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Updated Analysis of Radon Exposure and Lung Cancer Mortality in the Cohort of Newfoundland Fluorspar Miners (1950–2016)

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The commercial mining of fluorspar in St. Lawrence Newfoundland began in 1933. Miners who worked underground were exposed to high levels of radon progeny, especially before ventilation was introduced into the mines in 1960. The mean cumulative radon exposure for underground miners in this cohort was 380.9 working level months (WLM). A series of studies of this cohort have characterized the increased risks of lung cancer mortality due to radon. We have extended the follow-up of this cohort an additional 15 years to provide additional insights on the risks of low levels of radon exposure, and the modifying effects of time since exposure, age at first exposure, attained age, duration of exposure, and cigarette smoking. The cohort consisted of 1,735 underground and 315 male surface miners who, combined, accrued 81,650 person-years of follow-up. The mortality experience of the cohort was determined from 1950–2016 through record linkage to Canadian national death data. Individual-level estimates of exposure to radon progeny, in WLMs, were determined for each year of employment. We compared the mortality experience of the underground miners to Newfoundland men using the standardized mortality ratio (SMR). Poisson regression models were fit to estimate excess relative risks (ERR) per 100 WLM. There were 236 lung cancer deaths identified, and of these, 221 occurred among underground workers. The SMR for lung cancer among underground miners compared to Newfoundland men was 2.67 (95% CI: 2.33, 3.04). The ERR per 100 WLM for lung cancer mortality, assuming a 5-year exposure lag, was 0.41 (95% CI: 0.23, 0.59). Attained age and time since exposure were important modifiers to the radon-lung cancer relationship. The joint relationship between smoking and radon on lung cancer risk was sub-additive, however, the smoking data were limited and available for only half of the cohort.

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INTRODUCTION

Radon and its radioactive decay products (radon progeny)[2] are established carcinogens, and in Canada, residential radon exposure was estimated to have caused 6.9% of incident lung cancers diagnosed in 2015 (*1*). The overall number of lung cancers in Canada due to occupational exposure to radon has been estimated to be substantially lower (0.8%), and workplace exposure to radon is highly variable across occupational groups (*2*). Underground miners, particularly for uranium, have substantially higher levels of exposure to radon than the background concentrations that the general population is exposed to (*3*). Epidemiological studies of underground miners have played a prominent role in the decision to classify radon as a human carcinogen (*4*).

There are relatively few cohorts of radon-exposed miners in the world, and the Newfoundland fluorspar miners cohort has been included in previous pooled analyses that have explored variations in lung cancer risk by time since exposure, age at first exposure, attained age, duration of exposure, as well as the role of cigarette smoking (*4*, *5*). The cohort of Newfoundland fluorspar miners has several important features including radon exposures that are higher than most other cohorts included in the BEIR VI report (*4*), and other pooled analyses (*5*). Another important feature of this cohort is that, unlike other cohorts of radon-exposed miners, the source of exposure to radon was from the ground water that flowed through the mines, and not from the ore. As a result, the fluorspar miners were not exposed to the other recognized lung carcinogens of uranium miners: gamma, thoron, and radioactive dusts.

The mining of fluorspar in St. Lawrence, Newfoundland began in 1933, and continued until the closure of the mines in 1978. Mining operations for fluorspar in this area recently restarted in 2018; however, operations again ceased in 2022. The analyses presented in this paper only considered those miners who worked until 1978. When the mines first opened in the 1930s, they provided employment opportunities to coastal communities devastated by a 1929 tsunami and the

[2] We refer to radon and its radioactive decay products (radon progeny) as "radon" synonymously throughout this article.

challenges of residents of these towns are well-chronicled (*6*, *7*). The fluorspar mines were especially active during the Second World War, and the mined ores were used to produce aluminum. Radon exposures in the series of these underground mines were quite high, particularly before the introduction of mechanical ventilation in 1960. For context, the current recommended occupational levels for radon exposure is 4 working level months (WLM) per year (*3*). Before 1950, the typical estimated median annual radon exposure among underground miners was above 100 WLM, and the maximum annual exposure was 564.7 WLM.

In St. Lawrence, a local physician first noticed an increased incidence of lung cancer in the 1950s. More formal assessments of the increased risks of lung cancer due to occupational radon exposure in these miners were published by Parsons et al. in 1969 (*8*) and then Wright and Couves in 1977 (*9*). We published a series of studies thereafter (*10–12*) with the most recent publication including deaths identified through December 31, 2001 (*10*). In this paper, we present findings from an updated analysis of this cohort that includes an additional 15 years of mortality follow-up; 67 years of mortality follow-up overall (1950–2016).

We were motivated to extend the follow-up of this cohort for several reasons. First, the additional 15 years of follow-up provided us the opportunity to better describe changes in lung cancer risk with an increased number of years since last exposure. Second, the size of the cohort and the number of previously identified lung cancer deaths is relatively small, and the identification of additional outcomes increases the precision of our risk estimates. Third, the increased follow-up provided an opportunity to revisit the risks of lung cancer from radon among those miners employed after 1960 when levels were much lower.

