# CANCER INCIDENCE AND MORTALITY AMONG URANIUM MINERS IN THE PŘÍBRAM REGION OF THE CZECH REPUBLIC

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ABSTRACT

Kaitlin E. Kelly-Reif: Cancer incidence and mortality among uranium miners in the Příbram region of the Czech Republic
(Under the direction of David B. Richardson)

There is strong evidence that radon is carcinogenic to humans, and the positive relationship between radon exposure and lung cancer mortality has been demonstrated among several cohorts of uranium miners. However, information is lacking on radon-cancer dose-response relationship at low level exposures, differences between cancer incidence and mortality, the joint effects of smoking and radon, and risks associated with radon exposure and cancers other than lung.

To better understand cancer incidence and mortality among miners occupationally-exposed to low levels of radon progeny, we analyzed data for uranium miners in the Příbram region of the Czech Republic. A total of 16,434 male employees who worked at least 12 months underground between 1949 and 1991, and were alive and residing in Czechoslovakia at the start of the Czech cancer registry (1/1/1977), were included in the cohort. The case-cohort data included more precise radon exposure estimates and smoking information. Standardized mortality and incidence ratios were calculated. Expected disease rates were based on age- and calendar period-specific national mortality and cancer incidence rates. For internal analyses, the association between cumulative radon exposure and cancers was modeled using log-linear rate and linear excess relative rate models

We observed a 52% increase in deaths from all malignant causes compared to expected rates. Miners had higher rates of death than expected due to lung and extrathoracic cancer. Higher than expected incidence was observed for lung, stomach, rectal, liver, extrathoracic, and some hematopoietic cancers. Positive associations were observed between radon and lung cancer incidence along with modification by smoking. The ERR/100WLM was 0.12 (95%CI: -0.09, 0.33) among non-smokers and 1.34 (95%CI: 0.88, 1.80) among smokers. Associations between cumulative radon exposure and extrathoracic cancer incidence (ERR/100 WLM = 0.07; 95%CI: -0.17, 0.31) and chronic lymphocytic leukemia (ERR/100 WLM = 0.24; 95%CI: -0.80, 1.27) were positive but imprecise.

Consistent with other published studies of uranium miners, we observed positive associations between radon exposure, and lung cancer and the joint effect of smoking and radon exposure is greater than additive. Further investigation of associations between radon and extrathoracic cancer and chronic lymphocytic leukemia are needed to estimate more precise exposure-response associations.

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# LIST OF ABBREVIATIONS AND SYMBOLS

| | |
|---|---|
| α | Alpha |
| β | Beta |
| BEIR | Biological Effects of Ionizing Radiation |
| CI | Confidence Interval |
| CLL | Chronic Lymphocytic Leukemia |
| CMR | Causal Mortality Ratio |
| COGEMA | Compagnie Générale desMatiéres Nucléaires |
| CR | Czech Republic |
| ERR | Excess Relative Rate |
| γ | Gamma |
| HL | Hodgkin's Lymphoma |
| ICRP | International Commission on Radiological Protection |
| km | kilometers |
| m | meters |
| mg | milligram |
| Sv | Sievert |
| NHL | Non-Hodgkin's Lymphoma |
| NIEHS | National Institute of Environmental Health Sciences |
| Rn | Radon |
| RR | Relative Rate |
| Σ | Sigma |
| RRC | Risk Set Regression Calibration |

| | |
|---|---|
| SIR | Standardized Incidence Ratio |
| SMR | Standardized Mortality Ratio |
| START | Strategic Arms Reduction Treaty |
| WL | Working level |
| WLM | Working Level Months |
| RDPs | Radon Decay Products |

# CHAPTER I: SPECIFIC AIMS

Radon and its decay products (henceforth referred to as radon) is a known carcinogen.[1] However, identification of radon as a cause of cancer is not sufficient for environmental regulation; quantification of the radon-lung cancer association is also needed. Research focused on low levels of radon exposure and the joint effects of smoking will improve understanding of risks associated with exposures in contemporary occupational and environmental settings and modern populations with varying smoking rates. Quantifying associations between radon exposure and cancers other than lung is also of interest for determining the full population health impacts, and for occupational compensation purposes. Recent studies suggest that radon inhalation may also cause kidney, liver, extrathoracic, and hematopoietic cancers.[2–4]

Many populations other than uranium miners are at risk of cancers from radon exposure. Radon exposure is the second leading cause of lung cancer worldwide after smoking. Radon and its decay products are ubiquitous, and general population exposures are increasing as people more frequently live in underground dwellings and tightly sealed energy efficient homes. Furthermore, a wide range of workers increasingly inhabit modern subterranean environments such as parking garages, utility and subway tunnels, and underground offices, laboratories, and hospitals.

