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Mortality (1950–1999) and cancer incidence (1969–1999) of workers in the Port Hope cohort study exposed to a unique combination of radium, uranium and γ-ray doses

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ABSTRACT

Objectives: Uranium processing workers are exposed to uranium and radium compounds from the ore dust and to γ-ray radiation, but less to radon decay products (RDP), typical of the uranium miners. We examined the risks of these exposures in a cohort of workers from Port Hope radium and uranium refinery and processing plant.

Design: A retrospective cohort study with carefully documented exposures, which allowed separation of those with primary exposures to radium and uranium.

Settings: Port Hope, Ontario, Canada, uranium processors with no mining experience.

Participants: 3000 male and female workers first employed (1932–1980) and followed for mortality (1950–1999) and cancer incidence (1969–1999).

Outcome measures: Cohort mortality and incidence were compared with the general Canadian population. Poisson regression was used to evaluate the association between cumulative RDP exposures and γ-ray doses and causes of death and cancers potentially related to radium and uranium processing.

Results: Overall, workers had lower mortality and cancer incidence compared with the general Canadian population. In analyses restricted to men (n=2645), the person-year weighted mean cumulative RDP exposure was 15.9 working level months (WLM) and the mean cumulative whole-body γ-ray dose was 134.4 millisieverts. We observed small, non-statistically significant increases in radiation risks of mortality and incidence of lung cancer due to RDP exposures (excess relative risks/100 WLM=0.21, 95% CI <−0.45 to 1.59 and 0.77, 95% CI <−0.19 to 3.39, respectively), with similar risks for those exposed to radium and uranium. All other causes of death and cancer incidence were not significantly associated with RDP exposures or γ-ray doses or a combination of both.

Conclusions: In one of the largest cohort studies of workers exposed to radium, uranium and γ-ray doses, no significant radiation-associated risks were observed for any cancer site or cause of death. Continued follow-up and pooling with other cohorts of workers exposed to by-products of radium and uranium processing could provide valuable insight into occupational risks and suspected differences in risk with uranium miners.

ARTICLE SUMMARY

Article focus

- Cancer mortality and incidence in the cohort of workers from Port Hope radium and uranium refinery and processing plant exposed to a unique combination of radium, uranium and γ-ray doses and with no mining experience.
- Comparison of risks estimated for radium and uranium processors with estimated risks for uranium miners primarily exposed to radon decay products (RDP).

Key messages

- Small but not significant associations between workers' occupational RDP exposure and lung cancer mortality and incidence were observed, which were somewhat smaller compared to the risks for Canadian uranium miners.
- No significant increases in risks were estimated for any other cancer site or cause of death from RDP or γ-ray doses or a combination of both.

Strengths and limitations of this study

- One of the largest cohort studies of workers exposed to a unique combination of radium, uranium and γ-ray doses as a result of the refining and processing of radium and uranium.
- Long-term incidence and mortality follow-up provided a complementary view of the effects of RDP exposures and γ-ray doses on the risk of cancer.
- Limited statistical power due to low RDP exposures could be addressed through further follow-up and pooling of the data with other cohorts from similar radium and uranium processing operations.

INTRODUCTION

The mortality and cancer incidence follow-up of uranium mine, mill and processing workers are essential to improve our understanding of radiation risks and to ensure that radiation protection programmes protect workers' health appropriately. Epidemiological studies, primarily of underground miners, show increases in lung cancer risk from exposures to radon decay products (RDP).[1 2] Uranium processing workers are exposed to a wide array of uranium compounds from ore dust and other radioactive mill products, but less to RDP, typical of the workers in the uranium mines. Only a few studies have examined the risks of these exposures[3–7] and had contradictory results, necessitating further research in this area.

The Port Hope radium and uranium refinery and processing plant became operational in 1932 and continues to operate today as Cameco Corporation Port Hope Conversion Facility (Port Hope). Port Hope workers were exposed to a wide variety of chemicals and radiation types. In addition to γ-ray and RDP radiation, they were exposed to relatively concentrated forms of uranium (sulfates and nitrates during the refining years and UO_2, UO_3 and uranium fluorides more recently) through inhalation and ingestion. The solubility of these compounds in lung fluids is highly variable, with UO_3 and UO_2F_2 being transported rapidly through the body, in the bloodstream, and excreted through the kidneys.[8 9] The inhaled particles of insoluble uranium, such as UO_2, are more likely to be retained by the lungs for a long period of time, and may produce a larger radiation dose to the lungs compared to the readily soluble uranium compounds. The chemical toxicity of natural and depleted uranium is considered to be potentially more harmful than its radioactive properties and depends on the route of exposure (inhaled or ingested) and the solubility of its chemical form (compounds), with the most soluble and, therefore, readily absorbed uranium compounds being the most potent toxins.[8] Chemically toxic soluble uranium compounds could potentially impair kidney function, as has been shown in high-dose laboratory animal studies,[8–10] while lower dose studies indicated only transient changes.[11] Workers were also exposed to radium, which tends to naturally concentrate in the bones, potentially exposing the surrounding tissues, including bone marrow, to ionising radiation.[10]

To improve our understanding of radiation risks of exposure to a complex combination of radium, uranium and γ-rays, we analysed the data from a cohort of Port Hope radium and uranium refining and processing workers with no mining experience. This analysis is based on a slightly different cohort with more detailed exposure information than was included in the Eldorado cohort[12] and excludes all workers with any mining experience (see Cohort characteristics and follow-up below).[12] Because of the hypothesised differences in the effects of radium and uranium, we examined risks separately for those exposed primarily to radium and those primarily exposed to uranium. In addition, we used different analytical methods than in the Eldorado cohort[12] to analyse and compare mortality and cancer incidence in the cohort with special attention to cancers of the lung and bronchi, leukaemia and lymphoma, bone, liver and kidney cancers, as well as non-malignant respiratory, renal and cardiovascular diseases (CVD).