MATERIALS AND METHODS

Study Population

Previous publications have described the study cohort (*10*, *12*). In brief, occupational records were used to create the initial cohort of fluorspar miners, and it included 2,661 miners. Of these, 2,111 miners worked underground at some point, while the remaining 550 worked exclusively on the surface. All individuals included in these analyses were male. Annual working histories were constructed from employment records. We excluded from analysis miners who lacked sufficient personal identifying information needed for record linkage to national mortality data. As detailed in our previous papers (*10*, *12*) most of these were short-term workers employed during World War II. We reconstructed the cohort using archived data stored by the Canadian Nuclear Safety Commission.

Radon Exposure

An annual estimate of cumulative radon exposure was derived for each miner. These exposures incorporated details about mine location, and occupational data on working hours and location from 1933–1960 that were available for each cohort member (*13*). Radon exposure estimates were based on sampling measures (*14*), as well as the general mine layout, amount of water inflow, mining method, and general working conditions (*13*).

Over time, there were important improvements in the working environments including going from three to two eight-hour shifts per day (at the end of World War II) with four hours between shifts. Between shifts, compressed air was used to provide some ventilation. In 1960, before the introduction of mechanical ventilation in the mines, 80 samples of radon were taken at 50 different underground locations in the Director mine (the principle mine). Values ranged from 0.4 to 183 Working Levels (WLs) in unventilated areas, and from below the level of detection to 12 WLs in ventilated areas of the mine. Unfortunately, there are no realistic means to verify the accuracy of radon exposures before 1960. The introduction of mechanical ventilation resulted in large decreases in radon exposure. For example, from 1955–1959, the mean annual exposure to radon for underground workers was 64.8 WLMs, whereas from 1961–1965 it was 1.3 WLMs. From 1986 onwards, radon levels for each worker were measured daily based on the site location in the mine. The mean exposure for underground miners from 1968–1978 was 0.6 WLM. Cumulative exposures were expressed in working level months (WLMs).[3]

Previous analyses of the cohort incorporated a lag interval of 5 years into the calculation of cumulative exposure (*5*), and we followed this approach herein. This assumes that the risk of lung cancer mortality is unrelated to radon exposures received in the five years before death.

Cigarette Smoking

Miners provided smoking information by completing a series of smoking surveys. We administered the last smoking survey in 2003 to update previously collected information on smoking behaviors and sought to identify former miners with no smoking data. Smoking surveys were previously administered in 1966, 1970, 1978, and 1993. For the 2003 survey, we identified participants using the personal identifying information (name, birth date, years worked in mine, and place of residence) from past smoking surveys. Internet search engines were used to help interviewers (hired from the St. Lawrence region) to locate former miners. For this current paper, we compiled data from all five smoking surveys to classify miners based on last known smoking status (current, former, never), and according to the average number of cigarettes smoked per day. When the reported number of cigarettes smoked per day varied across surveys, we derived the average of these values of all surveys. Smoking data were available for approximately half the cohort. It is important to also note for miners with smoking data, data were usually only collected from a single smoking survey. Therefore, it was not possible to construct time-dependent measures of smoking behaviors, nor model lung cancer risk in relation to the time since smoking cessation.

Ascertainment of Mortality (1950–2016)

We created a linkage file with personal identifying information using archived data maintained by the Canadian Nuclear Safety Commission. This file combined data from occupational records, smoking surveys, and vital status from previous linkages. This file contained 2,121 observations each of which represented a unique miner. Statistics Canada staff linked these individual-level data to the Canadian Vital Statistics Death Database (CVSD) and the Canadian Mortality Database (CMDB). The CVSD is an administrative survey that collects demographic and cause of death information annually from all provincial and territorial vital statistics registries on all deaths in Canada (*15*). Death records were sourced from both the Canadian Mortality Database (CMDB) (data from 1950–2011 inclusive) (*16*), and Canadian Vital Statistics Database (CVSD) that covered the periods from 1930–1949, and 2011 onwards. Linkage assignments employed both probabilistic and deterministic methodologies, using the "matchit" program on the STATA 14.2 platform. Following the identification of deaths from the record linkage, the lead author (PV) performed a manual review of all death links. He had

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

previously reviewed mortality linkages for past analyses of this cohort that were done in 1994 and 2005.

Miners for whom no death link was found were assumed to be alive at the end of follow-up (December 31, 2016). We made an exception to this rule for miners who were born before 1910 with no link. Namely, these miners ($n = 55$) were assumed deceased but lost to follow-up and we excluded them from analyses. The final cohort analysis file consisted of 2,055 miners, which is slightly less than the 2,070 miners that formed the basis of our previous analyses (*10*). The ability to link occupational cohorts to national mortality has been previously demonstrated (*17–19*). We obtained date of death, and underlying cause of death from the record linkage. The International Classification of Diseases 9th Revision (ICD-9) determined the underlying cause of death for deaths before 2000, while the ICD-10 classified deaths from 2000 onwards. Lung cancer deaths were identified with the ICD-9 rubric of 162, and ICD-10 codes of C33 and C34.

We adhered to Statistics Canada's rules of disclosure governing the use of files linked to national mortality. We performed all analyses within the Statistics Canada's Research Data Center Network (*20*). We were bound to adhere to the rule that all frequencies, including deaths, would be rounded to the base unit of five. For this reason, unlike previous analyses of this cohort, all frequencies presented and referred to in this paper have been rounded to base five. However, the risk estimates derived from the regression models were not subject to rounding.