The aim of this study is to address current radon research priorities through the study of underground uranium miners in the Příbram region of the Czech Republic who were occupationally exposed to radon in underground mines. My research will contribute new epidemiological evidence about the health effects of radon by examining the association

between radon inhalation and cancer rates among this large, well enumerated population of workers.

The Příbram uranium mining cohort has several distinct features that make it well suited to advance the study of radon exposure and its association in the development of cancer. It is one of two uranium miner cohorts with cancer incidence data in addition to mortality data. It also has sufficient follow-up times to meaningfully examine cancers with protracted latency and induction periods for several cancer types, and it has individual smoking information for a subset of the cohort. The Příbram miner cohort is also unique in that many workers were exposed to low levels of radon compared to other cohorts of uranium miners, and less co-pollutants compared to other cohorts of uranium miners, namely diesel exhaust exposure and silica.

The following aims were developed in order to improve epidemiological understanding of the association between radon exposure and development of several cancer subtypes:

**Aim 1:** Estimate standardized incidence and mortality ratios, as well as causal mortality ratios, among the cohort of Příbram underground miners using standard national population reference rates. Examine trends over time in mortality ratios, loosen assumptions of comparability in standard populations over time using random effects models, and evaluate possible influences of healthy worker bias and workplace hazards.

**Aim 2:** Estimate the association between radon exposure and mortality. Examine cancer deaths for *a priori* cancer sites of interest, based on prior models of radon energy deposition.

**2a:** Address concerns regarding measurement error of cumulative radon exposure in the full cohort by leveraging detailed data from a subcohort of workers to inform estimates of exposures in the full cohort.

**2b:** Examine changes in risk estimates by duration of exposure, timing of exposure relative to age, and 5- and 10-year exposure lags.

**Aim 3:** Estimate the association between radon exposure and lung cancer incidence, and radon exposure and extrathoracic cancer incidence, in a case-cohort study of Příbram underground miners.

**3a:** Address confounding of the radon-lung cancer association by tobacco smoking and other co-pollutants by developing models informed by Directed Acyclical Graphs (DAGs) and prior literature.

**3b:** Assess modification by smoking using models for departures from additive effects of smoking and radon.

The results gained by this study contributes knowledge to worker protection practices and compensation guidelines for Czech uranium miners and underground miners worldwide. In the early 1990s, 40% of all incident occupational cancers in the Czech Republic were attributed to employment in the uranium mines of the Příbram region. Aim 1 provides population-based knowledge about the differences in cancer incidence and mortality among the uranium miners and the rest of the Czech Republic. Aims 2 and 3 contribute to projections developed by the National Research Council's Committee on Health Risks of Exposure to Radon, which inform international worker protection guidelines. This study addresses health concerns among Czech miners and provides cancer rate estimates for low radon exposure levels comparable to some contemporary occupational and environmental settings.

# CHAPTER II: INTRODUCTION

## 2.1 Radon

Radon is an odorless, colorless gas which occurs naturally from the radioactive decay of uranium. It is ubiquitous in the environment because uranium is found in trace amounts in soils and rocks, and is always accompanied by its decay products.[5,6] While uranium itself is a radioactive material which can also cause cancer, the focus of this dissertation is exposure to radiation from inhalation of radon and its decay products.

Radon gas can enter enclosed structures such as buildings or mines, and because its half-life is 3.82 days, it can accumulate over time. It is estimated that more than half the average annual background radiation dose globally is due to radon and its decay products.[7]

The term 'radon and its decay products' is used interchangeably with 'radon' in this document, and refers to the isotope Rn-222, α particle radiation emissions from its decay into Polonium-218, and all subsequent radiation released from the chain of radioactive decay. Radioactive decay of radon results in the release both alpha and beta radionuclides, but the majority of energy emissions are in the form of α particles.

