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Original Article

Association between exposures to radon and γ-ray radiation and histologic type of lung cancer in Eldorado uranium mining and milling workers from Canada

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BACKGROUND: The authors assessed the association between radon decay products (RDP) exposure and histologic types of incident lung cancer in a cohort of 16,752 (91.6% male) Eldorado uranium workers who were first employed from 1932 to 1980 and were followed through 1969–1999. **METHODS:** Substantially revised identifying information and RDP exposures were obtained on workers from the Port Radium and Beaverlodge uranium mines and from the Port Hope radium and uranium refinery and processing facility in Canada. Poisson regression was conducted using the National Research Council's Biological Effects of Ionizing Radiation (BEIR) VI–type models to estimate the risks of lung cancer by histologic type from RDP exposures and γ-ray doses. **RESULTS:** Lung cancer incidence was significantly higher in workers compared with the general Canadian male population. Radiation risks of lung cancer for all histologic types (n = 594; 34% squamous cell, 16% small cell, 17% adenocarcinoma) increased with increasing RDP exposure, with no indication of curvature in the dose response (excess relative risk per 100 working level months = 0.61; 95% confidence interval, 0.39–0.91). Radiation risks did not differ by histologic type (p = .144). The best-fitting BEIR VI–type model included adjustments for the significant modifying effects of time since exposure, exposure rate, and attained age. The addition of γ-ray doses to the model with RDP exposures improved the model fit, but the risk estimates remained unchanged. **CONCLUSIONS:** The first analysis of radiation risks of lung cancer histologic types in the Eldorado cohort supported the use of BEIR VI–type models to predict the future risk of histologic types of lung cancer from past and current RDP exposures. ***Cancer*** **2022;128:3204-3216**.

LAY SUMMARY:

- Lung cancer survival depends strongly on the cell type of lung cancer.
- The best survival rates are for patients who have the *adenocarcinoma* type.
- This study included 16,752 Eldorado uranium workers who were exposed to radon and γ-ray radiation during 1932–1980, were alive in 1969, and were followed for the development of new lung cancer during 1969–1999.
- One third of all lung cancers were of the *squamous cell* type, whereas the *adenocarcinoma* and *small cell* types accounted for less than 20% each.
- Radiation risks of lung cancer among men increased significantly with increasing radon exposure for all cell types, with the highest risks estimated for *small cell* and *squamous cell* lung cancers.

KEYWORDS: adenocarcinoma, histologic type, lung carcinoma, radiation, radon decay products, small cell, squamous cell.

INTRODUCTION

Lung cancer is the most commonly diagnosed and leading cause of cancer death in Canada.[1] Age-adjusted rates of incident lung cancer cases decreased in the last 20 years for men and in the last 12 years for women, whereas 5-year survival rates are still low (19%) compared with other cancers. Survival strongly depends on lung cancer histologic type, with the majority of studies reporting the highest survival rate for lung adenocarcinomas.[2,3] Adenocarcinoma is also the most common histologic type diagnosed in Canada, accounting for 48% of specified cases, followed by squamous cell (20%), small cell (12%), and other types (20%).[1] The distribution of cases by histologic type is mostly similar between sexes.

Epidemiological studies, primarily of underground miners, demonstrate that radon decay products (RDP) exposures significantly increase lung cancer risk.[4,5] Lubin et al.[6] pooled the original data from 11 studies of radon-exposed underground miners and developed risk models that became the basis for the National Research Council's *Biological Effects of Ionizing Radiation (BEIR) VI* report.[5] However, the report did not estimate radiation risks for incident lung cancers or by histologic type. Since the BEIR VI report, several new and updated studies of radon-exposed uranium miners have reported

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significantly higher radiation risks for squamous cell and small cell carcinomas than for other histologic types.[7–10] Among workers occupationally exposed to radiation, the most commonly reported histologic type is squamous cell carcinoma, with adenocarcinomas accounting for a much smaller proportion of all cases (e.g., 43% and 23%, respectively, in German Wismut uranium miners and 31% and 20%, respectively, in Ontario uranium miners from Canada).[7,8,11,12]

The biggest challenge of conducting research in occupationally exposed workers is the reliance on death certificates, which do not report cancer histology. Therefore, it is important to analyze incidence data, but only a few studies have done so to date.[7–10] We previously reported statistically significant increased risks of lung cancer incidence and mortality in Eldorado uranium workers who were first employed between 1932 and 1980[13] and nonstatistically significant increased risks of lung cancer incidence and mortality in an updated cohort of Port Hope uranium workers.[14] We used the data from those studies to examine lung cancer incidence (1969–1999) and differences in radiation risks by histologic type in a cohort of 16,752 Eldorado uranium workers.

MATERIALS AND METHODS

Cohort

We previously described the methods used to assemble the Eldorado cohort from the personnel records of Eldorado Nuclear Limited.[13] Briefly, eligible workers were first employed at one of Eldorado's facilities from 1932 to 1980, had last contact after 1940, were alive at the start of incidence follow-up in 1969, and were employed at ages 15 to 75 years. We assigned subcohorts based on where the worker spent the longest time working for Eldorado (Port Radium, Beaverlodge, Port Hope, or *other sites*, which included head office, aviation, research and development, and exploration). The current analysis includes 3000 Port Hope facility workers with updated exposure information from a recently updated study.[14] Previous analyses of the Eldorado cohort included a slightly different set of 3003 Port Hope workers.[13] We conducted the study in accordance with accepted ethical practices with ethical approval from Health Canada's Research Ethics Board and Institutional Review Board Services.

Record linkage

Figure 1 shows a STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) flow diagram of sample recruitment. Briefly, after eliminating duplicates and invalid records, the combined Eldorado nominal roll contained 19,855 workers and was linked to the Canadian Mortality Data Base (CMDB) from 1940 to 1999 through probabilistic record linkage using given name, surname; day, month, and year of birth; and other available data.[15] The CMDB contains information on deaths from 1940 to 1949 and cause of death information since 1950.