MATERIALS AND METHODS

Cohort characteristics and follow-up

The Port Hope cohort's materials and methods have been described previously in preparation for the updated analysis of Eldorado uranium workers, which also included Port Radium and Beaverlodge miners.[12] In brief, 3338 potential study individuals came from the personnel records provided by the radium and uranium refining and processing plant in Port Hope, Ontario, originally owned by Eldorado Nuclear Ltd. For inclusion in the study, workers had to be employed at Port Hope during the ages of 15–75 years sometime between 1932 and 1980, had their last contact after 1940, and had to be alive at the start of follow-up in 1950 (mortality analysis) or 1969 (cancer incidence analysis). All workers were included regardless of the duration of employment. This cohort of 3039 eligible workers included 36 workers who were previously included in 'other sites' category in the Eldorado cohort analysis,[12] but more detailed exposure information available in this analysis allowed us to ascertain that they worked for Port Hope. We used National Dose Registry (NDR) information and Eldorado's personnel records to exclude Port Hope workers with any mining experience (n=39), leaving a cohort for analysis of 3000 workers.

The nominal roll file was linked to the Canadian Mortality Data Base (CMDB) and to the Canadian Cancer Data Base (CCDB) to ascertain mortality from 1950 to 1999 and cancer incidence from 1969 to 1999. Data in the CMDB are obtained through the vital statistics system for national reporting of vital statistics data. Since the registration of deaths is a legal requirement through the Vital Statistics Acts (or equivalent legislation) in each Canadian province and territory, reporting is virtually complete. Death records originate with the provincial and territorial registrars of vital statistics and are provided regularly to Statistics Canada. Undercoverage is thought to be minimal (1% or less).[13]

The 'alive' follow-up (1984–2000) was completed via deterministic linkage with the Historic Tax Summary file using the social insurance number (SIN). This linkage was carried out for the 60% of individuals in the cohort with a valid SIN. Using this method, 41% of the cohort was confirmed 'alive' as of 31 December 2000 and 7% were confirmed alive at some time between 1984 and 1998. In addition, probabilistic linkage of the cohort file with the CMDB and the CCDB resulted in ascertainment of death or cancer diagnosis for an additional 43% of cohort subjects (1295 of 3000). The remaining 9%,

who could not be linked to the Historic Tax Summary file or the CMDB or the CCDB, were considered lost to follow-up and had their termination date at work as the last date alive.

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 ICD-9.[14] Based on the literature review,[8 15] we paid special attention to several outcomes that have been shown to be associated with exposures to radium and uranium processing, including cancers of the lung and bronchi, leukaemia and lymphoma, bone, liver and kidney cancers, as well as non-malignant respiratory, renal and liver diseases. We also investigated possible associations with CVD outcomes based on recent reports of increased risks from low-dose RDP[16] and γ-ray exposures,[17] in uranium miners and nuclear workers, respectively.

Assessment of exposures

Initially, high-grade pitchblende ores (10–50% U_3O_8) were processed for the recovery of radium (1930–1942). In 1942, the focus shifted to processing of pitchblende for the recovery of uranium, with the final phasing out of the radium processing in 1954. In 1955, a solvent extraction (SX) process was implemented for the recovery of pure uranium trioxide (UO_3) for the nuclear power industry. With pitchblende feed disappearing after the closure of the Port Radium mine in 1960, the feed material to the plant became predominantly yellowcake (U_3O_8). In the late 1950s, a process was developed to convert UO_3 into reactor-grade uranium dioxide (UO_2), and in 1970 a uranium hexafluoride (UF_6) plant was set up. Natural uranium metal production started in 1957 and both depleted and enriched uranium metallurgical operations continued through the 1960s and 1970s. In 1984, the SX operations closed, and since then Port Hope only receives UO_3 for conversion into UO_2 or UF_6.

There were no early radon or RDP measurements taken at Port Hope at the time of the start-up in 1932. In the 1930s to 1950s, the RDP estimates were based on the quantities of radium present in the plant in ore and at various stages of refinement, measured radon emanation rates from various radium-bearing materials, building air volumes and estimates of air exchange rates. In the early 1970s, RDP measurements were done in the yellowcake warehouses, but occupancy was generally low and no exposure estimates were made. The individual annual exposures in working level months (WLM) were calculated from working level[i] estimates for each type of workplace, the proportion of employees in each occupation and the proportion of time spent in each type of workplace by employees in each occupation.