Although α radiation cannot penetrate through the thickness of human skin, the chemical and physical characteristics of α particles allow them to easily attach to air particles and dissolve in water. Upon inhalation, α radiation can penetrate the thin cellular structures in the airways. They can then be transported into the blood and reach the cells of internal organs and bone marrow. Damage from α radiation occurs numerous ways including breaks in DNA, chromosomal aberrations, and oxidation.

## 2.2 Underground uranium mining

Uranium mining activities are extensive and widespread, with underground mining operations in Canada, the United States, Western Europe, Australia, South Africa, and sites within the former Soviet Union.[5]. Uranium ore is mined for the production of Uranium-235, the fissile material used in weapons and reactors, but only a small proportion of radiation in natural ore comes from Uranium-235. Uranium miners are at risk of cancer because they are exposed to alpha particle energy from radon and its decay products.[8]

In underground mining activities, radon and its short lived decay products contribute the largest proportional dose of radiation to workers. Uranium miners can also be exposed to long-lived radionuclides from uranium ore dust and external gamma radiation.[9] Health effects from these additional forms of radiation, and health effects of radon other than lung cancer are not well characterized in epidemiological research.

The most well-known and extensively studied health effect of inhalation of radon and its progeny is lung cancer. But, the occupational hazards of uranium mining extend beyond cancer. The most well-known non-radiological hazard of uranium mining is silicosis, a range of serious pulmonary diseases caused by the inhalation of silica dust, characterized by breathlessness, cough, weight loss and fatigue.[10]. Miners are also at an elevated risk of other non-malignant respiratory diseases such as chronic obstructive pulmonary disease, and are often exposed to fuel combustion byproducts, heavy metals, and are at an elevated risk of traumatic injury.

## 2.3 Studies of inhalation of radon progeny and lung cancer

Inhalation of radon and its decay products are the leading cause of occupational lung cancer, and, globally, radon inhalation is the second leading cause of lung cancer deaths after smoking.[11] The International Agency for Research on Cancer (IARC) classified radon as a Group

1 human carcinogen.[12] It is well established that miners exposed to radon and its progeny are at an increased risk of lung cancer mortality.[13–15]

The elevated risks of lung cancer from radon inhalation are well characterized among numerous uranium mining cohorts. There are five North American uranium mining cohorts.[8,16–18,2,19,20] Notably, the Colorado Plateau cohort of 4,137 white and American Indian miners found excess lung cancer mortality among white miners and American Indian miners (SMR=4.96 95%CI: 4.55-5.39 and SMR=3.18 95%CI: 2.54-4.07 respectively). Excess stomach cancer mortality was also found among American Indian miners.[2] The Canadian cohort of Ontario miners has both incidence and mortality follow up and a low mean cumulative radon exposure (31 WLM). The Ontario study estimates a doubled rate of lung cancer mortality (RR= 2.32 95%CI: 1.72-3.14) and lung cancer incidence (RR=1.89 95%CI: 1.43-2.50).[19]

There are four European cohorts of underground uranium miners. In addition to the present study of Czech miners in Central Bohemia, an earlier cohort of Czech uranium miners in Western Bohemia has been followed for cancer mortality for 30-60 years.[21–26] Excess lung cancer mortality was reported (SMR=3.47 95%CI: 3.27-3.68), and time since exposure was found to modify the association between radon and lung cancer.[26] A cohort of 5,086 French uranium miners identified an excess of kidney cancer mortality (SMR=1.60; 95% CI: 1.03–2.39) in addition to excess lung cancer mortality (SMR=1.34, 95% CI: 1.16-1.53).[27–30] The largest single study of uranium miners is a cohort study of German miners similar in size to the pooled Biological Effects of Ionizing Radiation (BEIR VI) analysis. Studies of these miners have demonstrated a dose response association between radon and lung cancer, and identified excess rates of stomach and extrathoracic cancers. The German cohort has information on numerous covariates including external gamma radiation, long-lived radionuclides, arsenic, fine dust and silica dust.[31,32,3,33]

Generally, the findings from these studies support the BEIR VI lung cancer models of a positive linear association. The BEIR IV committee estimated radon-lung cancer associations by combining 11 mining cohorts and estimated a pooled ERR/100WLM of 0.59.[11] Although studies agree on a positive association, magnitudes of effect differ, as do estimates related to smoking and time-varying modifiers. For instance, several the modifying effects observed in BEIR IV estimates have not been confirmed in the large German cohort.[31]