We conducted *alive* follow-up of the nominal roll file linking to the Historic Tax Summary file (1984–2000) by using Social Insurance Numbers.[13] Various sources were used to ascertain the vital status of 15,548 individuals (78.3%), including 41.4% who were confirmed alive at the end of follow-up (1999), 6.8% who were confirmed alive from 1984 to 1998, and 30% who were confirmed dead. The 4307 individuals (21.7%) without a vital status had their termination date at work recorded as the last date alive. We further excluded 2195 individuals (11.1%) who were missing critical information (missing information on sex or birth year, no occupational record, no exposure data, an out-of-range age of employment [not within 15–75 years], age 100 years with no death recorded, last contact before 1940, and recorded exposure after recorded death). In contrast to the previous analysis of this cohort,[13] we excluded 11 workers who died before the start of mortality follow-up in 1950. We then linked the cohort to the Canadian Cancer Data Base (CCDB) from 1969 to 1999 through probabilistic linkage.[15] This database contains records of all cancer cases diagnosed in Canada among people who resided in a province or territory at the time of diagnosis and voluntarily reported cases of Canadian residents diagnosed in the United States since 1969. We excluded workers who died before the start of incidence follow-up in 1969 (*death clearance*; $n = 886$) and 11 workers who were diagnosed with cancer before their first year of work. The final incidence cohort included 16,752 workers.

Outcomes

Information on incident cancer diagnoses in the CCDB was re-coded from the original International Classification of Diseases code used at the time of diagnosis to the *International Classification of Diseases,* Ninth Revision.[16] Greater than 82% of the lung cancers in the CCDB were histologically or cytologically confirmed. We used *International Classification of Diseases for Oncology*, second edition, codes[17] to subdivide them into four histologic types: squamous cell, small cell, adenocarcinoma, and other types (see Table S1).

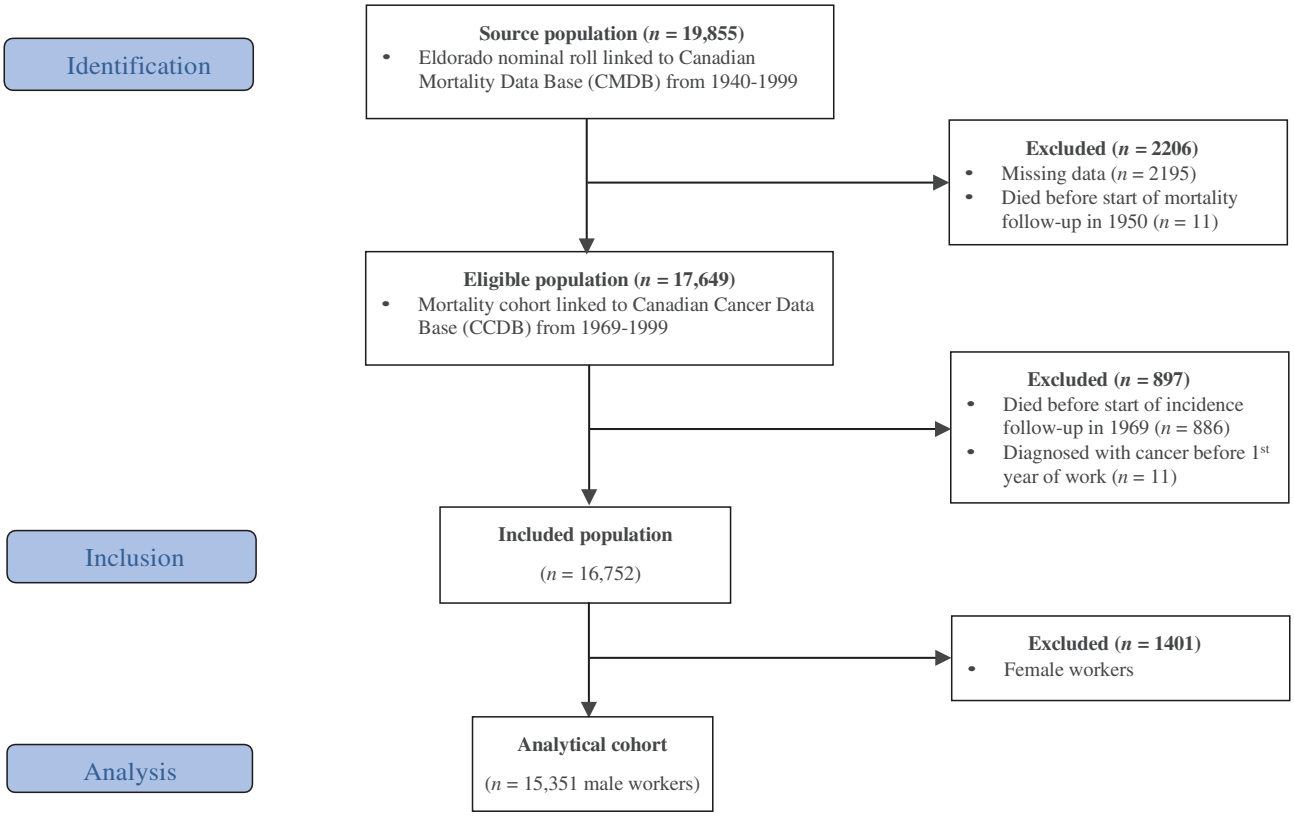

Figure 1. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) flow diagram.

Morphology codes were available for all but three lung cancer cases, which were included in the category *other types*.

EXPOSURES

We provided detailed descriptions of the Eldorado cohort's exposure methods elsewhere.[13,14] Briefly, we measured RDP concentrations in workplace air in working levels (WL), where 1 WL is the RDP concentration per liter of air that would release 1.3×10^5 megaelectronvolts (MeV) of potential α-particle energy. Occupational RDP exposure is the product of time in the workplace and the RDP concentration in workplace air, measured in working level months (WLMs), where 1 WLM is equivalent to 1 working month (170 hours) in a concentration of 1 WL.