γ-Radiation was the primary type of radiation exposure at Port Hope. There were no measurements at the time of start-up. Film badges were used on some individuals in the late 1940s, and were worn by most radium workers and a sampling of others from mid-1947 to early 1953. Full individual external dosimetry (100% coverage) was in place by about 1970 and individual records were kept. In this analysis, personal γ-ray doses were calculated from the average dose-rates and time on the job and expressed in millisieverts (mSv) for each individual who had not been wearing a badge. All γ-ray doses were whole-body effective doses.

Measured individual doses were recorded in Eldorado's radiation exposure files; thus, company records were used if available rather than doses from the NDR of Health Canada. The NDR collects and records radiation exposure and dose data for all exposed workers in Canada from 1951 (with some records going back to 1944).[18] Recent work by Cameco indicates that when differences existed between company records and the NDR, they were relatively small (John Takala, personal communication, 2012). For all other non-Eldorado radiation exposures from 1951 to 1999, the nominal roll was linked to the NDR records.

Urinalysis for uranium has been done since the early 1960s and fluorides were added after the UF_6 plant started up. α-Counting of urine samples from workers exposed to enriched uranium was also done, but on a limited basis. Direct measurement of uranium in the thorax by whole-body counting was added to the monitoring programme in the early 1980s, but no regular internal dose calculations were performed.

Using information not available to Lane *et al*,[12] we have further divided this cohort into those exposed primarily to radium and those primarily exposed to uranium. Workers who had worked in radium operations at any time were classified as radium workers, while all other workers who had never worked in radium operations were classified as uranium workers.

Statistical analyses

Each individual contributed person-years at risk from the later of the date of hire or the start date of follow-up, defined as 1 January 1950, for mortality analysis and 1 January 1969, for cancer incidence analysis, to the exit date of 31 December 1999, or the date of cancer diagnosis or death, or the last date known alive defined as the date of last employment or contact, whichever occurred earlier. The first series of analyses was a comparison of the cohort with the general Canadian population. Observed and expected values were used to estimate standardised mortality ratios (SMRs) and standardised incidence ratios (SIRs) by means of indirect standardisation. Expected values were derived from the Canadian national population mortality (1950–1999) and cancer

[i]The concentration of RDP per litre of air that would result in the ultimate release of 1.3×10^5 MeV of potential α-particle energy. One WLM is equivalent to one working month (170 h) in a concentration of 1 WL.

Table 1 Basic characteristics of the Port Hope cohort

Characteristic	All workers with no mining experience	Radium workers	Uranium workers
Total number of individuals	3000	528	2472
Males (%)	2645 (88.2)	497 (94.1)	2148 (86.9)
Females (%)	355 (11.8)	31 (5.9)	324 (13.1)
Lifetime* RDP exposure, WLM, mean (range, SD)			
Males	13.3 (0–627.6, 45.9)	43.9 (0–627.6, 86.9)	6.3 (0–408.2, 24.1)
Females	4.9 (0–62.7, 9.6)	19.7 (0.5–62.7, 15.5)	3.5 (0–45.1, 7.5)
Lifetime* γ-dose, mSv, mean (range, SD)			
Males	116.4 (0–5098.8, 312.1)	325.6 (0.4–5098.8, 562.1)	67.9 (0–2433.2, 185.7)
Females	36.2 (0–464.7, 69.7)	129.0 (1.9–329.4, 85.8)	27.3 (0–464.7, 61.1)

*Individual exposures cumulated up to the end of follow-up.
mSv, millisieverts; RDP, radon decay products; WLM, working level months.

incidence (1969–1999) rates. Expected values were adjusted for age and calendar year at risk. Incidence and mortality by leukaemia subtypes were not available for the general Canadian population, and therefore, SMRs and SIRs were not possible for leukaemia subtypes.

The second series of comparisons was based on internal comparisons and used grouped Poisson regression analyses[19 20] to estimate risks from a simple linear relative risk (RR) model:

$$RR = 1.0 + (\beta X)\exp(\Sigma_i \gamma_i z_i) \qquad (1)$$

where X represents factors such as RDP exposure or γ-ray whole-body 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.[21] The β coefficient is referred to as the excess RR (ERR) per unit of exposure; by adding 1.0 to the ERR, one obtains the RR at 100 WLM for RDP exposure and per 1 Sv for γ-ray dose. In exploratory analyses, we also entered both γ-ray and RDP exposure terms into the model simultaneously.

The summary person-year experience was cross-classified by age at risk (15–19, 20–24, …, 85–100 years), calendar-year at risk (1950–1954, 1955–1959, …, 1995–1999 for mortality and 1969–1974, …, 1995–1999 for incidence follow-up), total duration of employment (<6 months and 6 months+),[ii] and age at first exposure, cumulative exposure, and years since first exposure, separately for RDP exposures and γ-ray doses. The person-year-weighted mean cumulative exposure in each cross-classified cell was used in the regression analysis. In contrast to Lane *et al*,[12] for all analyses, RDP exposures and γ-ray doses were lagged by 5 years to account for latency period between exposure and cancer incidence and mortality. In exploratory analyses, 10-year and 15-year lags were used for CVD outcomes for comparability with previous studies.[17 23]

[ii]Total duration of employment was split at 6 months, as risk drops after 6 months but then remains constant. Similar phenomena have been previously observed in other studies.[22]

Regression parameters, confidence intervals around these point estimates and p values were estimated using the method of maximum likelihood in the AMFIT module of the EPICURE software.[19] Tests of statistical significance were based on the likelihood ratio test comparing the two nested models with and without RDP exposure variable, and all p values quoted were two-sided. Because of the form of equation 1, the possible values of β are limited by the requirement that the corresponding RR should not be negative. If the likelihood being sought for a point or bound estimate did not converge, the minimum value for β was given by $-1/D_{max}$, where D_{max} was the maximum dose.