The focus of most uranium miner studies has been lung cancer mortality, often among workers exposed to high cumulative levels of radon. Table 2.1 shows the mean cumulative radon exposure among the German and several BEIR VI uranium miner cohorts and the proportion of lung cancer deaths or cases with less than 100 cumulative WLM. This table illustrates how the current study contributes to estimates of lower exposure by reporting on a cohort with low mean cumulative exposure, a large number of cases, and a large portion of those cases whose exposures were less than 100 WLM.

**Table 2.1: Effect estimates, proportion of lung cancers among workers exposed to <100 WLM cumulative exposure, and mean exposure among major uranium mining cohorts***

| Cohort, Country | Mean cumulative exposure to radon (WLM) | Number of lung cancer deaths <100 WLM (%) | ERR/100WLM |
|---|---|---|---|
| Colorado Plateau, US | 578.6 | 20 (6.0%) | 0.42 |
| Ontario, CA | 31 | 225 (79%) | 0.89 |
| New Mexica, US | 110.9 | 10 (15%) | 1.72 |
| CEA-COGEMA, FR | 59.4 | 33 (73%) | 0.36 |
| West Bohemia, CR | 196.8 | 73 (10%) | 0.34 |
| WISMUT, DE | 323 | 280 (~10%)[±] | 0.20 |
| **Cohort, Country** | **Mean cumulative exposure to radon (WLM)** | **Number of lung cancer cases <100 WLM** | **ERR/WLM** |
| Central Bohemia, CR (Present Study) | 53 | 455 (62%) | - |

*BEIR VI data from Appendix tables D1-D11. Wistmut data from Kreuzer et al 2015 and Grosche et al 2006.[31,34] Some cohorts have additional cancer deaths due to extended follow up after BEIR VI publication.
[±]Among workers with mean cumulative WLM of 135 or less

As research interests shift focus to lower and more protracted radon exposures, a few studies of underground miners have investigated sub-cohorts of workers with low radon exposures. Table 2.1, adapted from Kreuzer et al, summarizes the findings from underground miner studies with average cumulative doses of less than 100 WLM.[9,11,20,23,28] A recent study of lung cancer mortality among a subcohort of German uranium miners restricted to a subcohort exposed after 1960 (radon concentrations in mines were very high in the 1940s and 1950s).[9] With 334 lung cancer deaths and an average cumulative radon exposure of 17 WLM, a linear association was still seen between low cumulative radon exposure and lung cancer mortality (ERR/WLM=0.013; 95% CI: 0.007 - 0.021).[9] A combined lung cancer mortality study of French and Czech miners with a mean cumulative exposure of 47 WLM reported a ERR/WLM of 0.027; 95%CI: 0.017 – 0.043).[35]

**Table 2.2: Risk of lung cancer deaths and incidence among underground miners exposed to low levels of radon, and covariate information on smoking and gamma (γ) radiation***

| Study (publication) | Deaths | Smoking | γ radiation | Mean cumulative exposure to radon | ERR/100WLM |
|---|---|---|---|---|---|
| BEIR VI joint miner cohort[±] (NRC, 1999) | 677 | Some | No | <100 WLM | 0.8 |
| | 468 | Some | No | <50 WLM | 1.2 |
| French and Czech miners (Tomasek et al, 2008) | 574 | No | No | 47 WLM | 4.2 |
| French miners1956+ (Rage et al, 2014) | 94 | No | Yes | 18 WLM | 2.4 |
| German miner sub-cohort 1960+ (Kreuzer et al, 2016) | 334 | Yes | Yes | 17 WLM | 1.3 |
| **Study (publication)** | **Incidence** | **Smoking** | **γ radiation** | **Mean cumulative exposure to radon** | **ERR/100WLM** |
| Ontario uranium miners (Navaranjan et al, 2016) | 1291 | No | No | 21 WLM | 0.6 |

*Portions of this table are adapted from Kreuzer et al 2016
[±]BEIR VI estimates include 11 pooled cohorts of underground miners. There are 8 uranium miner cohorts: Australian, French, Czech, 2 US cohorts (New Mexico and the Colorado Plateau), 3 Canadian cohorts (Ontario, Beaverlodge, and Port). There are 3 non-uranium cohorts: Chinese Tin miners, Swedish Iron miners, Newfoundland Fluorspar miners,
¨Although the mean cumulative exposure to radon is higher than other low exposure cohorts, at least 30% of workers had exposures less than 10 WLM and over 70% of workers had exposures less than 50 WLM.