Workers were initially exposed to radon and later to RDP. We based the original RDP estimates on quantities of radium present 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. The most important radiation protection measure in uranium mining was the introduction of mechanical ventilation systems and regular radon progeny measurements in work areas and/or individuals as part of regulatory requirements. These were the main factors reducing radiation exposures in the Eldorado cohort over time. Detailed information about this is provided in the original publications.[13,14]

In addition to RDP exposures, we had information on individual γ-ray doses for all workers. Many Eldorado workers worked for other early western Canadian mines, and many worked for other companies with radiation exposure potential after leaving Eldorado. We determined workers' non-Eldorado radiation exposures from 1951 through 1999 by linking the nominal roll to the Canadian National Dose Registry.[18]

We estimated total lung doses from RDP exposures and γ-ray doses by converting RDP exposure in terms of WLM to lung-absorbed dose by multiplying by 8.19 milligrays (mGy) per WLM. This absorbed dose conversion factor was based on the reference values from

International Commission on Radiological Protection (ICRP) Publication 137[19] and additional assumptions:[20] an equilibrium factor of 0.4; unattached, nucleated, and accumulation fractions of 0.08, 0.184, and 0.736, respectively; and particle sizes for unattached, nucleated, and accumulation modes of 0.001, 0.06, and 0.5 μm activity median aerodynamic diameter, respectively. The total dose to the lungs was the sum of γ-ray doses and absorbed lung doses from RDP exposures.

Statistical analysis

Each worker contributed person-years at risk from the later of the *date of hire* or the *start date of follow-up* (January 1, 1969). The *exit date* was defined as December 31, 1999, the date of cancer diagnosis or death, or the last date known alive (i.e., the date of last employment or contact), whichever occurred first. Several confounding variables were considered. Job type, a proxy for socioeconomic status, was not associated with lung cancer and so was not included in the final statistical models. The summary person-year experience was cross-classified by 5-year categories of attained age (ages 15–19, 20–24… 85–100 years) and calendar year at risk (1969–1974… 1995–1999). We further stratified the person-year table by subcohort (Port Radium, Beaverlodge, Port Hope, other sites), total duration of employment (<6 months; from 6 months to <1 year; 1–4, 5–9, 10–19, or 20–29 years; and from 30 to ≥60 years), time since first exposure (0–19, 20–29, 30–39, or 40–70 years), histologic type of lung cancer (squamous cell, small cell, adenocarcinoma, all other histologic types, and individuals without noncancer), 30 cumulative RDP exposure categories, and 25 cumulative γ-ray dose categories.

For dose–response analyses, we lagged RDP exposures and γ-ray doses by 5 years and used the person-year weighted mean dose in each cross-classified cell in the regression analyses. First, we calculated expected lung cancer cases using Canadian population-based sex-specific, age-specific, and calendar year-specific cancer incidence rates from 1969 to 1999 (R. Semenciw, personal communication, 2006). We used the observed and expected lung cancer cases to calculate standardized incidence ratios (SIRs). We compared SIRs by histologic type from 1985 to 1999 because the CCDB started collecting information on histologic types only in 1985. Confidence intervals (CIs) for the SIR and *p* values were based on treating the observed numbers of cancer cases as Poisson variables.[21]

Next, we conducted internal comparisons (i.e., with no reference to an external general population) using Poisson regression.[21] The relative risk (RR) was calculated as:

$$\text{Relative Risk} = 1.0 + (\beta \text{X}) \exp\left(\sum_i \gamma_i z_i\right) \quad \text{(Equation 1)}$$

where X represents RDP exposure, γ-ray dose, or total absorbed lung dose; z_i are potential modifying factors; and β and γ_i are coefficients estimated using maximum likelihood techniques. β coefficient (β) refers to the excess RR (ERR). Adding 1.0 to the ERR provides the RR per 100 WLM for RDP exposure and per 1 sievert for γ-ray doses.

When we investigated γ-ray dose as a potential risk factor, we entered it into the model simultaneously with RDP exposure (a model with two linear terms). In addition to examining a linear dose response, we also examined linear-quadratic, linear-exponential, and power models. Best fitting models were chosen by comparing model Akaike Information Criterion (AIC) for different models.[22] We considered models that were >2 AIC units lower than the comparison model significantly better. We estimated regression parameters and CIs around these point estimates and *p* values using the maximum likelihood method and EPICURE software.[23] All statistical tests were two-sided.

Effect modifiers of the dose response

We investigated modifying effects of various factors using the BEIR VI Committee *exposure-age-concentration* model[5]:

$$\text{RR} = 1.0 + \beta * (w_{5-14} + \theta_{15-24} w_{15-24} + \theta_{\geq 25} w_{\geq 25}) \exp(\varphi_{\text{attained age}}, \gamma_{\text{exposure rate}}) \quad \text{(Equation 2)}$$

where RDP exposure is partitioned into time windows (WLM 0–5, 5–14, 15–24, and ≥25 years previously); and φ and γ represent estimates of modifications to the dose response by categories of attained age and exposure rate.

We also examined the BEIR VI *exposure-age-duration* model:

$$\text{RR} = 1.0 + \beta * (w_{5-14} + \theta_{15-24} w_{15-24} + \theta_{\geq 25} w_{\geq 25}) \exp(\varphi_{\text{attained age}}, \gamma_{\text{exposure duration}}) \quad \text{(Equation 3)}$$

where γ represents estimates of modifications to the dose response by categories of exposure duration.

RESULTS

Demographic characteristics

Table 1 presents results for both men and women; however, we restricted our main analyses to men (N = 15,351; 91.6%) because there were relatively few

