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LEUKEMIA, LYMPHOMA AND MULTIPLE MYELOMA MORTALITY (1950–1999) AND INCIDENCE (1969–1999) IN THE ELDORADO URANIUM WORKERS COHORT

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Abstract

Uranium workers are chronically exposed to low levels of radon decay products (RDP) and gamma (γ) radiation. Risks of leukemia from acute and high doses of γ-radiation are well-characterized, but risks from lower doses and dose-rates and from RDP exposures are controversial. Few studies have evaluated risks of other hematologic cancers in uranium workers. The purpose of this study was to analyze radiation-related risks of hematologic cancers in the cohort of Eldorado uranium miners and processors first employed in 1932–1980 in relation to cumulative RDP exposures and γ-ray doses. The average cumulative RDP exposure was 100.2 working level months and the average cumulative whole-body γ-radiation dose was 52.2 millisievert. We identified 101 deaths and 160 cases of hematologic cancers in the cohort. Overall, male workers had lower mortality and cancer incidence rates for all outcomes compared with the general Canadian male population, a likely healthy worker effect. No statistically significant association between RDP exposure or γ-ray doses, or a combination of both, and mortality or incidence of any hematologic cancer was found. We observed consistent but non-statistically significant increases in risks of chronic lymphocytic leukemia (CLL) and Hodgkin lymphoma (HL) incidence and non-Hodgkin lymphoma (NHL) mortality with increasing γ-ray doses. These findings are consistent with recent studies of increased risks of CLL and NHL incidence after γ-radiation exposure. Further research is necessary to understand risks of other hematologic cancers from low-dose exposures to γ-radiation.

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Ethics in publishing

The 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.

Keywords

hematologic cancers; uranium miners; gamma radiation; leukemia; chronic lymphocytic leukemia; lymphoma

1. Introduction

Significantly increased risks of leukemia associated with exposure to high acute doses of ionizing radiation are well-studied and recognized (UNSCEAR, 2008). The evidence of radiation-associated risks of other hematologic cancers, including Hodgkin lymphoma (HL), multiple myeloma (MM) and non-Hodgkin lymphoma (NHL), is mixed (Boice, 1992; Ron, 1998), with some studies showing significantly increased risks of NHL in some subgroups (Hsu et al., 2013; Richardson et al., 2009), and little evidence of increased risks of MM or HL. The risks of protracted low-dose radiation are also not clear. Recent studies of nuclear workers occupationally exposed to low doses of radiation showed increased radiation risks of leukemia, NHL and MM, but little evidence of radiation-associated risks of HL or chronic lymphocytic leukemia (CLL) (Cardis et al., 2007; Muirhead et al., 2009; Vrijheid et al., 2008).

Ionizing radiation was thought to have little evidence of an effect on CLL in the study of atomic bomb (A-bomb) survivors from Hiroshima and Nagasaki, based mainly on the first 40-years of follow-up of (Preston et al., 1994). However, CLL is very rare in the Japanese population (~6%) (Tamura et al., 2001), making risk assessment difficult (Richardson et al., 2005). Recent results of the A-bomb survivors reported a significant increased risk of CLL, albeit based on 12 cases diagnosed over 55 years of follow-up (Hsu et al., 2013). A significantly increased radiation risk of CLL, similar in size to risks of other types of leukemia, was also found in a recent study of Chornobyl cleanup workers exposed to protracted low-dose external radiation (Zablotska et al., 2013).

Once inhaled, radon decay products (RDP) can be distributed to the red bone marrow and consequently may increase the risk of leukemia (Laurier et al., 2001). Since uranium miners are also exposed to gamma (γ) radiation doses, there is growing interest in understanding the risks of leukemia and other hematologic cancers in these workers. Past mortality-based cohort and case-control studies of uranium miners and processing workers (Darby et al., 1995; Laurier et al., 2001; Polednak and Frome, 1981), as well as recent ecological studies (Boice et al., 2009; Boice et al., 2007; Boice et al., 2010), provide little evidence of an association between radon and leukemia. However, recent studies based on cancer incidence reported elevated risks of CLL and NHL (attributed to radon, RDP, and γ-rays) (Mohner et al., 2010; Rericha et al., 2006).

The updated Eldorado cohort consists of 17,660 uranium mine, mill and processing workers, first employed in 1932–1980, with relatively recent mortality (1950–1999) and cancer incidence (1969–1999) follow-up (Lane et al., 2010). The purpose of the current analysis is to assess the radiation risks (RDP exposures and γ-ray doses) of hematologic cancers (combined), malignant lymphoma (HL and NHL), leukemia (CLL and non-CLL) and MM among Eldorado workers.