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

RESULTS

Demographic and exposure characteristics

Table 1 presents the basic characteristics of the cohort. The mean sex-specific values of lifetime RDP exposures and γ-ray doses are presented for the cohort as a whole (n=3000), and separately for those strictly in radium processing (n=528) and uranium refining and processing jobs (n=2472). Radium workers had higher RDP and γ-ray doses compared to workers involved in uranium refining and processing because there were limited radiation protection standards from 1932 to 1954 during radium extraction (both p<0.001). The majority of workers were male (N=2645, 88.2% of the cohort). Historically, females tended to work at office jobs or as laboratory technicians. Few worked in the plant until recent years. Thus, all further analyses were restricted to males. At the end of the follow-up on 31 December 1999, over 40% of the male workers were deceased (observed=1097, N=2645) with 82 999 person-years of mortality follow-up. There were 55 493 person-years of incidence follow-up with 411 cancers during this time.

The average age at the start of employment was 30 years (SD=11). Workers were employed for an average of 6.4 years (range 0–46, SD=9.3). The actual duration

of exposure from active working days was shorter at 5.6 years (range 0–42, SD=8.6). A majority of workers were exposed to γ-ray doses (4.0% unexposed), but only slightly more than half of the workers had any recorded RDP exposures (42.4% unexposed).

Comparison of the cohort with the general population

Tables 2 and 3 present results of SMR and SIR analyses, respectively. Overall, Port Hope workers had similar all-cause mortality and slightly lower all-cancer mortality and all-cancer incidence compared to the similar age and calendar-time general population of Canada. CVD were the leading cause of death and CVD mortality overall was higher compared to the general population (observed=514, SMR=1.08, 95% CI 0.99 to 1.18, p=0.08). However, both overall and for specific outcomes, estimated SMR CIs included unity, except for hypertensive disease (observed=13, expected=4.87, SMR=2.67, 95% CI 1.42 to 4.57, see Discussion section) and chronic obstructive pulmonary disease (COPD) and asthma (observed=25, expected=43.22, SMR=0.58, 95% CI 0.37 to 0.85), indicating the similarity of risks with the general population.

Cancer was an underlying cause for a quarter of deaths (observed=266), among which 99 deaths were due to lung cancer. Similarly, approximately 15% of male workers (observed=418, N=2645) had a cancer diagnosis, among which 108 were due to lung cancer. Mortality and incidence from lung and laryngeal cancer were elevated compared to the general male Canadian population, but the p values were not significant (p=0.47 and 0.44 for lung and p=0.80 and 0.72 for laryngeal cancer, mortality and incidence, respectively), and the estimated CIs included unity. In addition, estimates for rectal, bladder and other urinary cancer mortality, as well as malignant melanoma, brain and other central nervous system (CNS) cancers incidence, were non-significantly higher compared to the general population, based on very small numbers of deaths/cases.

Diseases potentially related to radium and uranium exposures, such as kidney cancer and non-malignant kidney diseases (nephritis and nephrosis), leukaemia, lymphoma and non-malignant respiratory diseases (COPD) and asthma had mortality and cancer rates significantly lower or similar to the general population. There were no cases of liver or bone cancer.

Table 2 SMR for various causes of death and 95% CIs, male Port Hope workers (1950–1999)

Cause of death (ICD-9 code)	Observed	Expected*	SMR (95% CI)	p Value
All infectious diseases (1–139)	8	11.88	0.67 (0.29 to 1.33)	0.33
All cancers (140–208)	266	282.46	0.94 (0.83 to 1.06)	0.34
Oesophageal cancer (150)	6	7.19	0.83 (0.31 to 1.82)	0.84
Stomach cancer (151)	14	18.25	0.77 (0.42 to 1.29)	0.38
Colon cancer (153)	22	26.74	0.82 (0.52 to 1.25)	0.42
Rectal cancer (154)	15	9.39	1.60 (0.89 to 2.63)	0.11
Pancreatic cancer (157)	10	14.63	0.68 (0.33 to 1.26)	0.28
Laryngeal cancer (161)	5	4.15	1.21 (0.39 to 2.81)	0.80
Lung cancer (162)	99	91.62	1.08 (0.88 to 1.32)	0.47
Prostate cancer (185)	21	25.81	0.81 (0.50 to 1.24)	0.40
Kidney cancer (189.0)	6	6.91	0.87 (0.32 to 1.89)	0.93
Bladder and other urinary cancer (188, 189.1–189.9)	11	8.27	1.33 (0.66 to 2.38)	0.42
Bladder cancer (188)	10	7.82	1.28 (0.61 to 2.35)	0.52
Brain and other CNS cancers (191–192)	5	7.61	0.66 (0.21 to 1.53)	0.46
Brain cancer (191)	5	6.75	0.74 (0.24 to 1.73)	0.67
NHL (200, 202)	7	8.65	0.81 (0.33 to 1.67)	0.73
All leukaemia (204–208)	6	9.50	0.63 (0.23 to 1.37)	0.33
Diabetes mellitus (250)	14	19.39	0.72 (0.39 to 1.21)	0.26
All nervous system diseases (320–389)	11	17.56	0.63 (0.31 to 1.12)	0.13
All CVD (390–459)	514	475.03	1.08 (0.99 to 1.18)	0.08
Hypertensive disease (401–405)	13	4.87	2.67 (1.42 to 4.57)	<0.01
Ischaemic heart disease (410–414)	346	322.36	1.07 (0.96 to 1.19)	0.20
Cerebrovascular disease (430–438)	71	68.88	1.03 (0.81 to 1.30)	0.83
Other CVD	84	78.93	1.06 (0.85 to 1.32)	0.60
Pneumonia (480–486)	29	26.62	1.09 (0.73 to 1.56)	0.70
COPD and asthma (490–496)	25	43.22	0.58 (0.37 to 0.85)	<0.01
All digestive diseases (520–579)	42	43.66	0.96 (0.69 to 1.30)	0.88
Nephritis and nephrosis (580–587)	7	6.36	1.10 (0.44 to 2.27)	0.90
Other genitourinary diseases (590–629)	11	12.78	0.86 (0.43 to 1.54)	0.75
All causes	1097	1071.89	1.02 (0.96 to 1.09)	0.45