TABLE 1. Basic Characteristics of the Eldorado Incidence Cohort, 1969–1999

Characteristic	No. of men (%)	No. of females (%)
Total	15,351 (91.6)	1401 (8.4)
Subcohort		
Port Radium	2677 (17.4)	246 (17.6)
Beaverlodge	9233 (60.1)	551 (39.3)
Port Hope	2411 (15.7)	337 (24.1)
Other sites	1030 (6.7)	267 (19.1)
Birth cohort		
1876–1910	933 (6.1)	45 (3.2)
1910–1919	1521 (9.9)	96 (6.8)
1920–1929	3604 (23.5)	265 (18.9)
1930–1939	3555 (23.2)	277 (19.8)
1940–1949	2529 (16.5)	249 (17.8)
1950–1959	2753 (18.0)	361 (25.7)
1960–1965	456 (3.0)	108 (7.7)
Year first employed		
1933–1939	43 (0.3)	0 (0.0)
1940–1949	2010 (13.1)	196 (14.0)
1950–1959	5725 (37.3)	351 (25.0)
1960–1969	2612 (17.0)	164 (11.7)
1970–1981	4961 (32.3)	690 (49.3)
Total person-years	367,253	34,646
Cumulative RDP exposure: Mean ± SD [range], WLM[a]	106.14 ± 239.92 [0.00–2727.70]	3.72 ± 9.34 [0.00–67.60]
Port Radium	230.02 ± 381.17 [0.00–2727.70]	1.87 ± 10.82 [0.00–67.60]
Beaverlodge	81.11 ± 47.35 [0.00–1616.80]	0.93 ± 2.55 [0.00–16.78]
Port Hope	18.74 ± 50.42 [0.00–590.32]	7.36 ± 11.81 [0.00–62.7])
Other sites	5.69 ± 40.81 [0.00–984.23]	0.07 ± 0.25 [0.00–1.70]
Cumulative γ-ray dose: Mean ± SD [range], mSv[b]	62.39 ± 163.13 [0.00–2920.90]	26.01 ± 69.46 [0.00–619.84]
Port Radium	49.89 ± 91.67 [0.00–1076.10]	17.51 ± 99.26 [0.00–619.84]
Beaverlodge	32.31 ± 42.53 [0.00–393.10]	1.55 ± 3.58 [0.00–22.19]
Port Hope	169.00 ± 331.11 [0.00–2920.90]	53.28 ± 83.95 [0.00–464.74]
Other sites	17.09 ± 36.75 [0.00–250.32]	1.57 ± 3.84 [0.00–30.94]
Cumulative total dose to the lung: Mean ± SD [range], mSv[b]	931.65 ± 1990.90 [0.00–22,680.00]	56.49 ± 143.14 [0.00–1173.50]

Abbreviations: mSv, millisieverts; RDP, radon decay products; SD, standard deviation; WLM, working level months.
[a]Weighted by person-years and lagged by 5 years.
[b]Weighted by person-years and lagged by 5 years.

women in the cohort and their exposures were low. Male workers accrued 367,253 person-years of follow-up from 1969–1999. Mean cumulative RDP exposure and γ-ray doses were 106.14 WLM and 62.39 millisieverts, respectively. Port Radium workers had the highest mean cumulative RDP exposures, whereas Port Hope workers had the highest mean cumulative γ-ray doses. Table 2 presents the distribution of incident lung cancers by histologic type and subcohort in men (distribution for the full cohort [men and women] is included in Table S2). The distribution of histologic types in men differed significantly by subcohort ($p = .02$; χ^2 test). Port Radium and Beaverlodge workers had higher proportions of squamous cell and small cell histologic types compared with Port Hope workers (Figure 1, Table 1).

Comparison with the general population

Overall, male uranium workers had significantly higher lung cancer incidence compared with the general Canadian male population (Table 3) (SIR, 1.16; 95% CI, 1.07–1.26). Female workers had higher observed number of lung cancer cases ($n = 26$) compared with the expected number based on rates in the general female population (SIR, 1.45; 95% CI, 0.89–2.01; not shown). SIRs for the full cohort (men and women) are included in Table S3. SIRs differed by subcohort, with the highest SIRs estimated for Port Radium and the lowest for other sites. The highest SIRs were for squamous cell and small cell carcinomas. Lung cancer SIRs increased significantly with increasing mean cumulative RDP exposure.

RDP-associated lung cancer risks

Radiation risks of incident lung cancer increased monotonically with increasing mean cumulative RDP exposure (p for linear trend < .001; see Table S4 and Figure 2A). Workers with mean cumulative RDP exposures ≥700 WLM were seven times more likely to develop lung cancer compared with unexposed workers (0 WLM; RR, 7.24; 95% CI, 4.55–11.52). The formal test indicated that there was no heterogeneity in risks between exposure categories ($p < .001$). A monotonic increase in lung

TABLE 2. Distribution of Lung Cancer by Histologic Type and Subcohort: Eldorado Incidence Cohort, Men, 1969–1999

Histologic type of lung cancer[b]	Subcohort, no. (%)[a]				
	Port Radium	Beaverlodge	Port Hope	Other Sites	Total
Squamous cell	59 (32.4)	110 (37.0)	27 (25.5)	3 (33.3)	199 (33.5)
Small cell	34 (18.7)	52 (17.5)	9 (8.5)	2 (22.2)	97 (16.3)
Adenocarcinoma	34 (18.7)	47 (15.8)	22 (20.8)	0 (0.0)	103 (17.3)
Other types	55 (30.2)	88 (29.6)	48 (45.3)	4 (44.4)	195 (32.8)
Total	182	297	106	9	594

[a]The p value of $\chi^2 = .04$ for four histologic types of lung cancer in four subcohorts and .02 for four types in the three main subcohorts.
[b]For International Classification of Diseases for Oncology (ICDO) codes for each histological type, see Table S1.

TABLE 3. Standardized incidence ratios of lung cancer by subcohort, histologic type, and cumulative radon decay product exposure categories: Eldorado incidence cohort, men, 1969–1999

Variable	No. observed[a]	No. expected[b]	SIR	95% lower limit	95% upper limit	p
Total	594	510.23	1.16	1.07	1.26	< .001
Subcohort						
Port Radium	182	147.37	1.23	1.06	1.41	.01
Beaverlodge	297	249.38	1.19	1.06	1.33	.01
Port Hope	106	93.38	1.14	0.92	1.35	.22
Other sites	9	20.11	0.45	0.16	0.74	< .001
Histologic type of lung cancer[c]						
Squamous cell	130	98.26	1.32	1.10	1.55	< .001
Small cell	56	43.78	1.28	0.94	1.61	.10
Adenocarcinoma	68	77.94	0.87	0.67	1.08	.23
Other types	95	111.62	0.85	0.68	1.02	.09
Cumulative RDP exposure, WLM						
0–99	431	425.11	1.01	0.92	1.11	.78
100–299	81	49.38	1.64	1.28	2.00	< .001
≥300	82	35.75	2.29	1.80	2.79	< .001

Abbreviations: CCDB, Canadian Cancer Data Base; RDP, radon decay products; SIR, standardized incidence ratio; WLM, working level months.
[a]The number of observed cases reflects the incidence of newly diagnosed cancer cases in which a single individual can contribute only one case of cancer.
[b]Adjusted for attained age and calendar year at risk by stratification. The number of expected cases is based on the incidence of newly diagnosed cancer cases in Canada in which a single individual can contribute more than one case of cancer.
[c]Analyses are based on the data for 1985–1999, when incidence rates by lung cancer histologic types are available in the CCDB.

cancer risk with mean cumulative RDP exposure was also seen when restricted to <100 WLM (Figure 2B).