As seen in Table 2.2 only 1 study other than ours evaluated lung cancer incidence among workers with relatively low levels of cumulative radon exposure. Among the Ontario uranium mining cohort the relative rate of lung cancer incidence from average radon exposure of 21 WLM is 1.47; 95%CI 1.11 - 1.95.[8] No other major uranium miner cohort has published cancer incidence data. While the first study of lung cancer incidence among Ontario miners has a lower mean cumulative radon exposure than the Příbram cohort (21.0 vs 53 WLM, respectively) the

proportion of workers in Příbram with exposures less than 50 WLM is higher than the Ontario cohort.

Table 2.2 also illustrates that few studies among workers with low average WLMs examined the joint of effects of smoking and radon, or external penetrating gamma radiation. Smoking is an important confounder or modifier of the radon-lung cancer association. The BEIR VI report, a pooling of case control studies nested within three European uranium mining cohorts, and detailed time-varying information from the Colorado Plateau cohort all suggest smoking has a sub-additive or sub-multiplicative interaction between radon and smoking. [11,36] Still, many mining cohorts lack smoking data or smoking data is unreliable, and estimates of the interaction between radon and smoking among workers at lower exposures is not well quantified. Also, gamma radiation is correlated with radon exposure and is also a carcinogen. To date, only two studies of cancer mortality have examined low radon exposures and gamma radiation. This will be the first low-dose radon study of lung cancer incidence which includes smoking covariate information and information on gamma radiation.

**2.4 Studies of inhalation of radon progeny and cancers other than lung**

The association between radon inhalation and cancers other than lung are not well understood. The BEIR VI committee reviewed evidence on health effects of radon exposure on development of other than lung cancer. They concluded that while evidence on non-lung malignancies was limited, ecological studies and dosimetric models suggested that radon exposure is associated with development of cancer types other than lung.[11]

Dosimetric models of α particle inhalation and energy deposition can help inform epidemiological hypotheses and identify *a priori* cancer sites of interest. Bio-kinetic studies indicate that α-radiation doses to the extrathoracic airway (the upper airway, including the

tongue, mouth, pharynx, nasal cavity, and larynx) are similar to some regions of the lung. While radon dosimetry studies have focused mainly on doses to the lungs and upper airways, models also suggest that radiation from the inhalation of α particle reaches other organs. But, the doses are estimated to be at least 10 - 100 times lower than lung doses. Doses to lymphocytes, while considerably lower, may still be important.[11,37] Radon gas is soluble in blood, and inhaled radon may cause leukemia through irradiation of T lymphocyte blood cells close to the airways. Radon gas is also soluble in adipose tissue. Therefore, organs which are surrounded by adipose tissue are thought to receive higher doses of α radiation such as adult bone marrow, and kidney.[37]

Prior uranium miner studies have examined cancer subtypes with varying results. Excess mortality from leukemia[24] and cancers of the stomach[2,38,39] and kidney[28] have been identified. To date, only one study of uranium miners cancer incidence estimates other than lung has been published, and no associations between cumulative radon exposure and stomach, kidney, and extrathoracic cancers, or leukemia were observed.[8] Studies of the extrathoracic airway, which dosimetric models suggest receives a substantial radon dose, show a small increase but are inconclusive.[8,40] A recent study of extrathoracic cancer incidence and mortality rates among Ontario uranium miners was positive but statistically imprecise (ERR/100 WLM = 0.37 for incidence, and 0.15 for mortality).[8] Another recent study showed a small increase in extrathoracic cancer mortality rates among German uranium miners (ERR/100 WLM = 0.036).[40]

Overall, dosimetric findings suggest that radon inhalation results in radiation exposure to organs other than the lungs.[37] Occupational studies occasionally support dosimetric models, but not consistently and are subject to many limitations.[2,4,24,40] Studies of cancer sites other than lung often have low power because these cancers are rare and/or receive low site-specific doses. Only in a few studies have incidence records been analyzed, many studies have limited follow-up

periods and are missing co-pollutant and confounder data, and some findings solely rely on comparisons of rates in a standard population.[8,40]

**2.5 Research priorities**

While it is established that radon inhalation is carcinogenic[1], more studies are needed to understand exposure-response relationships at low and moderate levels (current recommendations limit workers to 4WLM per year), differences between cancer incidence and mortality, the effect of smoking and other co-exposures, and associations with cancers other than lung, particularly extrathoracic cancers.