2. Materials and methods

A detailed description of the Eldorado cohort, record linkages, outcomes and exposures has been published previously (Lane et al., 2010).

2.1. Cohort

The cohort included uranium mine 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 (N=19,855). The sub-cohort membership was based on the employment site where a worker spent the longest period of time working for Eldorado. Cohort members were first employed between 1932 and 1980, were between the ages of 15 and 75 years, and alive at start of follow-up in 1950 (mortality analysis) or 1969 (cancer incidence analysis).

2.2. Record linkage

An internal linkage and data processing led to the exclusion of 2,195 (11.0%) records with missing information (i.e., sex, birth year, age out of range, no occupational record, and no exposure data). The final cohort for mortality analysis included 17,660 subjects (88.9% of the original cohort). Information on "fact of death" was used for "death clearance" between 1940 and 1969 (n=886) and 4 additional subjects were excluded because their RDP exposure occurred after cancer diagnosis. The incidence analysis included 16,770 subjects.

The cohort was linked to the Historic Summary Tax File (HSTF), the Canadian Mortality Database (CMDB) and the Canadian Cancer Database (CCDB) to ascertain mortality and cancer incidence until the end of 1999. In total, the vital status of 15,580 (78.5%) cohort subjects was ascertained. Individuals (N= 4,307, 21.8%) who could not be linked to the HSTF or the CMDB had their termination date at work as the last date known alive.

The HSTF includes identifiers and the minimal amount of data required to ascertain the vital status and location of individuals since 1984. The HSTF was used to enhance the Eldorado linkage by filling in data gaps, to determine the vital status of the cohort members at the end of the follow-up period, and to evaluate the results of the mortality linkage. The CMDB (1950 to present) is based on the vital statistics program at Statistics Canada, that routinely collects demographic and cause of death information from all provincial and territorial vital statistics registries on all deaths in Canada. Some data is also collected on Canadian residents who died in some states of the United States. Registration of deaths is a legal requirement through the Vital Statistics Acts (or equivalent legislation) in each Canadian province and territory, so reporting is virtually complete. Under-coverage is thought to be minimal (1% or less) (Goldberg et al., 1993). Cancer incidence records from provincial and territorial cancer registries are sent to Statistics Canada where it is edited, standardized and transformed into a format suitable for record linkage, thereby creating the CCDB (1969 to present). Cancer reporting is virtually complete and of high quality, since it is routinely checked for accuracy through regular assessments by Statistics Canada and the cancer

registries. The cancer data is also linked with mortality data to ensure the completeness and correctness of vital status information and capture missed cancer cases. Both linking procedures optimize the accuracy of the data (Canadian Cancer Society, 2013).

2.3. Outcomes

For the mortality and cancer 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 the *International Classification of Diseases, Ninth Revision (ICD-9)* (WHO, 1998) or the *International Classification of Diseases for Oncology: Morphology of Neoplasms, Third Edition (ICD-O-3)* (Fritz et al., 2000). This included all hematologic cancers combined (ICD-9: 200.0–208.9) and all malignant lymphoma (ICD-9: 200.0–202.9), Hodgkin lymphoma (HL, ICD-9: 201.0–201.9), non-Hodgkin lymphoma (NHL, ICD-9: 200.0–200.9 & 202.0–202.9), multiple myeloma (MM, ICD-9: 203.0–203.9), all leukemia (ICD-9: 204.0–208.9), CLL (ICD-9: 204.1, ICD-O-3: M9823/3) and non-CLL, which were evaluated separately.

2.4. Exposures

The detailed work history file was obtained from Eldorado company records. A detailed description of how RDP exposure was estimated is available (Howe et al., 1986; Howe et al., 1987; Lane et al., 2010). In brief, the annual mean RDP exposure in WLM[1] was calculated by summing over the WL measurements available for each type of workplace, the proportion of workers in each occupation and the proportion of time spent in each type of workplace by workers in each occupation. Workplace RDP concentration measurements were supplemented by data on seasonal mine ventilation rates, building air volumes and air exchange rates. Other studies of uranium miners used similar methods to assign personal exposures based on the job-exposure matrix (NRC, 1999). Exposures for workers with additional mining experience in early non-Eldorado Western Canadian mines were estimated based on the Beaverlodge WL data. Any additional RDP exposures (i.e., from Ontario uranium mines) were obtained from the National Dose Registry (NDR[2]). The current study also has information on individual γ-ray doses for all cohort subjects. Personal γ-ray doses were calculated from the average dose-rates and time on the job and expressed in millisieverts (mSv) for workers who did not wear a personal dosimeter.