*Adjusted for age and calendar-year at risk by stratification.CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular diseases; NHL, non-Hodgkin's lymphoma; SMR, standardised mortality ratio.

Table 3 SIR for various cancers and 95% CIs, male Port Hope workers (1969–1999)

Cause	Observed*	Expected†	SIR (95% CI)	p Value
Lip cancer	5	6.12	0.82 (0.27 to 1.91)	0.85
Oesophageal cancer	5	6.23	0.80 (0.26 to 1.87)	0.82
Stomach cancer	13	17.38	0.75 (0.40 to 1.28)	0.35
Colon cancer	33	39.78	0.83 (0.57 to 1.16)	0.32
Rectal cancer	22	23.95	0.92 (0.58 to 1.39)	0.79
Pancreatic cancer	10	12.37	0.81 (0.39 to 1.49)	0.62
Laryngeal cancer	11	9.55	1.15 (0.58 to 2.06)	0.72
Lung cancer	108	99.92	1.08 (0.89 to 1.30)	0.44
Malignant melanoma	11	8.24	1.33 (0.67 to 2.39)	0.42
Prostate cancer	89	94.32	0.94 (0.76 to 1.16)	0.63
Kidney cancer	5	13.11	0.38 (0.12 to 0.89)	0.02
Bladder and other urinary cancer	30	29.59	1.01 (0.68 to 1.45)	0.99
Bladder cancer	26	28.54	0.91 (0.60 to 1.33)	0.72
Brain and other CNS cancer	9	7.43	1.21 (0.55 to 2.30)	0.66
Brain cancer	9	6.91	1.30 (0.60 to 2.47)	0.52
NHL	15	15.35	0.98 (0.55 to 1.61)	>0.99
All leukaemia	10	12.23	0.82 (0.39 to 1.50)	0.65
All cancers	418	453.52	0.92 (0.84 to 1.01)	0.10

*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.
†Adjusted for age and calendar year at risk by stratification.
CNS, central nervous system; NHL, non-Hodgkin's lymphoma; SIR, standardised incidence ratio.

Dose–response analysis of lung cancer

The person-year weighted mean cumulative RDP exposure was 15.9 WLM (SD=53.9), higher among radium workers compared to uranium workers (26.8 (78.0) and 9.6 (31.1), respectively). Person-year-weighted mean cumulative γ-ray doses were also higher among radium workers (205.7 (430.3) and 93.4(210.7), respectively; all workers: 134.4 (314.2)). (All cumulative exposures were lagged by 5 years.)

Both lung cancer mortality and incidence tended to increase with RDP exposure, but linear trend tests did not reach statistical significance (p=0.56 and 0.21, mortality and incidence, respectively, table 4). In the continuous analysis, we estimated ERR/100 WLM=0.21 (95% CI <−0.45 to 1.59, p=0.54) and ERR/100 WLM=0.77 (95% CI <−0.19 to 3.39, p=0.15) for lung cancer mortality and incidence, both non-significant. Formal tests of heterogeneity within the cohort by type of worker (uranium vs radium workers) were not significant, indicating that risks were similar in both groups (p=0.83 and 0.15, mortality and incidence, respectively, table 4), although the point estimate for RDP-associated risks was fourfold higher for incident lung cancer among uranium workers compared to radium workers. Risks of lung cancer due to γ-ray doses were somewhat increased but not statistically significant both for mortality (ERR/Sv=0.21, 95% CI <−0.29 to 1.94, p=0.66) and incidence (ERR/Sv=0.69, 95% CI −0.28 to 3.43, p=0.26). Models with RDP exposures had smaller deviances compared to the models with only γ-ray doses (not shown), and addition of γ-ray dose term to the model with RDP exposures did not significantly improve the model fit (p=0.71 and 0.54, mortality and incidence, respectively, not shown), indicating that the observed increases in risks were primarily due to RDP exposures. RDP exposures and γ-ray doses were strongly correlated (Pearson's r=0.94 in the mortality and r=0.92 in the incidence analysis).