Several studies of underground miners have demonstrated strong exposure–response relationships with cumulative radon exposure and lung cancer mortality, but more information is needed about lung cancer incidence and occupational co-exposures. Incidence estimates are less frequently studied but are preferable because they increase statistical precision, are less subject to outcome misclassification, and occur closer to carcinogenesis. Uranium miners are also occupationally exposed to other potential carcinogens including dust, diesel exhaust, long-lived radionuclides from uranium ore dust, and external gamma radiation.[9] Exposures to these pollutants are often unaccounted, but have been analyzed in some studies of underground uranium miners.[4,24,33] Generally, the measurements of these co-pollutants are poorly characterized and subject to exposure misclassification, especially during early periods of mining operations. Their impact on the association between radon exposure and development of cancer is not well understood.

Additionally, the modifying effect of smoking has been characterized among several studies but more information is needed to understand the modifying effect of smoking at low exposure levels. Modification by smoking has been studied in several populations of uranium

miners, namely in analyses from the Committee on Health Risks of Exposure to Radon (BEIR VI) report[11], a pooled case control study of three European uranium mining studies[36], and the Colorado Plateau cohort[17]. All concluded that there is a sub-additive or sub-multiplicative interaction between radon and smoking.[11,17,36] However, mean cumulative radon exposures in these studies were much higher than levels experienced in modern occupational settings. More research is needed to understand the effect of smoking at low cumulative radon exposures and at low exposure rates.

It is unclear if radon causes cancers of the extrathoracic respiratory system (the upper airway, including the tongue, mouth, pharynx, nasal cavity, and larynx). Dosimetric models indicate that α-radiation doses to the extrathoracic airways occur with inhalation. Although the magnitudes of these doses are smaller than to lungs, estimates doses may still be substantial. Extrathoracic cancer subtypes were historically examined as separate groups, which led to very small numbers of deaths in each subgroup, but two recent studies of uranium miners examined rates of extrathoracic cancer as a group based on the International Commission on Radiological Protection (ICRP) models for energy deposition following radon inhalation.[41] One study reported a positive imprecise association between radon and extrathoracic cancer mortality while the other found a negative imprecise association with both incidence and mortality.[8,39] Smoking is an important risk factor for extrathoracic cancer and was not accounted for in either of these prior studies.[8,39] Also, associations with liver, kidney, stomach, and hematopoietic cancers have been reported in other cohorts of uranium miners,[2,4,24] which warrants further exploration.

This research aimed to address multiple research gaps by estimating lung cancer incidence among a population of low- to moderately-exposed miners with covariate information on smoking and gamma radiation. This study is also significant because lung cancer risks have

not been reported in this historically important cohort. To our knowledge, this dissertation work is only the second study of radon exposure and lung cancer incidence among underground miners. The study of these cohort attributes will contribute important estimates to the low-dose radon exposure literature for lung cancer incidence, and the combined effects of radon exposure and smoking.

# CHAPTER III: METHODOLOGY

## 3.1 The Příbram uranium miners study

In 1992, the National Institute of Environmental Health Sciences (NIEHS) initiated a cancer incidence and mortality study of uranium miners in Příbram, in collaboration with the Prague Institute of Advanced Studies and the Health Institute for Uranium Industry in Příbram, in order to better understand the health effects of radon exposure.