2.5. Statistical analysis

Each individual contributed person-years at risk from the later of the date of hire or the start date of follow-up, to the exit date. ‘Start date’ was defined as January 1st, 1950, for the mortality analysis and January 1st, 1969, for the incidence analysis. ‘Exit date’ was defined

[1]The concentration of RDP in workplace air was 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 alpha 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 hours) in a concentration of 1 WL.

[2]The NDR had no early records from Eldorado or other early Western Canadian mines. For all other non-Eldorado radiation exposures, the cohort was linked to the NDR. Miners’ γ-ray doses only became available in the NDR from 1981 onward. Miners were not included in the IARC15 country study of nuclear workers (Cardis et al., 2007); there is no evidence of a problem in the transfer of mining company records to the NDR.

as December 31st, 1999, the date of cancer diagnosis or death, or the last date known alive (defined as date of last employment or contact), whichever occurred earlier.

The initial set of analyses was based on external comparisons of the cohort with the general Canadian population. Observed (O) and expected (E) 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 population mortality (1950–1999) and cancer incidence (1969–1999) rates, adjusted for sex, age and calendar year at risk. Incidence and mortality for leukemia subtypes were not available for the general Canadian population so SMRs and SIRs were provided for all leukemia combined.

The second set of analyses was based on internal comparisons of the cohort and used grouped Poisson regression (Breslow and Day, 1987; Preston et al., 1993) to estimate risks using a simple linear relative risk (RR) model:

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

where X represents factors such as RDP exposure or γ-ray dose, z_i are potential modifying factors such as age at first γ-ray dose and β and γ_i are coefficients, estimated using maximum likelihood techniques. The beta coefficient (β) is referred to as the excess relative risk (ERR) per unit of exposure; by adding 1.0 to the ERR one obtains the relative risk (RR) per 100 WLM for RDP exposure and RR per one sievert (Sv) for γ-ray dose. The summary person-years at risk was cross-classified by age at risk (15–19, 20–24… 85–100 years), calendar year at risk[3] (1950–54, 1955–59… 1995–1999), employment site (Port Hope, Port Radium, Beaverlodge, "other sites"), total duration of employment (<6 months, 6 months +)[4], age at first exposure, cumulative exposure, and years since first exposure. This was done separately for RDP exposures and γ-ray doses. In contrast to Lane *et al*. (Lane et al., 2010), both RDP exposures and γ-ray doses were lagged by 5 years to account for the latency period between exposure and cancer incidence and mortality. Finally, an exploratory analysis was performed for both RDP exposures and γ-ray doses, lagged by 10 years, to compare our findings with a previously published study (Richardson et al., 2009). The person-year weighted mean RDP exposures and γ-ray doses in each cross-classified cell were used in the regression analysis. We also estimated relative risks (RR) for γ-ray dose categories and evaluated linear trend tests based on mean doses for dose categories (0–14, 15–49 and 50–3,420 mSv).

Regression parameters, 95% confidence intervals (95% CI) and p-values were estimated using the maximum likelihood method in the AMFIT module of the EPICURE software (Preston et al., 1993). Tests of statistical significance were based on the likelihood ratio test and all p-values were two-sided. Because of the form of Equation 1, the possible values of β were limited by the requirement that the corresponding relative risks were not negative. If the likelihood of a point or bound estimate did not converge, the minimum value for β was given by <0.

[3]Calendar year at risk for the cancer incidence analysis was (1969–1974, … 1995–1999).
[4]Total duration of employment was split at 6 months, as risk drops after 6 months but then remains constant, as previously observed (Howe et al., 1988).

The number of cancer cases in this paper may differ between the external and internal analyses. In the external analysis, the population incidence rates, used to calculate expected cases, are based on newly diagnosed cancer cases. Thus, an individual can contribute more than one cancer case to the rates. In the internal analysis, the earliest diagnosed case is used so an individual can only contribute one cancer case to the analysis.

3. Results

Thirty percent of Eldorado workers (O=5,332, N=17,660) died from 1950 to 1999 and 23% (O=2,210, N=16,770) developed cancer from 1969 to 1999. Table 1 presents the basic characteristics of the cohort. Most workers were male (N=16,236, 91.9% of the cohort), so all further analyses were restricted to "all male workers." The mean RDP exposures and γ-ray doses (weighted by person-years) are presented in Table 1 separately for the mortality and incidence analyses. Mean RDP and γ-ray doses were higher in the mortality analysis cohort, probably because workers with the higher exposures (i.e., Port Radium workers in the 1930s and 1940s) died prior to 1969. Women had lower RDP exposures than men, although γ-ray doses were comparable. Port Hope workers had the highest γ-ray doses; ~2-fold and ~4-fold higher than Port Radium and Beaverlodge workers, respectively.