Dose–response analysis of causes of death and cancers other than lung cancer

There was no meaningful evidence of an association between RDP exposure and increased risk of any causes of death (table 5) or cancer incidence (not shown). Likewise, an analysis of γ-ray doses, which were higher among Port Hope workers compared to their mining counterparts,[12] found that none of the causes of death were significantly associated with γ-ray dose, and a number of them had negative risk estimates (table 5). All risk estimates for cancer incidence outcomes were negative except for colon cancer (ERR/100 WLM=0.15, 95% CI <−0.29 to 1.66, p=0.59 and ERR/Sv=0.73, 95% CI <−0.50 to 5.91, p=0.34, n=32, not shown) and non-Hodgkin's lymphoma (ERR/Sv=0.32, 95% CI < −0.34 to 11.7, p=0.85, n=14, not shown).

In the exploratory analyses with both RDP exposures and γ-ray doses, addition of the γ-ray doses to the model with RDP exposures did not significantly improve model fits for any of the models, indicating that independent effects of γ-ray doses were very low or none (not shown). Cancer sites potentially related to radium and uranium exposures, such as kidney cancer, leukaemia and lymphoma, had negative risk estimates for mortality and cancer incidence. Risk estimates for other cancers of interest could not be estimated because of no cases or a very small number of cases (<5).

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 2645 male Port Hope, Ontario, radium and uranium processing workers first employed sometime in 1932–1980. This is one of the largest cohort studies comprised of workers exposed to a unique combination of radium, uranium and γ-ray doses as a result of the refining and processing of radium and uranium. Overall, workers had similar rates of all causes of death and had lower rates of all cancers compared to the age-adjusted and calendar year-adjusted rates for the general male Canadian population, a likely healthy worker effect.[22] A small but not significant association between workers' occupational RDP exposure and lung cancer mortality was observed. It was somewhat smaller compared to the risks estimated in studies of Canadian uranium miners (ERR/100 WLM=0.21 (95% CI <−0.45 to 1.59), compared to 0.96 (0.56 to 1.56), 0.37 (0.23 to 0.59) and 0.47 (0.28 to 0.65) for Beaverlodge, Port Radium and Fluorspar miners, respectively).[12 24] This was probably due to lower mean lifetime cumulative occupational RDP exposures (13.3, compared to 84.80, 180.08 and 377.70 WLM, respectively) and associated lower statistical power. The formal test of heterogeneity in risks with Beaverlodge and Port Radium miners was significant ($p<0.001$), indicating that RDP-associated risks of lung cancer were significantly different among Port Hope workers. While RDP risk estimates were generally similar for lung cancer mortality, risks of incident lung cancer were fourfold higher among uranium workers compared to radium workers, but CIs overlapped. No statistically significant increases in risks were estimated for any other cancer site or cause of death from RDP or γ-ray doses or a combination of both.

One of the strongest advantages of this study is its long-term follow-up with essentially complete ascertainment of cancer incidence and mortality. Another advantage is the comparatively high rates of follow-up, which were achieved by substantial improvements to the completeness of the nominal roll and work history files, multiple internal linkages to eliminate duplicate records, linkages to the Historic Tax Summary File, CMDB and CCDB, and the manual resolution of potential computer links. The large size of the cohort with detailed annual exposure information (n=2645), percentage of workers deceased (41.5%) and the length of follow-up for mortality (50 years) and cancer incidence (31 years) were substantially greater compared to other studies.[3–7] Incidence and mortality data provided a complementary view of the effects of RDP exposures and γ-ray doses on the risk of cancer. Finally, we were able to identify workers primarily exposed to radium and those primarily exposed to uranium. This identification and analysis of radium workers are of particular interest since their risks would be expected to be different from those of uranium workers not exposed to radium. Although there is evidence of internal exposures to radium and uranium, the data are insufficient for meaningful dose calculations.

The most important limitation of this study is its limited statistical power due to the cohort size and low RDP exposures. This could be addressed through further follow-up and pooling of this study cohort with others from similar radium and uranium processing operations. There was no information on behavioural risk factors. For smoking to confound the RDP-related risk for lung cancer, it should be correlated with both RDP exposure and lung cancer. Smoking was banned at the Port Hope facility in the 1940s and 1950s, and was allowed on a very limited basis thereafter; however, people still smoked outside the workplace. There is no evidence it is associated with RDP exposure in Port Hope workers. We observed that mortality and incidence of tobacco-related cancers were similar to the general population of Canada, suggesting that smoking was not substantially elevated relative to the general population.

No assessment of RDP or γ-ray dose measurement errors on the risk estimates was conducted. RDP concentration estimates were based on plant inventories of radium-bearing materials, published or otherwise known values of radon emanation rates from various materials, building volumes and estimated air exchange rates. The material inventories very likely varied from day to day, but over the year it would have been exact and, therefore, not a significant contributor to error in annual average concentrations. Random errors in the radon emanation rates and building volumes would have been small and a small contributor to error. The equilibrium factor relating RDP to radon concentrations is a function of the air exchange rate and could be a significant contributor to errors in RDP exposures.