External Comparisons of Mortality to the General Male Newfoundland Population

We applied the method of indirect standardization to compare the patterns of mortality for the underground fluorspar miners to the general male population of Newfoundland from 1950–2016. Analyses were restricted to the underground miners because we wanted to describe the relative differences in mortality between those with above background levels of exposure to radon to the general population. We obtained cause-specific mortality rates for the Newfoundland male population from Statistics Canada, and tabulated these rates by 5-year age-groupings and 10-year calendar periods. These cause-specific rates were multiplied by the corresponding number of person-years of follow-up accrued over the same calendar and age-group stratum among the underground fluorspar miners to obtain the expected number of deaths. For each cause of death, we calculated the standardized mortality ratio (SMR) by dividing the observed by the expected number of deaths, and estimated the accompanying 95% confidence interval using formulae published by Breslow and Day (*21*).

Internal Cohort Comparisons of Mortality

Internal cohort analyses explored variations in risk across different features of radon exposure. These analyses are more powerful than external comparisons as they provide a means to characterize exposure-response relationships while adjusting for the influence of other individual-level risk factors including cigarette smoking. They also are less prone to bias from the healthy worker effect than comparisons to the general population (*22*). The standard approach to characterize risks in these cohorts is the calculation of an excess relative risk (ERR) per 100 WLM using Poisson regression. Person-years, cross-classified across a series of categorical variables, were tabulated using a program adapted from that published by Pearce and Checkoway (*23*). The person-years of follow-up and number of lung cancer deaths were tabulated across the following categorical variables: attained age, age at first exposure, cumulative radon exposure, calendar period, smoking status, number of cigarettes smoked daily, and a binary variable that captured the periods before and after mechanical ventilation was introduced into the mine. All variables were modelled as categorical variables. For cumulative exposure to radon, we used the following categories: 0, $>$ 0–$<$2.5, 2.5–$<$5, 5–10, 10–$<$25, 25–$<$75, 75–$<$150, 150–$<$300, 300–$<$600, 600–$<$1,200, 1,200–$<$1,800, 1,800–$<$2,500, 2,500–$<$3,500, and $\geq$3,500 WLM. We chose these categories so that there were enough lung cancer deaths ($n > 10$) in each category. For each exposure category, we calculated a mean exposure weighted by the person-years of follow-up. The number of deaths in each stratum were Poisson distributed with the variance estimated by the observed number of deaths.

The AMFIT program of the software package EPICURE was used for all Poisson regression modeling (*24*). We first estimated relative risks for each cumulative WLM category with adjustment for attained age and calendar period. Linear excess relative risk models were fit using the mean WLM generated for each cumulative WLM category. Mathematically, the form of this model was: $RR = 1 + \beta WLM$, where β describes an increase in the ERR per unit increase in cumulative WLM. All linear ERR models were adjusted for attained age and calendar period.

Effect Modification

Similar to methodology used in other cohorts of radiation exposure workers (*4*), we evaluated variations in the ERR/WLM across a series of potential effect modifiers that included: attained age, age at first exposure, exposure rate, time since last exposure, and duration of exposure. This was done by first fitting the linear ERR model: $RR = 1 + \beta WLM$. We evaluated heterogeneity in the ERR/WLM across categories of the potential effect modifier by fitting the model $RR = 1 + \beta_j WLM$ where j represents the number of categories of the modifying factor. The ERR/WLM for each of the j categories was obtained from this model, and we assessed whether these risks were heterogeneous across these categories by deriving a test of significance for the improvement in fit based on the likelihood ratio test statistic with *j-1* degrees of freedom. We evaluated effect modifiers one at a time because, given the small number of lung cancer cases and the nature of the cross-classified data, it was not possible to test for effect modification in more complex models.

Joint Effects of Smoking and Radon on Lung Cancer Mortality

We evaluated the associations between smoking, radon exposure and lung cancer following the methodological approach by Lubin et al. (*5*). We fitted multiplicative and additive main effects models, as well as a full model. The form of the joint association between smoking and WLM was assessed relative to a joint relationship that was either multiplicative or additive. As described by Lubin (*25*), with a linear ERR form for RR, a multiplicative joint association for lung cancer mortality would be expressed as the following:

$$r(x,s,w) = r_0(x)\theta_s(1 + \beta w)$$

whereas an additive RR association would be given by the following:

$$r(x,s,w) = r_0(x)(\theta_s + \beta w)$$

We then considered models where both the multiplicative and additive associations are nested. One such model was the geometric mixture model. This is defined as the following:

$$r(x,s,w) = r_0(x)[\theta_s(1 + \beta w)]^{\lambda} \cdot (\theta_s + \beta w)^{1-\lambda}$$

We proceeded to fit a series of models with different values of λ until we identified a model that minimized the deviance from the full model. The value of $\hat{\lambda}$ from this iterative approach was used to characterize the joint association between radon and smoking on lung cancer risk.

Funding and Ethics

The Canadian Nuclear Safety Commission funded this study. The Carleton Research Ethics Board provided ethics approval (Clearance no.: 108564). Finally, Statistics Canada reviewed and approved the study as part of their record linkage processes.