The simple linear model adequately described the risk with no evidence of curvature in the dose response. The addition of quadratic or exponential terms to the linear term did not improve the model fit (all $p > .9$; not shown). The lowest deviance and AIC were for the power model (Figure 2). By using a simple linear model, we estimated a highly statistically significant ($p < .001$) ERR of 0.61 per 100 WLM (95% CI, 0.39–0.91) for male uranium workers (Table 4). There was an apparent heterogeneity of effect between subcohorts when using a simple ERR model, but the formal test of statistical heterogeneity was not statistically significant ($p = .093$). When we examined effect modification by age at risk, RDP dose rate, and RDP duration of exposure using a simple linear model, there was significant effect modification by attained age ($p \leq .001$) and RDP duration of exposure ($p = .012$). The complex joint effect modification by these variables was further explored using BEIR VI–type interaction models for the RDP exposures described below.

Effects of γ-ray doses on lung cancer risk

The simple linear model with mean cumulative RDP exposures explained variability in the data better than the model with a linear term for γ-rays (deviances of 6071.018 and 6135.966, respectively; not shown). Addition of the γ-ray term to the background of the model with RDP exposure did not improve the model fit ($p = .399$; not shown). The model with two independent linear terms had a slightly better fit (deviance of 6065.47), but any advantage disappeared when we fit more complicated models with adjustment for modifying effects of attained age and exposure rate (see below). By using a total absorbed

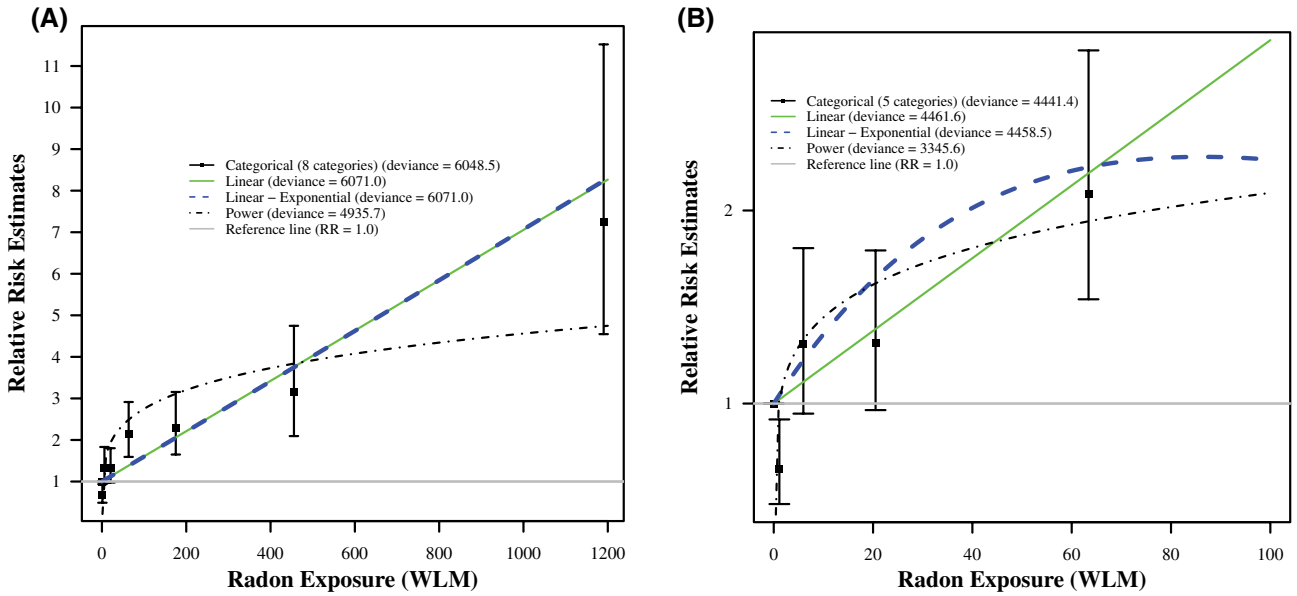

Figure 2. Categorical relative risks (95% confidence intervals) and fitted exposure-response lines for lung cancer, Eldorado incidence cohort, men, 1969–1999. (A) Full cumulative RDP exposure range; and (B) Cumulative RDP exposures restricted to <100 WLM. RDP indicates radon decay products; RR, relative risk; WLM, working level months.

TABLE 4. Excess relative risk estimates of radon decay product-associated lung cancer from the simple linear model: Eldorado incidence cohort, men, 1969–1999

Categorical effect modifier	No. of cases	Mean cumulative RDP exposure, WLM	ERR per 100 WLM (95% CI)[a]	*p*	Deviance
All subjects[b]	594	106.14	0.61 (0.39–0.91)	< .001[c]	6071.02
Subcohort[d]					
Port Radium	182	230.02	0.38 (0.21–0.66)	.093[e]	6009.06
Beaverlodge	297	81.11	0.93 (0.48–1.61)		
Port Hope	106	18.74	1.43 (−0.10, 6.05)		
Histologic type[f]					
Squamous cell	199	210.77	0.65 (0.31–1.24)	.144[e]	2247.23
Small cell	97	138.05	0.51 (0.14–1.32)		1266.57
Adenocarcinoma	103	101.24	0.45 (0.11–1.19)		1266.57
Other types	195	121.90	0.93 (0.41–1.90)		2220.35

Abbreviations: CI, confidence interval; ERR/100 WLM, excess relative risk per 100 working level months; RDP, radon decay products; WLM, working level months.
[a]Adjusted for subcohort, attained age, calendar year at risk, and duration of employment by stratification.
[b]Based on analysis including workers from *other sites;* baseline model, unadjusted for effect modifiers of risk.
[c]The *p* value from the likelihood ratio test comparing models with and without the exposure variable.
[d]Based on analysis excluding workers from *other sites* (2 degrees of freedom).
[e]The *p* value for effect modification.
[f]Based on analysis including subjects with known histologic type of lung cancer and those with no lung cancer.

lung dose from RDP exposures and γ-ray doses, we estimated an ERR per gray of 0.76 (95% CI, 0.48–1.14), similar to that from the model with RDP exposures only (not shown).

