner, M. Lindtner, H. Otten and H. G. Gille, Leukemia and exposure to ionizing radiation among German uranium miners. *Am. J. Ind. Med.* **49**, 238–248 (2006).
21. National Dose Registry, 2006 Report on Occupational Radiation Exposures in Canada. HC Pub. 5904, Ministry of Health Canada, 2007. [Available online at http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/occup-travail/2006-report-rapport-eng.pdf]
22. J. P. Ashmore, Creation of Combined Dose Records for the Cameco Study Cohort. RSP-0187, Canadian Nuclear Safety Commission, 2005. [Available online at http://www.cnsc-ccsn.gc.ca/eng/about/researchsupport/reportabstracts/]
23. G. R. Howe, A. M. Chiarelli and J. P. Lindsay, Components and modifiers of the healthy worker effect: evidence from three occupational cohorts and implications for industrial compensation. *Am. J. Epidemiol.* **128**, 1364–1375 (1988).
24. N. E. Breslow and N. E. Day, *Statistical Methods in Cancer Research. Volume 2 – The Design and Analysis of Cohort Studies*. International Agency for Research on Cancer, Lyon, 1987.
25. D. L. Preston, J. H. Lubin, D. A. Pierce and M. E. McConney, *EPICURE User's Guide*. Hirosoft International Corporation, Seattle, WA, 1993.
26. M. Kreuzer, M. Kreisheimer, M. Kandel, M. Schnelzer, A. Tschense and B. Grosche, Mortality from cardiovascular diseases in the German uranium miners cohort study, 1946–1998. *Radiat. Environ. Biophys.* **45**, 159–166 (2006).
27. V. P. Doria-Rose and P. M. Marcus, Death certificates provide an adequate source of cause of death information when evaluating lung cancer mortality: an example from the Mayo Lung Project. *Lung Cancer* **63**, 295–300 (2009).
28. P. N. Lee, Comparison of autopsy, clinical and death certificate diagnosis with particular reference to lung cancer. A review of the published data. *APMIS Suppl.* **45**, 1–42 (1994).
29. IARC, *Tobacco Smoking*. Monographs on the Evaluation of Carcinogenic Risks to Humans, World Health Organization, International Agency for Research on Cancer, Lyon, 1986.
30. IARC, *Tobacco Smoke and Involuntary Smoking*. Monographs on the Evaluation of Carcinogenic Risks to Humans, World Health Organization, International Agency for Research on Cancer, Lyon, France, 2002.
31. R. Doll and A. B. Hill, The mortality of doctors in relation to their smoking habits: a preliminary report. 1954. *Br. Med. J.* **328**, 1529–1533 (2004).
32. K. A. L'Abbe, G. R. Howe, J. D. Burch, A. B. Miller, J. Abbatt, P. Band, W. Choi, J. Du and J. Feather, Radon exposure, cigarette smoking, and other mining experience in the Beaverlodge uranium miners cohort. *Health Phys.* **60**, 489–495 (1991).
33. M. Schnelzer, G. P. Hammer, M. Kreuzer, A. Tschense and B. Grosche, Accounting for smoking in the radon-related lung cancer risk among German uranium miners: results of a nested case-control study. *Health Phys.* **98**, 20–28 (2010).
34. IARC, *Some Metals and Metallic Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, World Health Organization, International Agency for Research on Cancer, Lyon, 1980.
35. D. Taeger, G. Johnen, T. Wiethege, S. Tapio, M. Mohner, H. Wesch, A. Tannapfel, K. M. Muller and T. Bruning, Major histopathological patterns of lung cancer related to arsenic exposure in German uranium miners. *Int. Arch. Occup. Environ. Health* **82**, 867–875 (2009).
36. P. Duport, Is the radon risk overestimated? Neglected doses in the estimation of the risk of lung cancer in uranium underground miners. *Radiat. Prot. Dosimetry* **98**, 329–338 (2002).
37. B. Vacquier, A. Rogel, K. Leuraud, S. Caer, A. Acker and D. Laurier, Radon-associated lung cancer risk among French uranium miners: modifying factors of the exposure–risk relationship. *Radiat. Environ. Biophys.* **48**, 1–9 (2009).
38. S. C. Darby, E. Whitley, G. R. Howe, S. J. Hutchings, R. A. Kusiak, J. H. Lubin, H. I. Morrison, M. Tirmarche and L. Tomasek, Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. *J. Natl. Cancer Inst.* **87**, 378–384 (1995).
39. V. Rericha, M. Kulich, R. Rericha, D. L. Shore and D. P. Sandler, Incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners: a case-cohort study. *Environ. Health Perspect.* **114**, 818–822 (2006).
40. B. Vacquier, S. Caer, A. Rogel, M. Feurprier, M. Tirmarche, C. Luccioni, B. Quesne, A. Acker and D. Laurier, Mortality risk in the French cohort of uranium miners: extended follow-up 1946–1999. *Occup. Environ. Med.* **65**, 597–604 (2008).
41. D. Laurier, M. Valenty and M. Tirmarche, Radon exposure and the risk of leukemia: a review of epidemiological studies. *Health Phys.* **81**, 272–288 (2001).
42. P. J. Villeneuve and H. I. Morrison, Coronary heart disease mortality among Newfoundland fluorspar miners. *Scand. J. Work. Environ. Health* **23**, 221–226 (1997).
43. P. J. Villeneuve, R. S. Lane and H. I. Morrison, Coronary heart disease mortality and radon exposure in the Newfoundland fluorspar miners' cohort, 1950–2001. *Radiat. Environ. Biophys.* **46**, 291–296 (2007).
44. M. Kreuzer, B. Grosche, M. Schnelzer, A. Tschense, F. Dufey and L. Walsh, Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: follow-up 1946–2003. *Radiat. Environ. Biophys.* **49**, 177–185 (2010).
45. M. Kreuzer, L. Walsh, M. Schnelzer, A. Tschense and B. Grosche, Radon and risk of extrapulmonary cancers: results of the German uranium miners' cohort study, 1960–2003. *Br. J. Cancer* **99**, 1946–1953 (2008).
46. S. Nusinovici, B. Vacquier, K. Leuraud, C. Metz-Flamant, S. Caer-Lorho, A. Acker and D. Laurier, Mortality from circulatory system diseases and low-level radon exposure in the French cohort study of uranium miners, 1946–1999. *Scand. J. Work Environ. Health* **36**, 373–383 (2010).
47. UNSCEAR, *Sources and Effects of Ionizing Radiation, Vol. II: Effects*. United Nations, New York, 2000.
48. ICRP, *Recommendations of the International Commission on Radiological Protection. Annals of the ICRP*, Vol. 37, No. 2–4, Pergamon Press, Oxford, 2008.
49. UNSCEAR, *Sources and Effects of Ionizing Radiation*, Vol. I. United Nations, New York, 2008.