RESULTS

Table 1 describes the characteristics of 1,735 underground and 315 surface fluorspar miners employed from 1933–1976. A total of 1,365 deaths were identified in the cohort through December 31, 2016; of these, 235 were from lung cancer

TABLE 1
Descriptive Characteristics of the Newfoundland Fluorspar Cohort with Mortality Follow-up from 1950–2016

Characteristics	Miners[a]	Percentage (%)	Lung cancer deaths[a]	Percentage (%)
Surface miner (exclusively)	315	15.3	15	6.4
Underground miner	1735	84.7	220	93.6
Age at first exposure <20 years	375	18.2	65	27.7
Age at first exposure 20–24 years	535	26.0	60	25.5
Age at first exposure 25–29 years	290	14.1	30	12.8
Age at first exposure 30–39 years	320	15.6	45	19.1
Age at first exposure 40+ years	215	10.5	25	10.6
Birth year				
Before 1900	175	8.5	10	4.3
1900–1909	170	8.3	25	10.6
1910–1919	390	19.0	60	25.5
1920–1939	420	20.4	85	36.2
1940–1949	340	16.5	45	19.2
1950–1959	475	23.1	15	6.4
Death year				
1935–1949[b]	25	1.2	0	0.0
1950–1959	90	4.4	15	6.4
1960–1969	185	9.0	40	17.0
1970–1979	230	11.2	40	17.0
1980–1989	230	11.2	50	21.3
1990–1999	240	11.7	45	19.1
2000–2009	330	16.1	30	17.0
2010–2016	135	6.7	15	6.4
Alive at end of follow-up	690	33.6		
First employment				
1933–1939	285	13.9	60	20.9
1940–1944	590	28.6	75	27.9
1945–1949	115	5.6	20	7.4
1950–1954	190	9.3	40	14.1
1955–1959	80	4.0	15	5.0
1960–1964	240	11.6	30	10.9
1965–1969	375	18.2	30	10.9
1970–1976	180	8.8	10	3.5
Lifetime smoking status				
Ever	940	85.5	155	93.9
Never	160	14.5	10	6.1
Unknown	955		70	
Cigarettes smoked daily				
Never smoker	160	7.8	10	4.2
<0	45	2.2	5	2.1
10–19	270	13.1	40	16.8
20–29	420	20.4	75	31.9
30–39	120	5.9	20	8.4
40+	65	3.2	10	4.2
Unknown	970	47.2	70	29.8

[a] All counts have been rounded to base five to adhere to data dissemination requirements of Statistics Canada's Research Data Centre.
[b] Ascertainment of mortality was incomplete before 1950.

TABLE 2
Standardized Mortality Ratios (SMRs) for Newfoundland Underground Fuorspar Miners Relative to the Mortality Experience of Newfoundland Men, 1950–2016

Cause of death	ICD-9	ICD-10	Exp. Deaths	SMR	95% CI
All causes	0–999	A–Z	1091.4	1.03	0.97–1.09
Infective and parasitic diseases	1–139	A00–B99	15.0	1.00	0.56–1.65
All cancer	140–239	C00–D48	292.6	1.50	1.36–1.65
Bladder	188	C67	9.4	1.60	0.89–2.64
Large intestine (incl. rectum)	153, 154, 159	C18–C20	38.2	0.73	0.49–1.06
Leukemia	204–206, 207.0, 2, 8, 208	C90–C95	8.3	0.96	0.41–1.89
Trachea, bronchus and lung	162	C33, C34	82.8	2.67	2.33–3.04
Pancreas	157	C25	12.5	1.12	0.61–1.88
Prostate	185	C61	29.2	0.86	0.55–1.26
Endocrine, nutrition, metabolic	240–279	E00–E90	38.4	0.89	0.61–1.24
Mental diseases	290–319	F00–F99	28.3	0.35	0.17–0.65
Diseases of the nervous system	320–389	G00–G99	28.8	0.69	0.42–1.07
Circulatory	390–459	I00–I99	451.9	0.82	0.74–0.91
Coronary heart disease	410–414, 429.2	I20–I25	274.7	0.85	0.74–0.96
Cerebrovascular disease	430–438	I60–I69	79.4	0.58	0.42–0.77
Non-malignant respiratory disease	460–519	J00–J99	98.0	0.86	0.68–1.06
Digestive diseases	520–579	K00–K93	35.4	0.76	0.50–1.11
Genitourinary diseases	580–629	N00–N99	26.2	0.65	0.38–1.04
Symptoms Ill-defined	780–799	R00–R99	13.7	0.58	0.25–1.15
Accidents, poisonings and violence	800–999	S00–T98	53.3	1.31	1.02–1.66
Motor vehicle accidents	810–819	V01–V99	12.3	1.06	0.56–1.80
Falls	880–889, 929.3	W00–W19	6.0	2.50	1.40–4.13
Drowning	830, 832, 910	T75.1	7.9	1.27	0.61–2.33
Suicide	950–959	X60–X84	7.9	1.14	0.52–2.16

* Background mortality rates for Newfoundland males were derived for 5-year age groupings, and 10 year calendar periods.
ICD-9 = International Classification for Diseases 9th revision; ICD-10 = International Classification for Diseases 10th revision.

(220 among underground miners, and 15 among surface miners). This represents an additional 30 deaths from lung cancer since our last analyses. Smoking status was available for approximately 54% of the cohort, and of these individuals, 85% were ever-smokers.