BEIR VI–type interaction models for RDP exposures

RDP-associated risks were significantly higher for exposures from 5to 14years before diagnosis compared with later exposures when we used the BEIR VI–type *exposure-age-concentration* model (Table 5). There were also significant differences in risk by categories of exposure rate and attained age. The effects of attained age remained significant using the BEIR VI–type *exposure-age-duration* model (Table 5), and there was a significant modification of radiation risks by duration of employment ($p = .017$). Radiation risks of lung cancer were almost four times higher for those who worked for more than 15years

TABLE 5. The Biological Effects of Ionizing Radiation (BEIR) VI Interaction Model for Lung Cancer by Cumulative Radon Decay Product Exposure: Eldorado Incidence Cohort, Men

	"Exposure-age-concentration" model			"Exposure-age-duration" model		
Parameter	No. of cases[a,b]	Parameter estimate (95% CI)[a,c,d]	p[a,e]	No. of cases[b,f]	Parameter estimate (95% CI)[c,d,f]	p[e,f]
Cumulative RDP exposure[g]	594	27.08 (10.18–59.25)	< .001	594	6.64 (–0.10, 20.93)	< .001
Time-since-exposure windows, years						
WLM 5–14 previously		1.00			1.00	
WLM 15–24 previously		0.28	< .001[h]		0.11	< .001[h]
WLM ≥25 previously		0.08	< .001[h]		0.02	< .001[h]
Exposure rate, WL						
<0.5	248	1.00	.003			
0.5–0.9	77	0.37 (0.18–0.76)				
1.0–2.9	125	0.32 (0.17–0.59)				
3.0–53.9	144	0.15 (0.07–0.31)				
Exposure duration, years						
<0.5				208	1.00	.017
0.5–2.49				176	1.10 (0.32–3.81)	
2.5–4.9				62	0.98 (0.22–4.42)	
5.0–14.9				99	1.40 (0.36–5.49)	
15–46				49	3.76 (0.44–32.15)	
Attained age, years						
<55	110	1.00	.001	110	1.00	< .001
55–64	248	2.33 (1.24–4.36)		248	1.84 (0.91–3.72)	
65–98	236	1.19 (0.53–2.67)		236	0.76 (0.30–1.94)	

Abbreviations: CI, confidence interval; ERR/100 WLM, excess relative risk per 100 working level months; RDP, radon decay products; WL, working level; WLM, working level months.
[a]BEIR VI interaction model ("Exposure-age-concentration") for lung cancer by cumulative RDP exposure, Eldorado Incidence Cohort, men, 1969–1999.
[b]The number of cases in the incidence analysis based on the earliest cancer diagnosis for which each individual could contribute at most one cancer.
[c]ERR/100 WLM for cumulative RDP exposure and relative risks for time since exposure, exposure rate, and attained age variables.
[d]Adjusted for subcohort, attained age, calendar year at risk, and duration of employment by stratification.
[e]The p value of the test of heterogeneity of category-specific parameter estimates.
[f]BEIR VI interaction model ("Exposure-age-duration") for lung cancer by cumulative RDP exposure, Eldorado Incidence Cohort, men, 1950–1999.
[g]Cumulative RDP exposure lagged by 5 years.
[h]The p value for the difference between the specified time-since-exposure window and the earliest time-since-exposure window (5–14 years).

compared with those who worked less than 6 months. The *exposure-age-concentration* model fit the data significantly better than the *exposure-age-duration* model based on the AIC test (7592.98 and 7597.84, respectively) so we used this model for our analysis of lung cancer by histologic type.

RDP-associated lung cancer risks by histologic type

We observed significant linear trends and significantly increased radiation-associated risks for all four histologic types (Table 4). There was some heterogeneity of radiation risks, with the highest and lowest ERRs for squamous cell carcinomas and adenocarcinomas (ERR per 100 WLM, 0.65 and 0.45, respectively; Table 4), but the differences were not statistically significant ($p = 0.144$). We observed significantly increased lung cancer risks for all histologic types with cumulative RDP exposure using the BEIR VI–type *exposure-age-concentration* model (see Tables S5–S8). Small cell carcinoma had the highest risks, with significant effects of time since exposure, attained age, and RDP exposure rate.

DISCUSSION

Here, we have presented results from the first analysis of radiation risks of lung cancer incidence (1969–1999) by histologic type in a cohort of 15,351 male Eldorado uranium workers who were first employed from 1932 to 1980. Radiation risks of lung cancer for all histologic types increased with increasing RDP exposure, and there was no indication of curvature in the dose response. Radiation risks were higher for small cell and squamous cell carcinomas but were not statistically significantly different from other types. The addition of γ-ray doses to the model with RDP exposures improved the model fit, but the risk estimates remained unchanged.

The BEIR VI–type *exposure-age-concentration* model fit the data better than the *exposure-age-duration* model, with the highest risks estimated for small cell carcinoma. To our knowledge, this is the first time these models have been applied to incidence data. The BEIR VI report was based exclusively on mortality data, and it was not known whether these models work equally well with incidence data.[5] Application to incidence data is important because

they present more accurate information to evaluate radiation effects on the risk of lung cancer.

RDP-associated risks decreased with increasing exposure rate in the BEIR VI–type *exposure-age-concentration* model (Table 5). A similar inverse dose-rate (protraction enhancement) effect was observed in some studies[24,25] but diminished or disappeared at low cumulative radon exposures.[26] The mechanism of this effect is unknown but is hypothesized to be caused by multiple traversals of the nucleus of a target lung cell by radon α particles.[24]

Our results are similar to the results from recent studies of radiation risks of lung cancer histologic types in uranium miners from Germany,[8,10] Czech Republic,[9] and Ontario province in Canada,[7] which reported significantly higher radiation risks for squamous cell and small cell carcinomas than for other histologic types. However, the risk estimates from the Ontario study were a magnitude higher than the estimates from our study or other published studies. The authors did not report a formal test of heterogeneity of radiation risks by type. The distribution of histologic types was similar to our study, but the mean cumulative RDP exposures were substantially smaller than in our cohort (mean, 21 WLM[27]), primarily because of later years of operation.