There was no individual γ-ray external dosimetry at the time of start-up, so all early exposures were estimated. For some early years, there were missing data on inventories in specific steps of the operation, but a statistical analysis of film badge readings through these years showed that the variance was small and this was not a significant contributor to error. Of greater importance was the variation in individual work habits and the question of whether an individual was actually present in the assumed location in the specific time period. But since the γ-ray dose estimates were estimated based on annual averages, the likely errors would be small. The measurement errors in exposure estimation almost certainly decreased with calendar time; thus, recent workers had lower mean errors than earlier workers.

We had limited data on incorporation and internal exposures to radium and uranium from urinalyses tests conducted since the mid-1960s, which could not be used for internal dose calculations. A recent study of workers employed at the AREVA NC uranium processing plant in France indicated that uranium carcinogenicity may depend both on its radiological and chemical qualities.[25] The study reported a higher carcinogenic effect

Table 4 Risks of lung cancer mortality (1950–1999) and cancer incidence (1969–1999) and 95% CIs by category of cumulative RDP exposure and type of primary exposure, male Port Hope workers

Cumulative exposure (WLM)	Mean exposure (WLM)	Number of deaths	Number of person-years	RR* and 95% CI	p Value
		Lung cancer mortality			
0.00–	0	16	30688	1.00 (reference)	0.56†
0.01–	1.2	33	28666	0.80 (0.41 to 1.58)	
3.5–	7.9	30	12460	1.67 (0.34 to 3.33)	
15–	26.9	11	6518	1.37 (0.58 to 3.25)	
50.0–626.0	177.9	9	4668	1.42 (0.53 to 3.84)	
				ERR/100 WLM and 95% CI*	
All workers with no mining experience	15.9	99	82999	0.21 (<–0.45 to 1.59)	0.54‡
Uranium workers	9.6	78	64880	0.39 (<–1.22 to 4.52)	0.83§
Radium workers	26.8	21	18119	0.21 (<–0.34 to 1.63)	

Cumulative Exposure (WLM)	Mean exposure (WLM)	Number of cases¶	Number of person-years	RR* and 95% CI	p Value
		Lung cancer incidence			
0.00–	0	18	26550	1.00 (reference)	0.21†
0.01–	1.2	37	17113	0.89 (0.46 to 1.72)	
3.5–	7.9	29	6723	1.80 (0.91 to 3.57)	
15.0–	27.2	15	3289	2.28 (1.03 to 5.02)	
50.0–590.3	161.1	9	1857	2.05 (0.77 to 5.44)	
				ERR/100 WLM and 95% CI*	
All workers with no mining experience	11.9	108	55531	0.77 (<–0.19 to 3.39)	0.15‡
Uranium workers	7.0	86	46094	3.33 (–0.04 to 12.94)	0.15§
Radium workers	24.0	22	9437	0.83 (<–0.30 to 3.72)	

*Adjusted for age at risk, calendar year at risk and duration of employment by stratification.
†p Values of the test of linear trend based on mean values for exposure categories.
‡p Values from the likelihood ratio test comparing models with and without exposure variable.
§p Values from the likelihood ratio test for interaction by subcohort.
¶Number of cases based on the earliest cancer diagnosis where each subject could contribute at most one cancer.
ERR/100 WLM, excess relative risk per 100 WLM; RDP, radon decay products; RR, relative risk; WLM, working level months.

of slowly soluble reprocessed uranium on lung cancer and haematological cancers. Port Hope workers were exposed to a variety of uranium compounds of various levels of solubility (U_3O_8, UO_3, UO_2, UO_2F_2, UF_4 and UF_6) at higher concentrations and of greater solubility than was found in the ore. We did not have quantitative information on workers' exposures to processing chemicals or uranium compounds, but observed that uranium workers had a fourfold higher association between RDP exposures and lung cancer incidence compared to radium workers, although the difference was not statistically significant. We also did not have information on quartz or fine silica dust exposures, which have been shown to independently increase the risk of lung cancer.[26 27] However, a small fraction of Port Hope employees before 1955 would have had some dust exposure and the quartz content of that dust would have been much less than that from some of the other uranium properties operating at the time.

Cancers of the respiratory system (trachea, bronchus and lung; laryngeal and pleural cancer), lymphatic and haematopoietic tissue (leukaemia and non-Hodgkin's disease), digestive system (oesophageal, stomach, colorectal and pancreatic cancer), urinary system (kidney and bladder cancer) and other sites (bone, brain and CNS) and prostate were non-significantly elevated in several cohorts of nuclear workers with potential internal exposures to uranium.[28] Studies of uranium processing workers reported increased risks of lymphatic,[3 5] pleural cancers[5] and non-malignant respiratory[3 4] and renal diseases.[3 7] In our analysis, the observed rates of sites potentially related to radium and uranium were significantly lower or similar to the general population and none of these cancer sites were found to be significantly related to workers' RDP (internal) exposures or γ-ray doses. A similar absence of any significant increase in the risks of cancers potentially related to milling operations were recently reported for 904 non-miners employed at the Grants uranium mill in the USA.[4]

We observed higher rates of CVD mortality compared to the general population, especially a significantly increased mortality from hypertensive diseases. We retrieved and examined all death certificates for the

Table 5 Excess relative risk estimates and 95% CIs for RDP exposures and γ-ray dose for various causes of death (1950–1999)