After accounting for age and calendar period effects, the overall mortality experience of underground miners in the cohort was not different from Newfoundland men (SMR = 1.03; 95% CI: 0.97, 1.09) (Table 2). The SMR for all cancer deaths was statistically significant (SMR = 1.50; 95% CI: 1.36, 1.65), due predominantly to the excess lung cancer deaths at 2.67 (95% CI: 2.33, 3.04), but there was not a statistically significant excess of mortality observed for any other specific cancer site examined. Increased risks of mortality, relative to the provincial population, were also found for accidents, poisonings and violent deaths (SMR = 1.31; 95% CI: 1.02, 1.66). This excess appears to be largely driven by a higher-than-expected number of deaths for falls (SMR = 2.50, 95% = 1.40, 4.13).

Internal cohort analyses found that cumulative radon exposure was strongly associated with lung cancer mortality (Fig. 1). Those in the highest exposure category (>3,500 WLM) had a statistically significant relative risk of lung cancer mortality of 39.4 (95% CI: 19.1, 81.0) relative to surface miners. The ERR among underground miners, in the model adjusted for age and calendar period, per 100 WLM was 0.41 (95% CI: 0.23, 0.59). When analyses were restricted to cumulative exposures less than 100 WLM, the strength of the association was much stronger, specifically, the ERR per 100 WLM was 2.90 (95% CI:0.60, 5.20) (Fig. 2). The ERR per 100 WLM decreased substantially with increasing length of follow-up (Fig. 3).

Effect Modifiers

We found no evidence of heterogeneity between cumulative radon exposure and lung cancer deaths across age at first exposure categories (P = 0.39) (Table 3). In contrast, the ERR\100 WLM with attained aged decreased substantially with increasing age (P = 0.001). Similarly, the ERR\WLM decreased with increasing time since last exposure categories (P < 0.001) and those last exposed more than 35 years ago had increased excess risk (ERR\100 WLM = –0.24; 95% CI: –0.82, 3.29). The ERR\100 WLM increased with increasing duration of exposure, which is supportive of a pattern of inverse dose response, but this finding was not statistically significant (P = 0.11). While a smaller ERR\100 WLM was observed among those first employed after 1960 compared to those before this year, this difference was not statistically significant (P = 0.07).

We present the risks of lung cancer by time windows of exposure to radon in Table 6. The ERR\100 WLM was much

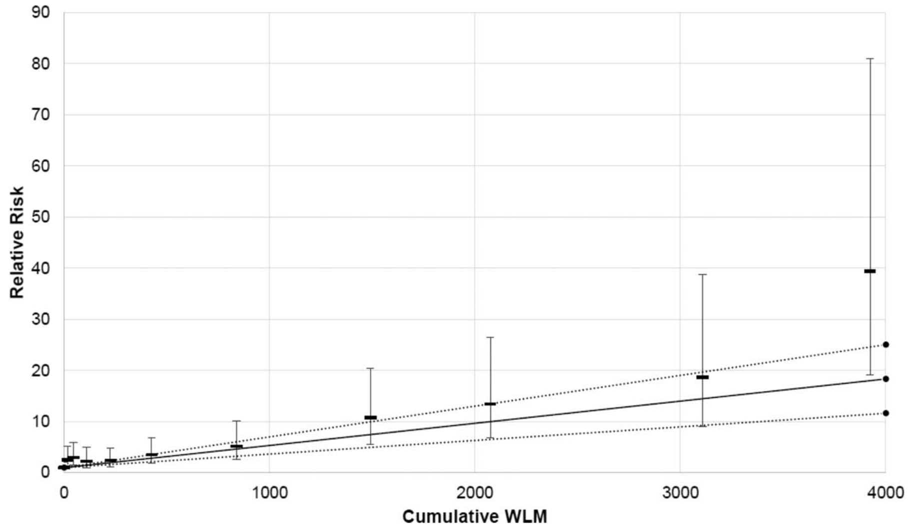

FIG. 1. Relative risk (RR)of lung cancer mortality from cumulative radon exposure in working level months (WLMs), Newfoundland Fluorspar cohort, 1950–2016. RRs (and 95% CIs) are plotted at the mean WLM for each exposure category and were adjusted for age and calendar period. The solid line was created from fitting model $RR = 1 + ERR(WLM)$ with adjustment for attained age and calendar period. The dashed lines represent the upper and lower 95% confidence intervals for the *ERR*. The ERR per 100 WLM was 0.41 (95% CI: 0.23, 0.59).

stronger for exposure received more recently. Specifically, the ERR\100 WLM for exposure received 5–14 years ago was 1.84 (95% CI: 0.19, 3.48), while for exposures received 35 years ago the ERR\100 WLM was 0.08 (95% CI: –0.00, 0.17).

The ERR\100 WLMs were similar between ever- and never-smokers ($P > 0.50$) (Table 4). In contrast, heterogeneity in the ERR\100 WLM was observed with cigarettes smoked daily ($P < 0.05$). For the latter, higher ERR\100 WLM were observed among those who smoked on average a pack or more per day. The joint effect of cigarette smoking and radon exposure was found to be sub-additive with the best estimate of $\hat{\lambda} = -0.36$ (Table 5).