An analysis of radiation risks of lung cancer in never-smoking atomic bomb survivors from Japan showed the highest risk estimates for the small cell type followed by the adenocarcinoma and squamous cell types.[28] Among patients who were treated for Hodgkin disease with radiotherapy and subsequently developed lung cancer, the highest radiation risks were for adenocarcinoma and large cell carcinoma.[29] Several recent case–control studies and meta-analyses of studies of residential radon exposures showed a significant dose–response relation for small cell lung cancer and a less pronounced but still significant dose–response relation for adenocarcinoma.[30–33]

Ramkissoon et al. 2018 suggested that the higher preponderance of small cell and squamous cell histologic types among uranium miners could be caused by the physical characteristics of radon decay, which creates α particles with a high linear energy transfer but very low penetrance.[7] Therefore, epithelial cells of the bronchoalveolar system would receive the majority of the radiation dose, eventually resulting in tumorigenesis and leading to squamous cell and small cell types of lung cancers in the middle part of a lung or in one of the main airways.[7] Animal studies also suggest this process of RDP deposition in the airway structures of the lungs.[34]

The main strength of our study is its use of incident lung cancer data with detailed histologic information. The availability of essentially complete Canadian cancer incidence data[35] for 30 years for the entire cohort allowed us to analyze the effects of RDP exposures and γ-ray doses on the risk of lung cancer by histologic type.

Our analysis of occupational radon exposures provides useful data on lung cancer effects relevant to the general population. Long-term exposure to radon is the second leading cause of lung cancer in Canada after smoking and the leading cause of lung cancer for individuals who have never smoked.[1] Health Canada estimates that approximately 16% of lung cancer deaths are related to radon exposure in the home. Several studies of residential radon exposure and lung cancer incidence and mortality suggest a stronger association with small cell and squamous cell carcinomas than with adenocarcinoma, consistent with our study.[30,31,33]

The Eldorado cohort workers were healthier compared with the general male population of Canada (standardized mortality ratio, 0.97; 95% CI, 0.92–1.03), although the finding was not statistically significant. This is likely caused by a *healthy worker effect*; Eldorado workers were likely healthier than the general population, which includes individuals who were too sick or disabled to work. They also likely benefited from regular income, workplace benefits, regular medical examinations, socialization, and strenuous physical activity. We previously discussed and addressed the healthy worker survivor effect in detail.[36] Of note, we compared different jobs of Eldorado workers who had lower radon exposures (i.e., open pit miners, mill workers) with underground miners who had the highest radon exposures and found no evidence that they were more or less healthy.[13,37] Finally, we observed no systematic difference in job types between those who had zero RDP exposure and those who had higher radon exposures.[36]

This cohort presented a unique opportunity to investigate the effects of RDP exposure and γ-ray doses in the same individuals. RDP exposures and γ-ray doses generally were not correlated (Pearson $r = 0.18$), except for the Port Hope site, where they were strongly correlated (Pearson $r = 0.93$). Figure 3 shows scatterplots of cumulative RDP exposures and γ-ray doses for all facilities combined and separately for Beaverlodge, Port Radium, and Port Hope. Although γ-ray exposure was not a major radiologic hazard in the Beaverlodge and Port Radium mines, it was the main exposure at the Port Hope radium and uranium refinery and processing facility (Table 1).