Table 2 shows that the SMRs for HL, NHL, MM, and all leukemia were lower than the Canadian general population; however, the SMR was only statistically significant for all leukemia (SMR=0.69, 95% CI: 0.48, 0.97, p-value=0.031). Similar results were observed for the SIR analysis, but all leukemia (SIR=0.79, 95% CI: 0.59, 1.03, p-value=0.088) was no longer statistically significant. Only the SIR for MM approached statistical significance (SIR=0.65, 95% CI: 0.40, 1.01, p-value=0.055).

Age at risk, calendar year at risk, employment site and total duration of employment significantly affected risk estimates so all subsequent analyses were controlled for these variables using stratification.

There were 101 deaths from hematologic cancers (7 HD, 42 NHL, 18 MM, and 34 all leukemia, Table 3) and 553,492 person-years at risk in the male Eldorado mortality cohort. During 1969–1999 incidence follow-up of this cohort, 160 cases of hematologic cancers were diagnosed (10 HD, 78 NHL, 20 MM, and 52 all leukemia, Table 3) and 373,477 person-years accumulated. Table 3 shows no relationship between RDP exposure and mortality or cancer incidence for any of the hematologic cancers (Table 3). HL incidence was borderline significant (N=10, ERR/100 WLM=20.7, 95% CI: <0, 324, p=0.081); however, this was based on few cases and a very wide confidence interval. In the γ-ray dose analysis, a statistically non-significant excess risk was also found for HL incidence (N=10, ERR/Sv=13.0, 95% CI: <0, 139, p-value=0.504) and CLL incidence (N=22, ERR/Sv=7.52, 95% CI: <0, 57.1, p-value=0.375) and NHL mortality (N=42, ERR/Sv=3.54, 95% CI: <0, 29.5, p-value=0.593). In the categorical analysis, risks of HL and CLL incidence increased with γ-ray dose, but linear trend tests were not statistically significant (p for linear trend=0.672 and 0.271, respectively, not shown).

Table 4 shows that HL incidence was significantly associated with γ-ray dose among Beaverlodge workers, but the finding was based on few cases (N=7, ERR/Sv=91.3, 95% CI:

<0, 415, p-value=0.145). A high, although not statistically significant increased risk of HL incidence related to RDP exposures was also observed among workers from this mine site. A correlation between RDP exposures and γ-ray dose (Pearson's r=0.45) was observed among Beaverlodge workers, so the effects of both exposures were examined in one model. The entire increase in risk of HL was primarily due to γ-ray dose since the addition of the RDP exposure term to the model did not significantly improve the model fit (p>0.50, not shown).

The risk of NHL incidence related to γ-ray dose, was statistically non-significantly increased among Port Radium workers (N=21, ERR/Sv=2.19, 95% CI: <0, 27.6, p-value>0.50). Risks increased with γ-ray dose: 15–49 mSv (RR=1.35, 95% CI: 0.46, 3.98) and ≥50 mSv (RR=1.53, 95% CI: 0.47, 5.00) compared to < 15 mSv (p for linear trend=0.537, not shown). The addition of the RDP exposure term to the model did not significantly improve the model fit (p >0.50, not shown).

The risk of CLL incidence related to γ-ray dose was statistically non-significantly increased among Beaverlodge workers (N=15, ERR/Sv=11.8, 95% CI: <0, 84.3, p-value=0.268) and Port Radium workers (N=3, ERR/Sv=10.2, 95% CI: <0, 731, p-value>0.50). Again, risks increased with γ-ray dose and the addition of the RDP exposure terms to the models did not improve the models' fit (both p-values>0.50, not shown). For Beaverlodge and Port Radium workers, risks increased with increasing γ-ray doses, but the risks for Port Hope workers, who had the highest γ-ray doses, were negative. Radiation-related risks of CLL did not differ across facilities (p heterogeneity across facilities>0.50, not shown).

Three of the NHL cases in our study were small cell lymphomas (ICD-O-3: M9670.3), a type of B-cell lymphoma of which CLL is considered one of the stages (Harris et al., 1999). When these were analyzed together with CLL cases, the combined estimate was ERR/Sv=4.91, 95% CI: <0, 41.2, p=0.497. The risk among Beaverlodge and Port Radium workers was ERR/Sv=7.69, 95% CI: <0, 57.5, p=0.387 and ERR/Sv=8.74, 95% CI: <0, 657, p>0.50, respectively (not shown).

4. 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 Eldorado uranium workers known to have worked sometime between 1932 and 1980 and followed-up until the end of 1999.

Overall, workers had lower rates of mortality and cancer incidence of hematologic cancers compared to the age- and calendar year at risk adjusted rates for the general Canadian male population, a likely healthy worker effect (Howe et al., 1988). No statistically significant relationship was observed between RDP exposures or γ-ray doses, or a combination of both, and mortality or incidence of any hematologic cancers. However, for γ-ray doses, there was suggestive, though statistically non-significant, evidence of increased risk of CLL and HL incidence and NHL mortality with increasing dose.