DISCUSSION

This paper is another update, and likely the last, of the risk of lung cancer among Newfoundland fluorspar miners occupationally exposed to high levels of radon exposure. Many of the patterns of risk are consistent with previously published values. However, the extension of the mortality follow-up of

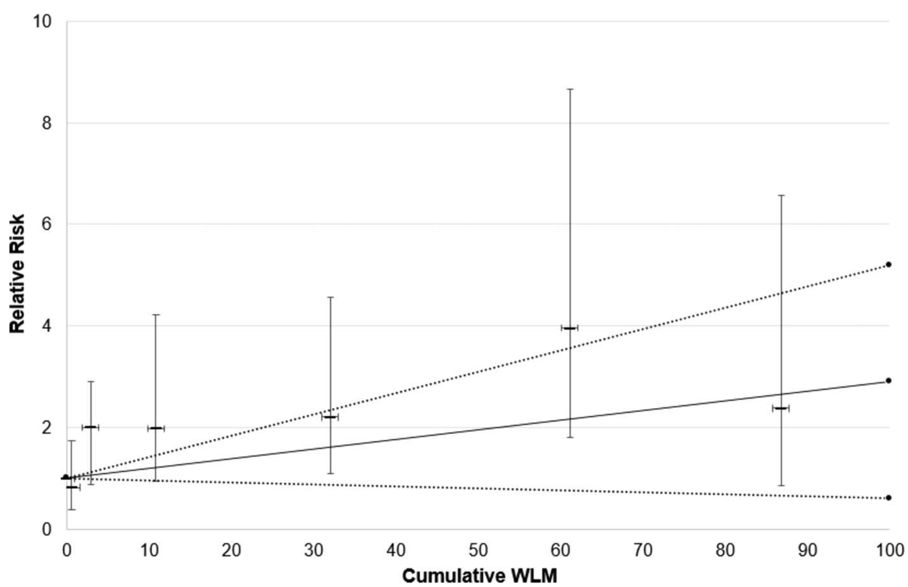

FIG. 2. Relative risk (RR) of lung cancer mortality from cumulative radon exposure less than 100 working level months (WLMs), Newfoundland Fluorspar cohort, 1950–2016. RRs (and 95% CIs) are plotted at the mean WLM for each exposure category and were adjusted for age and calendar period. The solid line was created from fitting model $RR = 1 + ERR(WLM)$ with adjustment for attained age and calendar period. The dashed lines represent the upper and lower 95% confidence intervals for the *ERR*. The ERR per 100 WLM was 2.90 (95% CI: 0.60, 5.20).

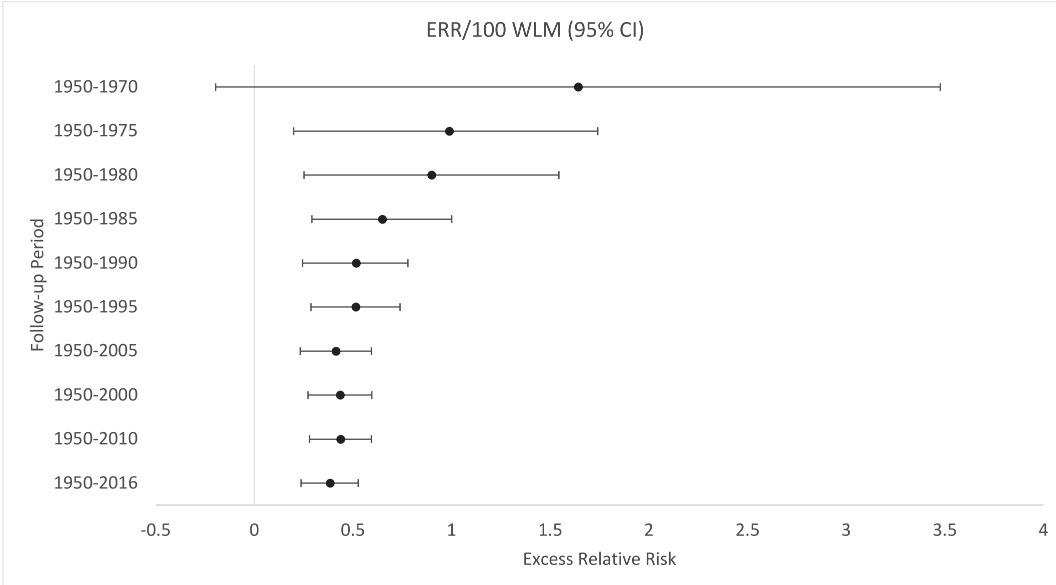

FIG. 3. Excess Relative Risk (ERR) per 100 WLM by follow-up period, Newfoundland Fluorspar miners, 1950–2016. ERR/100 WLMs were adjusted for 5-year age groupings, cigarettes smoked daily, and calendar periods.

this cohort provides increased precision in the risk estimates, particularly given the relative size of the cohort and corresponding number of lung cancer deaths. As with other cohorts of radon-exposed miners, the ERR\100 WLM for lung cancer mortality has decreased since the last set of analyses. However, this change was quite modest, specifically, in our previous analyses the ERR per 100 WLM for all underground miners was 0.43 (95% CI: 0.23, 0.62) (*10*), while in our current study the value is 0.41 (95% CI: 0.23, 0.59). Our earlier analyses involving mortality through the end of 1990 found a value of 0.70 per 100 WLM (95% C: 0.44, 1.11) (*26*). While approximately one-third of the cohort was determined to be alive at the end of the follow-up interval, it is our view that further extensions of the follow-up are unlikely to materially change this overall ERR\100 WLM.