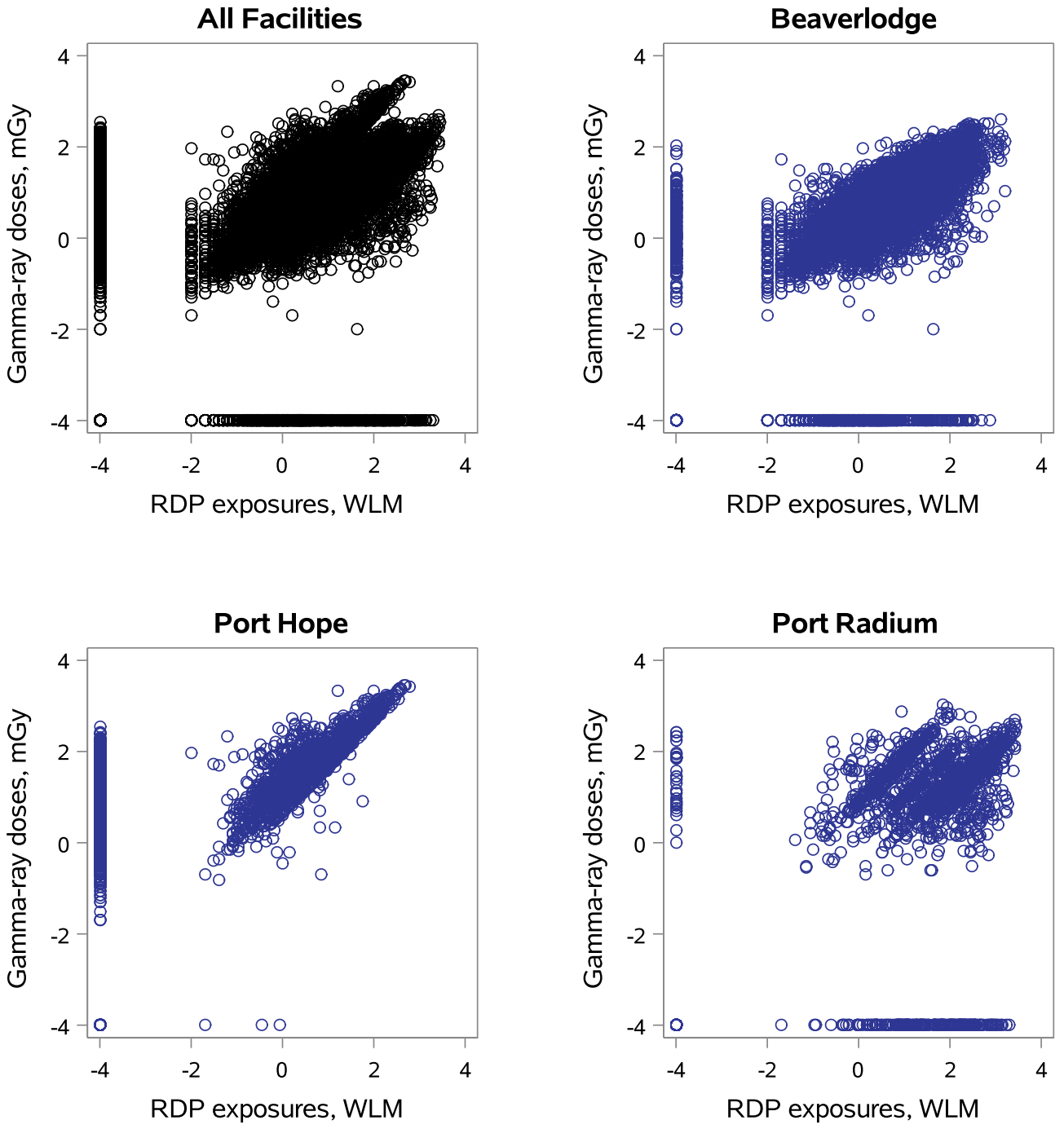

Figure 3. Correlation between cumulative unlagged RDP exposures and γ-ray doses, Eldorado incidence cohort, men 1969–1999. Scatterplots using a $\log_{10}$ scale for both axes. mGy indicates milligrays; RDP, radon decay products; WLM, working level months.

The two types of facilities (uranium mines compared with uranium processing) have very different processes, with the Port Hope workers additionally exposed to relatively concentrated forms of uranium and chemical hazards. However, despite these differences between facilities, the estimated lung cancer risks from RDP exposures did not differ between facilities (p for heterogeneity = .093), and all analyses were conducted for the entire Eldorado cohort.

There was no significant effect of γ-ray dose on the risk of lung cancer. After comparing estimated RDP

exposure-associated radiation risks with risks because of the total absorbed dose to the lung, we concluded that the majority of the observed effect was from RDP exposures, and little additional effect was caused by γ-ray doses.

An advantage 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 from 90% to 95% (www.naaccr.org/). Registration of deaths is a legal requirement in Canada: reporting of deaths is virtually complete, and under-coverage is thought to be minimal. Another advantage is the comparatively high rate of follow-up, which was achieved by multiple internal linkages. Data quality for CMDB and CCDB improved over time, with under-coverage in recent years thought to be minimal (≤1%).[38]

Several limitations should be considered when interpreting our results. In particular, analyses of radiation risks of lung cancer should consider smoking; however, the majority of occupational studies lack smoking information[7,9] or report that all workers were smokers.[8] Several studies[5,39–42] found that the smoking and RDP exposure interaction effect for lung cancer was intermediate between additive and multiplicative. Although no data on smoking in our cohort were available, a previous case–control study of the Beaverlodge cohort[43] did not find a correlation. In general, occupational studies frequently show a lack of any strong correlation between occupational exposures and smoking.[36] If these risk factors were acting multiplicatively in causing lung cancer and if smoking and RDP exposure were not correlated, then smoking should not affect the risk estimates for RDP exposure. Smoking-related cancers other than lung cancer were generally not elevated in our cohort,[13] further suggesting that smoking was not substantially elevated relative to the general population and was unlikely to have had an effect on the magnitude of RDP risk estimates.

The presence of other possible lung cancer carcinogens in our cohort also needs consideration. The uranium ore at Port Radium contained high arsenic levels. Arsenic is a known human lung cancer carcinogen,[44] particularly for squamous cell carcinoma, among uranium miners.[45] Unfortunately, there are no data on the correlation between arsenic and RDP in the cohort. The effect of arsenic on our risk estimates would have the same considerations as those given for smoking. Similarly, we did not have information on silica dust and diesel exposures. Asbestos was not a likely hazard among the Eldorado miners because of its absence within the ore contents of individual facilities. Likewise, there was no excess mortality (using standard mortality ratios) or cancer incidence (using SIRs) for mesothelioma, asbestosis, or pneumoconiosis among Eldorado workers compared with the general Canadian population (not shown).

The Beaverlodge facility used ore with a low content of other mineral carcinogens. Port Radium ore contained many elements, including arsenic and cobalt. In addition to ore, Port Hope workers were exposed to processing chemicals and various uranium compounds at higher concentrations and of greater solubility than those found in the ore. Some Port Hope workers were also exposed to radium compounds, uranium metal, and some enriched uranium. No data were available for the cohort members on any of these other potential risk factors.

We previously considered dust in the mines because long-lived α radionuclides attach to dust particles and can be inhaled into the lungs. Unfortunately, no information was available on dust or long-lived α radionuclides in our cohort. Studies of French uranium miners found that radon, γ, and long-lived α radionuclides were positively correlated. Analyses of lung cancer mortality in relation to lung doses among French uranium miners suggested that radon progeny accounted for 97% of the α-particle absorbed dose to the lung.[36]

Measurement error in exposure estimation decreased with calendar time; therefore, the Port Radium cohort had greater measurement error than the Beaverlodge cohort, and more recent Port Hope workers had lower mean errors than those working further back in time. However, we did significant work before this update to improve the identifying and dosimetry information in the cohort to reduce the degree of measurement error. We also added workers from the Port Hope radium and uranium refinery and processing facility, who were not part of previous updates.[14] Finally, residential radon exposure likely has a relatively greater contribution to total exposure in recent times, when occupational exposures are lower. If there was no correlation between residential exposure and total occupational radon exposure, the relative estimates of effect would be unaffected.

Conclusion

In summary, the current study (which is essentially independent of the data set used by the BEIR VI Committee) further supports conclusions about RDP-associated risks of lung cancer for occupationally exposed uranium

workers. To our knowledge, this is the first cohort incidence analysis that supports the use of BEIR VI–type models for the analysis of radiation risks by histologic type. Radiation risks of lung cancer did not differ significantly by histologic type, although, similar to other studies, we observed the highest point estimates for squamous cell carcinoma, possibly caused by the process of RDP deposition in the upper and middle airway structures of the lungs. Data on mortality and incidence from 80,000 Eldorado and Ontario uranium miners, as well as more recent uranium workers, until the end of 2018 are currently awaited and should shed further light on the effects of uranium mining and processing on the long-term health of workers.

AUTHOR CONTRIBUTIONS

Lydia B. Zablotska: Conceptualization, investigation, methodology, formal analysis, writing–original draft, and writing–review and editing. **Rachel S. D. Lane:** Investigation, methodology, project administration, validation, resources, data curation, and writing–review and editing. **Kristi Randhawa:** Project administration and writing–review and editing.

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CONFLICTS OF INTEREST

The authors made no disclosures.

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