One of the main strengths of this study is its long-term follow-up using very high quality cancer incidence and mortality population-based databases (Canadian Cancer Society, 2013;

Goldberg et al., 1993). Comparatively high rates of follow-up were achieved through substantial improvements to the completeness to the nominal roll and work history files, multiple internal linkages to eliminate duplicate records, linkages to the HSTF, CMDB, CCDB, and the manual resolution of potential computer links.

The follow-up of the entire cohort in terms of both incidence and mortality is unique and provided a complimentary view of the effects of RDP exposures and γ-ray doses on the risk of hematologic cancers. The total number of hematologic cancer cases (n=160) was significantly larger than the number of deaths (n=101), even though mortality follow-up was 19 years longer than incidence follow-up. This is most likely because people diagnosed with HL, NHL and CLL, the most indolent of hematologic cancers, often do not die from these conditions (Canadian Cancer Society, 2013); thus workers with these conditions will often not have them recorded as the underlying cause of death on death certificates. If any advances in treatment occur during the study period, mortality would become a less sensitive outcome, whereas incidence would be unaffected. Likewise, cancers with high survival rates, such as HL, NHL and CLL, would not be detected by mortality statistics.

Hematologic cancers, in particular leukemia, are among the most radiosensitive cancers (NRC, 2006). They originate in the mutated cells of the bone marrow and from the mutated cells of the immune system. Whole-body γ-ray doses have been found to significantly increase risks of leukemia in survivors of atomic bombings in Japan (Hsu et al., 2013), risks of leukemia, NHL and MM in the U.K. radiation workers (Muirhead et al., 2009), and risks of leukemia and NHL in Chornobyl cleanup workers (Kesminiene et al., 2008; Zablotska et al., 2013). Less is known about the effects of radon decay alpha particles on the bone marrow, but a recent study (Harley and Robbins, 2009) reported that the bronchial mucosa has an abundance of circulating lymphocytes, thus suggesting that RDP exposures could be associated with hematologic cancers originating from these cells.

Several limitations should be considered when interpreting the above results. First, the radiation exposure and corresponding doses to red bone marrow in uranium miners come from exposures to radon gas, RDP and long-lived radionuclides present in the uranium ore dust and to external gamma radiation (Marsh et al., 2012). Similar to other studies (NRC, 1999), the current analysis only evaluated RDP exposures, which were calculated as whole-body doses, while bone marrow doses would be a more relevant measure (NRC, 2006). The impact of this is to possibly underestimate radiation risks.

Another important limitation is the study's limited statistical power due to the low RDP exposures and γ-ray doses, and the rareness of hematologic cancers. This could be addressed through further follow-up and pooling of this cohort with other cohorts of uranium workers.

Effects of other carcinogens in ore require careful consideration. Beaverlodge ore was relatively clean with minimal amounts of other carcinogens, but Port Radium ore contained arsenic and cobalt. Arsenic, a known human carcinogen (IARC (International Agency for Research on Cancer), 1980), was recently shown to increase lung cancer among uranium miners (Taeger et al., 2009); however, no such relationship was reported for lymphoma,

MM or leukemia. It is unlikely that the suggested increased risk of CLL reported here is confounded by these carcinogens. In addition to ore, Port Hope workers were exposed to processing chemicals (i.e., ammonia, fluoride) and a variety of uranium compounds at higher concentration and of greater solubility (i.e., UO_3, UF_6) than that found in the ore. Port Hope workers were also exposed to radium compounds, uranium metal and some enriched uranium, which were recently shown to increase the risks of hematologic cancers (Guseva Canu et al., 2011). However, Port Hope workers provided no evidence of elevated risk of hematologic cancers.

A recent comprehensive report (Preston et al., 2013) evaluated radiation exposure assessment errors and their impact on health risks associated with exposure to ionizing radiation and listed numerous sources of uncertainty associated with exposure to radon-decay products. One of the main sources of exposure errors would be shared dose errors, common to all individuals within a group, as well as unshared errors, unique to an individual within a cohort. Most RDP exposure measurement errors in the current study are likely to be non-differential. As pointed out by Blair et al. (Blair et al., 2007), misclassification of exposure in studies of the association between airborne measurements of radon gas and cancer in underground miners is unlikely and the estimates of relative risk are generally unbiased. 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. The impact of such measurement errors depends on a number of factors, in particular, the quantitative nature of the error and the risk function considered. Further studies are necessary to better understand the effects of uncertainties in dose estimation on risk estimates.