		RDP exposures		γ-Ray dose	
Cause of death	**Number of deaths**	**ERR/100 WLM***	**p Value†**	**ERR/Sv‡**	**p Value†**
Solid cancers	225	0.10 (<−0.18, 0.66)	0.54	0.12 (<−0.35, 0.98)	0.66
Stomach cancer	14	0.43 (<−0.16, 7.48)	0.66	0.81 (<−1.41, 13.07)	0.60
Colon cancer	22	−0.16 (<−0.16, 3.40)	0.74	1.65 (<−2.16, 23.45)	0.40
Rectal cancer	15	0.21 (<−0.34, 2.31)	0.50	0.19 (<−0.61, 3.90)	0.73
Pancreatic cancer	10	n.c.		−0.29 (<−0.29, 8.11)	0.55
Laryngeal cancer	5	n.c.		n.c.	
Prostate cancer	21	0.58 (<−0.96, 8.07)	0.48	0.72 (<−1.47, 8.99)	0.53
Kidney cancer	6	−0.16 (<−0.39, 49.51)	0.92	n.c.	
Bladder cancer	10	−0.15 (<−0.39, 33.14)	0.90	−0.29 (<−0.29, 19.55)	0.76
Brain cancer	5	−0.15 (<−0.34, 1.74)	0.90		
All haematological cancers	17	−0.16 (<−0.34, 14.27)	0.79	−0.29 (<−0.29, 15.31)	0.76
NHL	7	−0.16 (<−0.34, 10.19)	0.80	−0.29 (<−0.29, 20.92)	0.80
Leukaemia	6	n.c.		n.c.	
All CVD	514	0.10 (−0.05, 0.32)	0.22	0.19 (−0.07, 0.55)	0.17
Ischaemic heart disease	346	0.16 (−0.05, 0.50)	0.16	0.31 (−0.05, 0.88)	0.10
Stroke	71	−0.10 (<−0.34, 0.38)	0.57	−0.29 (<−0.29, 0.33)	0.26
Other CVD	97	0.12 (<−0.18, 0.68)	0.49	0.29 (−0.18, 1.27)	0.31
All digestive diseases	42	−0.16 (<−0.34, 0.79)	0.49	−0.23 (<−0.29, 1.66)	0.67

*Model adjusted for age at risk, calendar year at risk and duration of employment by stratification. γ-Ray doses were not included in the model.
†p Values from the likelihood ratio test comparing nested model with and without the exposure term.
‡Model adjusted for age at risk, calendar year at risk and duration of employment by stratification. RDP exposures were not included in the model.
CVD, cardiovascular diseases; ERR/Sv, excess relative risk per 1 sievert; ERR/100 WLM, excess relative risk per 100 WLM; n.c., model did not converge; NHL, non-Hodgkin's lymphoma; RDP, radon decay products; WLM, working level months.

hypertensive deaths (no autopsies). One case was miscoded, while in several other deaths, hypertension was mentioned among as many as five underlying causes of death, including diabetes and stroke, suggesting that hypertension could have been one of the many symptoms arising from the underlying cause of death. The net effect of this examination was to reduce the number of deaths from hypertensive disease by as much as half, eliminating the statistical significance of the elevated SMR.

Our analyses also indicated increased radiation-related risks of CVD mortality (ERR/100 WLM=0.10, 95% CI −0.05 to 0.32 and ERR/Sv=0.19, 95% CI −0.07 to 0.55), mostly driven by increased risks of ischaemic heart disease, although not statistically significant (ERR/100 WLM=0.16, 95% CI −0.05 to 0.50 and ERR/Sv=0.31, 95% CI −0.05 to 0.88). In models with two terms for RDP exposures and γ-ray doses, risks were due to γ-ray doses only, and the fit of the model did not improve with addition of the RDP exposures term (p=0.70). While some studies of uranium miners reported no association between RDP exposures and CVD mortality,[16 29 30] a recent study suggested that increased risks might be due to slowly soluble uranium.[31] Significant positive associations between γ-ray doses and increased risks of CVD mortality were reported in relation to low-dose (ERR/Sv=0.10, 95% CI 0.04 to 0.15)[17] and moderate-dose radiation exposures (ERR/Sv=0.14, 95% CI 0.06 to 0.23).[32] No association in relation to γ-ray doses was reported in the cohort of Wismut uranium miners,[23] but the cumulative mean γ-ray dose for exposed miners was threefold lower compared to our cohort (47 vs 138 mSv). In the Wismut study,[23] and in the Techa River Cohort exposed to internal and external exposures from various uranium fission products,[33] CVD radiation-related risks increased with increasing lag time. In our analysis, risk estimates remained unchanged with 10-year and 15-year lags.

In conclusion, in this analysis of a cohort of workers exposed to radium and uranium refining and processing with detailed annual exposure information, over 90% of workers were followed up for at least 20 years, allowing sufficient time for occupationally induced cancers to develop. Port Hope workers were healthy compared to the general Canadian male population. We observed a small but not statistically significant increase in risk of lung cancer due to RDP exposures. Lung cancer risks of those exposed to uranium did not differ from those exposed to radium. All other causes of death or cancer incidence were not associated with occupational RDP exposures and γ-ray doses. Continued follow-up of the cohort and pooling with other cohorts of workers exposed to by-products of radium and uranium processing could provide valuable insight into risks from occupational uranium exposures and γ-ray doses and into suspected differences in risk with uranium miners.

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