A positive association between cumulative radon exposure and lung cancer risk was observed when analyses were restricted to those with less than 100 WLM of lifetime exposure. The ERR\100 WLM was 2.90 (95% CI: 0.60, 5.20). While we did observe a stronger ERR\100 WLM among workers who were first exposed after mechanical ventilation was introduced into the mines (7.3 vs. 0.44; $P = 0.067$), this estimate was based on only 35 lung cancer deaths. As these miners were younger relative to the other fluorspar miners (as they were employed in a more recent time), this ERR\100 WLM is expected to decrease with increased follow-up. This finding is consistent with other recent work (*27*).

As with previous analyses of this cohort, attained age was a strong modifier of the ERR\100 WLM. The ERRs per 100 WLM were 5.3, 0.6, 0.2, and 0.1 for those with attained ages of <50, 50–59, 60–69, and 70+, respectively. The decrease in ERR per unit exposure with increasing categories of attained age was similarly reported in the BEIR VI report and were 1, 0.66, 0.32, and 0.17 among those aged 45–54, 55–64, 65–74, and 75 years or older. In the more recent pooled analyses of the underground uranium miners (*27*), the decreases in the ERR\WLM for those aged <55, 55–64, 65–74, and 75+ years of age were 100, 0.64, 0.22 and 0.17.

A strength of our study was the availability of some smoking data that are often not available for many of the historical cohorts or radiation-exposed miners. Despite this, we acknowledge our smoking data have important limitations. We lacked the ability to characterize changes in smoking behaviors over time in our cohort as we typically did not have smoking data for each miner across multiple smoking surveys. This limitation precluded us from being able to reliably characterize "time since last smoked" for the miners for which we had smoking data. There were also some changes in the wording of the smoking surveys that were done as early as 1966 and as late as 2001 which presented challenges from harmonizing data. Where possible, we used data from multiple surveys to characterize smoking behaviors, particularly for the measure "average cigarettes smoked daily." Despite these limitations, we are confident that the data collected in the surveys provides a valid mechanism for identifying ever- and never-smokers, and those who were heavier smokers.

We found no substantial difference in the ERR\WLM among ever-smokers compared to never-smokers, and there was no clear pattern in the ERR\WLM based on the average number of cigarettes smoked daily. A recent analysis of German Wismut uranium miners (*28*) found that the centered ERR/WLM was higher for non/light smokers relative to those who smoked more (0.022 vs. 0.013). In contrast, Kelly-Reif and colleagues found a substantially higher ERR per 100 WLM among smokers ((ERR/100WLM = 1.35, 95% CI: 0.84, 2.15) relative to never-smokers (ERR/100WLM = 0.12; 95% CI: –0.05, 0.49) in a cohort of Czech uranium miners (*29*). Our analysis of the association between cigarette

TABLE 3
ERR/100 WLM Across Categories of Attained Age, Time Since Last Exposure, Age at First Exposure, Exposure Rate and, Year First Employed Among Underground Newfoundland Fluorspar Miners, 1950–2016

Covariate	Lung cancer deaths[c]	Person-years	ERR/100 WLM[a]	95% CI	P value[b]
Age first exposed (year)					
<20	65	17040	0.480	0.258–0.702	0.39
20–<25	60	24050	0.345	0.143–0.546	
25–<35	55	19315	0.285	0.080–0.490	
≥35	45	9680	0.374	0.039–0.709	
Attained age (year)					
<50	35	37935	5.270	–2.419–12.96	0.001
50–60	65	16495	0.617	0.201–1.034	
60–70	75	14080	0.234	0.061–0.407	
≥70	60	13140	0.947	–0.005–0.194	
Time since last exposure (year)					
<5	35	14234	1.397	0.574–2.220	
5–<15	40	15743	0.631	0.263–0.989	< 0.001
15–<25	45	13953	0.326	0.092–0.560	
25–<35	50	11764	0.383	0.118–0.655	
≥35	50	14395	–0.243	–0.815–0.329	
Duration of exposure (year)					
<5 years	70	47452	–0.204	–0.649–0.240	0.115
5–<15	40	13493	0.159	–0.039–0.357	
15–<25	40	5566	0.354	0.154–0.555	
15–<35	40	2019	0.467	0.234–0.699	
35+	30	1439	0.493	0.233–0.753	
First employed before 1960					
No	35	27550	7.326	–4.004–18.66	0.067
Yes	185	42535	0.443	0.236–0.651	
Underground miners	220	71892	0.406	0.226–0.587	
All miners	235	81991	0.442	0.271–0.613	

[a] The ERR/WLM was estimated by using a linear excess relative risk model ($RR = 1 + \beta \cdot WLM$); background rates were adjusted by age and calendar period and a lag interval was incorporated into the calculation of the cumulative WLM.
[b] P value for test of homogeneity of the ERR/WLM across categories.
[c] Lung cancer deaths were rounded to base unit of 5.

smoking, radon and lung cancer revealed that the joint model was sub-additive. This is consistent with the work by Lubin et al. (*5*) who determined that the optimal fit for the geometric mixture model for this fluorspar cohort was $\lambda = -0.1$. The value we found was $\lambda = -0.36$. Additional support for a sub-additive model was found with the analyses of three European case-control studies of miners (*30*). The BEIR VII report concluded that the data on smoking, radon and lung cancer in miners studies were compatible with a multiplicative effect and not with an additive one, but that the estimated interaction was sub-multiplicative (*31*). Hornung et al. remarked (*32*) that with increasing follow-up, associations between smoking, radon and lung cancer have a tendency to move from multiplicative to additive. We had limited power to discriminate between competing models that included radon and smoking due to the small number of lung cancers and the high prevalence of smoking in our cohort, and because smoking data were only available for approximately half of all miners.