A further consideration is that residential radon exposure likely had a greater relative contribution to total RDP exposure in recent times when occupational exposures were lower. It is known that many houses in Uranium City, Port Hope, and the Eldorado town site required remedial work for reduction of radon concentrations. It is likely Eldorado workers lived in these communities at some point; however, information is not available to assign individual residential radon exposures to workers, so it is not possible to estimate residential radon risks. However, if there is no relationship between residential radon and total occupational RDP exposure, the risk estimates would be unbiased. In general, random misclassification of residential radon exposure would bias relative risk estimates towards the null.

Tobacco smoking is a recognized risk factor for some leukemia subtypes (Musselman et al., 2013), but the evidence for association of smoking with NHL (Gibson et al., 2013) and multiple myeloma (Psaltopoulou et al., 2013) is less consistent. For smoking to modify RDP- or gamma-related risks of hematologic cancers it should also be correlated with RDP exposure and γ-ray doses. A case-control study of the Beaverlodge miners (L'Abbe et al., 1991), which accounted for close to 60% of uranium miners in the Eldorado cohort, provided no evidence that RDP exposure was correlated with cigarette smoking among miners. 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, our previous analysis of smoking-related cancers other than lung cancer in the Eldorado cohort (Lane et al., 2010) showed that generally they were not elevated, suggesting that smoking was not substantially elevated relative to the general Canadian male population. Recent nested case-control studies of German (Schnelzer et al., 2010), French (Leuraud et al., 2007) and Czech (Tomasek, 2011) uranium miners, as well as the pooled analysis of these cohorts (Leuraud et al., 2011), showed that the RDP-associated risks of lung cancer persist even after adjustment for smoking. Similarly, smoking did not modify the γ-ray associated risks of cardiovascular outcomes in the Japanese atomic bomb survivors (Shimizu et al., 2010) or workers of the Mayak Production Association in the Southern Urals region of the Russian Federation (Azizova et al., 2010).

This cohort presented a unique opportunity to investigate the effects of RDP exposures and γ-ray doses in the same subjects. In our cohort, RDP exposures and γ-ray doses generally were not correlated (Pearson's r=0.17) except for the Port Hope site, where they were strongly correlated (Pearson's r=0.93). Comparatively high γ-ray doses can increase the risk of several cancer sites (UNSCEAR, 2008), with leukemia being particularly sensitive. However, in the present context, the mean γ-ray dose was fairly low (mean γ-ray dose=52.2 mSv for men), so it is certainly possible that the study had low statistical power to detect any effect.

Risks of CLL recently received attention after two incidence-based studies of occupationally exposed uranium workers suggested that the increased risk of CLL may be due to γ-ray doses rather than RDP exposures. One study (Rericha et al., 2006) reported a significant increase in CLL among Czech uranium miners (RR=1.96, 95%CI: 1.12, 3.42, p=0.02 comparing the 80^{th} percentile of exposure (20 mGy) to the 20^{th} percentile of exposure (1 mGy)). The other study (Mohner et al., 2006) reported an elevated risk of CLL only when γ-radiation dose from diagnostic exposures was examined alone.

The current study also did not observe an increase in CLL risk with RDP exposures, but found a statistically non-significant increase in risk for γ-ray doses (ERR=7.52 per Sv, 95% CI: <0, 57.1, p=0.375). Relative risks increased with increasing dose but a linear trend test was not significant (15–49 mSv (RR=1.97, 95% CI: 0.65, 5.99) and ≥50 mSv (RR=2.25, 95% CI: 0.66, 7.64) compared to < 15 mSv, p for linear trend=0.271). Furthermore, radiation risks of CLL were increased both in Beaverlodge and Port Radium workers (although based on few cases and with wide confidence intervals) and there was not heterogeneity in risks across all facilities (p>0.50).

The larger magnitude of risk in our analysis compared to other studies may reflect the greater γ-ray doses observed in our cohort compared to other cohorts of uranium miners. While a recent pooled analysis of nuclear power industry workers from 15 countries found little evidence for an association between low doses of external ionizing radiation, primarily γ-ray dose, and CLL mortality (Vrijheid et al., 2008), recent studies of incident CLL among Chornobyl cleanup workers reported increased risks in relation to bone marrow doses of γ-radiation (Kesminiene et al., 2008; Romanenko et al., 2008). Twenty-year follow up of Chornobyl cleanup workers from Ukraine provided evidence of significantly increased risks

of CLL due to protracted gamma radiation exposures (ERR/Gy=2.93, 95% CI: 0.07, 9.64, p=0.041) (Zablotska et al., 2013), as did a fifty-five year follow up of the A-bomb survivors (Hsu et al., 2013).

