



# 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 ( $\gamma$ ) radiation. Risks of leukemia from acute and high doses of  $\gamma$ -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  $\gamma$ -ray doses. The average cumulative RDP exposure was 100.2 working level months and the average cumulative whole-body  $\gamma$ -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  $\gamma$ -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  $\gamma$ -ray doses. These findings are consistent with recent studies of increased risks of CLL and NHL incidence after  $\gamma$ -radiation exposure. Further research is necessary to understand risks of other hematologic cancers from low-dose exposures to  $\gamma$ -radiation.

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## 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 (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 reported in a recent study of Chernobyl cleanup workers exposed to protracted low-dose external irradiation (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 ( $\gamma$ ) radiation doses, there is growing interest in understanding the risks of leukemia and other hematologic

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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, 2007, 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  $\gamma$ -rays) (Mohner et al., 2006, 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  $\gamma$ -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 2195 (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 1950 and 1969 ( $n=886$ ) and 4 additional subjects were excluded because their RDP exposure occurred after cancer diagnosis. The incidence analysis is therefore based on 16,770 subjects.

The cohort was linked to the Historic Summary Tax File (HSTF), the Canadian Mortality Database (CMDDB) 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 ( $N=4307$ , 21.8%) who could not be linked to the HSTF or the CMDDB 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 cohort 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 CMDDB (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 are also collected on Canadian residents who died in some states of the United States of America. 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 they are 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 are also linked with mortality data to ensure the completeness and correctness of vital status information and to 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, 1987; Lane et al., 2010). In brief, the annual mean RDP exposure in WLM<sup>1</sup> 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<sup>2</sup>). The current study also has information on individual  $\gamma$ -ray doses for all cohort subjects. Personal  $\gamma$ -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 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:

$$\text{Relative risk} = 1.0 + (\beta X) \exp(\sum_i \gamma_i z_i) \quad (1)$$

where  $X$  represents factors such as RDP exposure or  $\gamma$ -ray dose,  $z_i$  are potential modifying factors such as age at first  $\gamma$ -ray dose, and  $\beta$  and  $\gamma_i$  are coefficients, estimated using maximum likelihood techniques. The beta coefficient ( $\beta$ ) 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  $\gamma$ -ray dose. The summary person-years at risk were cross-classified by age at risk (15–19, 20–24... 85–100 years), calendar year at risk<sup>3</sup>

<sup>1</sup> 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  $1.3 \times 10^5$  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 h) in a concentration of 1 WL.

<sup>2</sup> 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’  $\gamma$ -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.

<sup>3</sup> Calendar year at risk for the cancer incidence analysis was (1969–1974,... 1995–1999).

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