The Příbram mines are located in Central Bohemia, a rural and suburban region 60 kilometers southwest of the Czech capital of Prague. At the start of mining operations in 1946, there were about 40,000 inhabitants in the city of Příbram. In addition to uranium mining, the area has a long history of silver, lead, and zinc mining extending back 700 years, as well as coal mining and steel production. Some of the very first associations between mining activities and mortality were documented in this region in the 16$^{th}$ century. It was also in central Bohemia that radon was first suspected of causing lung cancer.[42]

Between World War II and the Cold War, extensive uranium mining in the Příbram region occurred, driven by demand from the Soviet Union.[5] Czechoslovakia was the third largest supplier of uranium to the Soviet Union during this time, with a cumulative production through 1990 of 98,500 metric tons.[5] Mine operations occurred between 1948 and 1992, during which time approximately 19,400 miners were employed. Because mining operations were so extensive in the region, health impacts were observed throughout the national population. For instance, though Příbram had safer and more regulated mining activities than other Czech mines, 40% of all incident occupational cancers in the Czech Republic were attributed to employment in

Příbram mines in the early 1990s.[43] With the collapse of the communist bloc, the importance of uranium as material for nuclear weapons was reduced and the demand for uranium declined substantially.[43] The START I treaty of 1991 committed the Soviet Union to reducing its total inventory of nuclear weapons[5] and the Příbram mines ceased operation by the end of 1992.

The main method of uranium mining in the Příbram mines was cut-and-fill stoping.[43] In this approach to mining, horizontal slices across the uranium ore are cut and then mined. These horizontal layers are referred to as stopes. Once one stope is depleted it is backfilled, sometimes with mine waste. The filled stope then becomes the platform upon which the next horizontal slice is mined. This process of cutting and filling continues progressively into layers upwards until the ore is depleted or stress fractures in the ore makes mining unsafe.[44]

Prior to the discovery of large uranium deposits in Příbram, uranium production in Czechoslovakia occurred mostly in the Jachymov mines of Western Bohemia, along the border with Germany. Germans occupied the Jachymov mines through World War II, and after the war Soviets took control of all uranium mining activities.[43] German prisoners of war and dissidents of the communist regime were forced to work in the mines, and many died during their sentence.[45]

The Jachymov working conditions were extremely poor. Hnidzo et al describes the magnitude of workplace hazards:

> "The Soviet takeover of the management of the mines from 1945 started a period of frenzied development, during which uranium production had the priority over human lives, not to mention miners' health. Although the uranium production during the first ten years was relatively small, its impact in terms of human suffering and the size of the population adversely affected was the greatest when compared to later periods."[43]

By 1960, Jachymov operations ceased as the uranium supplies diminished. As the strategic importance of the Příbram mines grew, 70% of all uranium production in

Czechoslovakia occurred Příbram.[46] Hazards in the Příbram mines were lower than those of the Jachymov mines, but mining operations were extensive.[43] Many forced laborers and former Jachymov employees were moved to work in the Příbram mines.

All mining operations in Příbram ceased in 1992.[46] Shortly after the fall of the Berlin wall, a series of protests in Czechoslovakia known as the Velvet Revolution led to the nonviolent overthrow of communist leadership. A few years later, Czechoslovakia underwent and amicable dissolution into the Czech Republic and Slovakia.[47]

### 3.1.2 Prior studies of Příbram miners

Two analyses of cancer incidence have been previously conducted among the Příbram miners. The first examined incidence of leukemia, lymphoma, and multiple myeloma among a subcohort of 2,393 workers, including 177 incident hematopoietic cancer cases. This study found an elevated rate of leukemia, including chronic lymphocytic leukemia (CLL). Authors reported a rate ratio (RR) of 1.75 (95% CI: 1.10–2.78) for all leukemia combined and a RR of 1.98 (95% CI: 1.10–3.59) for CLL comparing high radon exposure (110 working level months (WLM)) to low radon exposure (3 WLM). Suggestive associations between myeloid leukemia and Hodgkin lymphoma with radon exposure were also found.[24] Another study of this cohort, using a similar case-cohort design, analyzed the incidence of non-lung solid cancers and found no associations except among malignant melanoma and gallbladder cancer.[25]

## 3.2 Cohort Study

The source population of the Příbram uranium mining cohort is all workers employed by the Příbram Uranium Industry. Card records were kept for compensation purposes for each worker. These records were computerized into an employment register containing 41,741 males and 6,106 females and included unique identification numbers, dates of birth, dates of

employment, and location of employment within the mines (e.g. underground, surface, sorting ore).[46]