Richardson et al. (Richardson et al., 2009) reported elevated risk of NHL mortality associated with whole-body radiation dose in both a cohort of male nuclear workers and the a-bomb Life Span Study (LSS) participants with γ-ray doses lagged by 5 and 10 years. We observed statistically non-significantly increased radiation risks of NHL with γ-ray doses lagged by 5 years. Similar results were observed when we repeated our analyses using a 10-year lag (not shown). The results for radiation risks of NHL incidence were inconsistent across employment sites (negative for Beaverlodge workers; increased for Port Radium workers).

Finally, MM incidence and mortality were not related to RDP exposures or γ-ray doses under various lag assumptions, consistent with a prior study of Czech uranium miners (Rericha et al., 2006).

5. Conclusions

Overall, workers had lower rates of mortality and cancer incidence of hematologic cancers compared to the general Canadian male population. No statistically significant relationship was observed between RDP exposures or γ-ray doses, or a combination of both, and mortality or cancer incidence of hematologic cancers. However, there was suggestive, though statistically non-significant, evidence of an increased risk of CLL and HL incidence, and NHL mortality with increasing γ-ray dose. Further follow-up of hematologic cancer incidence may shed more light on the risks from low-dose γ-radiation. Pooling of the data from this and other uranium worker cohorts will improve the statistical power of future analyses.

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Highlights

- We analyzed long-term follow-up for hematologic cancers of the Eldorado uranium workers
- Workers were exposed to a unique combination of radon decay products (RDP) and gamma (γ) ray doses
- Exposures to RDP and γ-ray doses were not associated with significantly increased risks of cancers
- Radiation risks of chronic lymphocytic leukemia (CLL) and Hodgkin lymphoma were increased
- Study findings provide additional support for radiation-related risks of CLL.

TABLE 1

Basic characteristics of the Eldorado Uranium Workers Cohort.

Characteristic	Mortality cohort (1950–1999)	Incidence cohort (1969–1999)
Number of subjects TOTAL	17,660	16,770
Men (%)	16,236 (91.9)	15,366 (91.6)
Beaverlodge	9,498	9,231
Port Radium	3,047	2,687
Port Hope	2,652	2,416
Other sites	1,039	1,032
Women (%)	1,424 (8.1)	1,404 (8.4)
Mean[a] RDP exposure, WLM (SD, range)		
Men	100.2 (254.4, 0–2,569.0)	88.6 (229.1, 0–2,663.0)
Beaverlodge	84.8 (203.4, 0–2,441.0)	60.9 (143.5, 0–1,617.0)
Port Radium	180.1 (349.5, 0–2,569.0)	199.2 (362.0, 0–2,663.0)
Port Hope	14.2 (54.1, 0–626.0)	10.4 (43.0, 0–590.3)
Other sites	14.9 (85.8, 0–984.2)	7.9 (56.2, 0–984.2)
Women	4.6 (10.1, 0–67.6)	3.5 (9.0, 0–67.6)
Mean[b] γ-ray dose, mSv (SD, range)		
Men	52.2 (152.4, 0–3,420.0)	41.5 (116.4, 0–2,921.0)
Beaverlodge	25.6 (39.4, 0–393.1)	25.2 (39.5, 0–393.1)
Port Radium	46.8 (82.2, 0–897.3)	43.7 (84.4, 0–1,076.0)
Port Hope	121.5 (306.8, 0–3,420.0)	101.7 (257.0, 0–2,921.0)
Other sites	23.4 (42.3, 0–250.7)	18.5 (37.0, 0–250.7)
Women	34.4 (77.4, 0–619.8)	24.9 (66.6, 0–619.8)

Abbreviations: mSv, millisieverts; RDP, radon decay product; 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.

TABLE 2

SMRs and SIRs and 95% CIs for various cancers and causes of death compared to Canadian national incidence (1969–1999) and mortality (1950–1999) rates for males.

MORTALITY				
Cause of Death	**Observed**	**Expected**	**SMR[a] and 95% CI**	**p-value**
Hodgkin lymphoma	7	9.24	0.76 (0.30, 1.56)	0.594
Non-Hodgkin lymphoma	42	46.28	0.91 (0.65, 1.23)	0.59
Multiple myeloma	18	22.12	0.81 (0.48, 1.29)	0.45
All leukemia	34	49	0.69 (0.48, 0.97)	0.031
CANCER INCIDENCE				
Cancer Site	**Observed[b]**	**Expected**	**SIR[a] and 95% CI**	**p-value**
Hodgkin lymphoma	14	14.98	0.93 (0.51, 1.57)	0.935
Non-Hodgkin lymphoma	80	90.09	0.89 (0.70, 1.11)	0.312
Multiple myeloma	20	30.67	0.65 (0.40, 1.01)	0.055
All Leukemia	53	67.13	0.79 (0.59, 1.03)	0.088

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

[a] Adjusted for age and calendar year at risk by stratification.