As previously mentioned, the source of exposure for these miners differed from that of other radon-exposed cohorts as radon came from water that ran through the mines. Non-occupational exposure to radon was likely higher for the community relative to other communities based on water samples taken before 1960. Specifically, concentrations of radon in water samples in the Director mine, and Hares Ears shaft were 476 Bq/L and 445 Bq/L, respectively, while the corresponding concentrations in the town well were 532 Bq/L and 341 Bq/L (*13*). Residential radon measures taken in St. Lawrence in 1970 demonstrated substantial variability from home to home (*33*), and a more recent publication reported that indoor dwelling concentrations of radon in St. Lawrence Newfoundland were higher than for 16 other cities based on measures taken in the 1970s (*34*). The only other city with higher indoor

TABLE 4
Excess Relative Risk (ERR/100 WLM) of Lung Cancer, per WLM, Across Categories of Number of Cigarettes Smoked Daily and Smoking Status, Newfoundland Fluorspar Cohort, 1950–2016

Covariate	Lung cancer deaths[c]	Person-years	ERR/100 WLM[a]	95% CI	P value[b]
Smoking status					
Never	10	6990	0.354	0.029–0.736	> 0.50
Ever	155	38960	0.456	0.279–0.633	
Unknown	70	35700	0.386	0.134–0.639	
Cigarettes smoked daily					
Never smoker	10	7100	0.351	–0.3431–0.731	0.049
<15	20	6420	0.436	0.151–0.721	
15–<20	25	7055	0.305	0.095–0.515	
20–<25	60	12645	0.433	0.211–0.654	
25–<35	35	8595	0.780	0.348–0.121	
35+	15	3535	0.511	0.121–0.901	

[a] The ERR/WLM was estimated by using a linear excess relative risk model ($RR = 1 + \beta \cdot WLM$); background rates were adjusted by age and calendar period and a lag interval was incorporated into the calculation of the cumulative WLM.
[b] P value for test of homogeneity for smoking status, and cigarettes smoked daily.
[c] Lung cancer deaths were rounded to base unit of 5.

concentrations of radon than St. Lawrence was Winnipeg with an arithmetic mean of 146 Bq/m^3 (vs. 125 Bq/m^3). While non-occupational exposures to radon may be higher for residents of St. Lawrence Newfoundland when compared to other jurisdictions, we know of no reason why these exposures would be correlated with occupational exposures in the fluorspar cohort. This would be a condition necessary to introduce confounding.

In summary, the present study provides risk estimates like past analyses of this cohort, albeit with improved precision, and an ability to characterize risks with longer latency. Future analyses of this cohort that could be achieved by increasing the follow-up are unlikely to yield risk estimates for lung cancer that would be meaningfully different. Nonetheless, the updated data should be incorporated with other

TABLE 5
Relative Risk (RR) of Lung Cancer by Cumulative Radon Exposure (WLM) and Cigarettes Smoked Daily, Newfoundland Fluorspar Miners, 1950–2016

Cigarettes smoked daily	Cumulative WLM								
	<100			100–<1000			≥1000		
	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI
<12.5	10	1.0[a]		10	3.26	1.21–8.76	15	13.89	5.29–36.46
12.5–25	30	2.62	1.14–5.99	25	3.72	1.56–8.86	35	11.27	4.81–26.43
≥25	15	2.23	0.92–5.43	15	4.51	1.76–11.54	20	19.23	7.84–47.21

Model	Results of model fitting: Change in deviance	Degrees of freedom	P value[b]
Full model			
Mixture model ($\lambda = -0.36$)	2.902	3	0.41
Additive model	3.565	4	0.47
Multiplicative model	5.131	4	0.27
Background + WLM	9.456	6	0.15
Background + CDAY	80.030	6	<0.001
Background only	85.815	8	<0.001

[a] Referent category: relative risks were adjusted by age and calendar period.
[b] P value of fit relative to the full model.
Abbreviation: N = number of lung cancer deaths. These deaths were rounded to base unit of 5.

TABLE 6
Excess Relative Risk[a] (ERR/100 WLM) of Lung Cancer Mortality by Time Since Exposure Windows, Newfoundland Fluorspar Underground Miners, 1950–2016

	Time since exposure windows (years)				
	5–14 (θ_1)	15–24 (θ_2)	25–34 (θ_3)	35+ (θ_4)	P[b]
θ_i	1.0	0.58	0.22	0.05	
ERR/100 WLM[a]	1.837	1.066	0.395	0.083	<0.001
95% CI	0.193–3.480	0.276–1.857	0.092–0.697	–0.005–0.1711	

[a] ERR = Excess Relative Risk. Background rates adjusted for age and period. A lag interval of 5 years was incorporated into the calculation of cumulative exposure.
[b] *P* value for test of homogeneity of time since exposure effects.

occupational radon-exposed cohorts when future pooled analyses are considered.

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