[b] The number of observed cases reflects the incidence of newly diagnosed cancer cases where a single individual can contribute more than one case of cancer.

TABLE 3

ERRs for various causes of death and cancer in relation to RDP exposures and γ-ray doses.

		RDP Exposures		γ-Ray Doses	
MORTALITY					
Cause of Death	**Number of Deaths**	**ERR/100 WLM (95% CI)[a]**	**p-value[b]**	**ERR/Sv (95% CI)[c]**	**p-value[b]**
All malignant lymphoma	49	0 (n.e.)	0.9	−0.29 (n.e.)	0.825
Hodgkin lymphoma	7	0.2 (<0, 5.79)	0.576	−0.29 (n.e.)	0.752
Non-Hodgkin lymphoma	42	−0.03 (n.e.)	0.768	3.54 (<0, 29.5)[d]	0.593
Multiple myeloma	18	0.04 (<0, 1.07)	0.845	−0.29 (n.e.)	0.639
All Leukemia	34	0.02 (<0, 0.46)	0.808	−0.29 (n.e.)	0.824
All hematological cancers	101	0.02 (<0, 0.23)	0.799	−0.29 (n.e.)	0.572
CANCER INCIDENCE					
Cancer Site	**Number of Cases**	**ERR/100 WLM (95% CI)[a]**	**p-value[b]**	**ERR/Sv (95% CI)[c]**	**p-value[b]**
All malignant lymphoma	88	0.06 (<0, 0.52)	0.568	−0.34 (n.e.)	0.764
Hodgkin lymphoma	10	20.7 (<0, 324)	0.081	13.0 (<0, 139)[d]	0.504
Non-Hodgkin lymphoma	78	0.04 (<0, 0.46)	0.676	−0.34 (n.e.)	0.715
Multiple myeloma	20	0.01 (<0, 0.66)	0.935	−0.34 (n.e.)	0.593
CLL	22	−0.04 (n.e.)	0.59	7.52 (<0, 57.1)	0.375
Leukemia, excluding CLL	30	−0.04 (n.e.)	0.489	−0.34 (n.e.)	0.739
All hematological cancers	160	−0.01 (<0, 0.17)	0.823	−0.34 (n.e.)	0.536

Abbreviations: CLL, chronic lymphocytic leukemia; ERR, excess relative risk; n.e., not estimated; RDP, radon decay products; Sv, sievert; WLM, working level months.

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

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

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

[d] ERR estimate increased appreciably (≥10%), but remained not statistically significant in the analyses with lag times 10 years; all other estimates remained unchanged.

TABLE 4

Associations between RDP exposures and γ-ray doses and incidence of HL, NHL and CLL (1969–1999) by site.

Characteristic		Site			
		Beaverlodge	**Port Radium**	**Port Hope**	**Other sites**
Correlation between WLM and γ-ray dose		0.45	0.24	0.93	0.05
Hodgkin lymphoma					
	Number of cases	7	2	0	1
γ-ray doses	ERR/Sv (95% CI)	91.3 (<0, 415)	n.e.	n.e.	n.e.
	p-value[a]	0.145			
RDP exposures	ERR/100 WLM (95% CI)	23.2 (<0, 365)	n.e.	n.e.	n.e.
	p-value	0.19			
Non-Hodgkin lymphoma					
	Number of cases	37	21	15	5
γ-ray doses	ERR/Sv (95% CI)	−2.54 (n.e.)	2.19 (<0, 27.6)	−0.34 (n.e.)	n.e.
	p-value	0.388	>0.50	>0.50	
RDP exposures	ERR/100 WLM (95% CI)	−0.062 (n.e.)	0.14 (<0, 0.99)	−0.17 (n.e.)	n.e.
	p-value	>0.50	0.372	>0.50	
CLL					
	Number of cases	15	3	4	0
γ-ray doses	ERR/Sv (95% CI)	11.8 (<0, 84.3)	10.2 (<0, 731)	−0.34 (n.e.)	n.e.
	p-value	0.268	>0.50	>0.50	
RDP exposures	ERR/100 WLM (95% CI)	0.17 (<0, 1.89)	−0.04 (n.e.)	−0.17 (n.e.)	n.e.
	p-value	>0.50	>0.50	>0.50	

Abbreviations: CLL, chronic lymphocytic leukemia; ERR, excess relative risk; n.e., not estimated; RDP, radon decay products; SD, standard deviation; Sv, sievert; WLM, working level months.

[a]P-values from the likelihood ratio test comparing nested model with and without the continuous exposure term.