A cohort of underground miners was selected from the computerized registry of Příbram Uranium Industry employees. To qualify for inclusion in the cancer follow-up cohort, workers had to be male, listed in the employment card registry, work at least 12 months underground, be alive on January 1, 1977, and live in Czechoslovakia on January 1, 1977.[46]

Vital Status and/or emigration status was obtained for each worker primarily from the Czech Central Register of Inhabitants. For workers who died in the Příbram region (approximately 30% of all deaths) cause of death was derived from death certificates. For workers who died outside this region, underlying cause of death was obtained from district death registries, or if possible, death certificates were obtained. Additional sources of vital status follow up included pensions, Uranium Industry death records and medical documentation. Between 1977 and 1992, 4,212 workers died, and before 1977 1,932 workers died. 120 workers emigrated. Vital status was not determined for 511 (2.9%) workers. The remaining 16,434 workers were followed for cancer incidence. Last date of follow up, and vital status at end of follow (dead, alive, or emigrated) were coded. Primary cause of death and contributing causes of death (such as chronic diseases) was also coded.[46]

### 3.2.1 Case Ascertainment

Cancer incidence was determined for all 16,434 eligible cohort members. Workers diagnosed with cancer were not allowed to work underground. Therefore, all workers alive in 1977 and still working underground are assumed to be cancer free.[46] Cancers were identified from 1977 through 1992 for the full cohort, and through 1996 for a subcohort to workers. Cancer incidence was determined by matching the cohort subjects with the Czech and Slovak national

cancer registries. Matching was conducted using individual government identification numbers, names, and date of birth. Reporting to the registry was mandatory. The results from the Czech and Slovak registries and the Příbram Uranium Industry card registry were checked for duplicates.[46] All cancers were recoded according to the International Classification of Diseases, Ninth Revision until 1994, when ICD-10 codes were implemented.[24] The ICD code, date of cancer incidence and the source of cancer ascertainment are recorded as separate variables. Among the 16,434 miners who met eligibility for incidence follow up, 1,944 incident cancers were identified between 1977 and 1992. 146 workers had more than 1 incident cancer.[46]

### 3.2.2 Radon exposure estimates

Cumulative radon exposure is estimated in Working Level Months (WLM) for each miner. A WLM is 170 hours of exposure to radon decay products at a concentration of $1.3 \times 10^5$ MeV of alpha energy per liter of air.[48] Cumulative radon exposure is the sum of WLMs over the course of a miner's employment. In early mine operations, potential alpha energy measurements were not directly available so equilibrium ratios were used to convert radon measurements in mines into potential alpha energy. The equilibrium ratios used in the calculation of WLM estimates largely depend on ventilation practices.[43]

Radon exposure estimates in WLMs were assigned to each cohort member by calculating the product of duration of underground mining activities and average annual WL estimates. Duration of exposure is calculated by month and year based on start and end of employment, and was coded from industry employment records. WL estimates were calculated by the Czech Uranium Industry (UI), originally for compensation purposes. In the late 1960s, the UI used existing records of radon concentration measurements to construct tables of yearly averages. Radon exposure for individual miners was assigned by applying the annual industry estimates to

the duration of underground mining, and can be expressed as a sum of products of the mine average radon concentrations, equilibrium factors where relevant, and the duration of exposure by month.

Some changes to the UI tables were made by NIEHS investigators based on a review of UI exposure estimates (Hnidzo et al). First, UI-calculated averages were compared to averages of all available archived measurements. While there was general agreement between the original and recalculated exposure estimates, sampling errors and recording errors in the UI tables were identified and adjusted based on comparisons to recalculated averages. Secondly, estimates prior to 1968 measured as Rn decay activity were converted to potential alpha energy concentration using equilibrium factors. Different mean equilibria were assumed by the UI according to the system of ventilation used at the time, and the Rn concentration measured.

Radon exposures were highest at the start of mining operations and gradually decreased. Figure 1.1 shows the estimated average radon progeny concentration for each year of mine operations. In the late 1940s and early 1950s mines had mostly natural ventilation and average radon concentrations were high, but only a small number of miners were exposed to these conditions. In 1970, a ventilation system was introduced in Příbram. In 1975 an exposure limit of 3.4 WLM was set, and miners with more than 10 years of underground exposure from 1968-1975 were retired.[43] However, many miners exceeded these exposure limits.

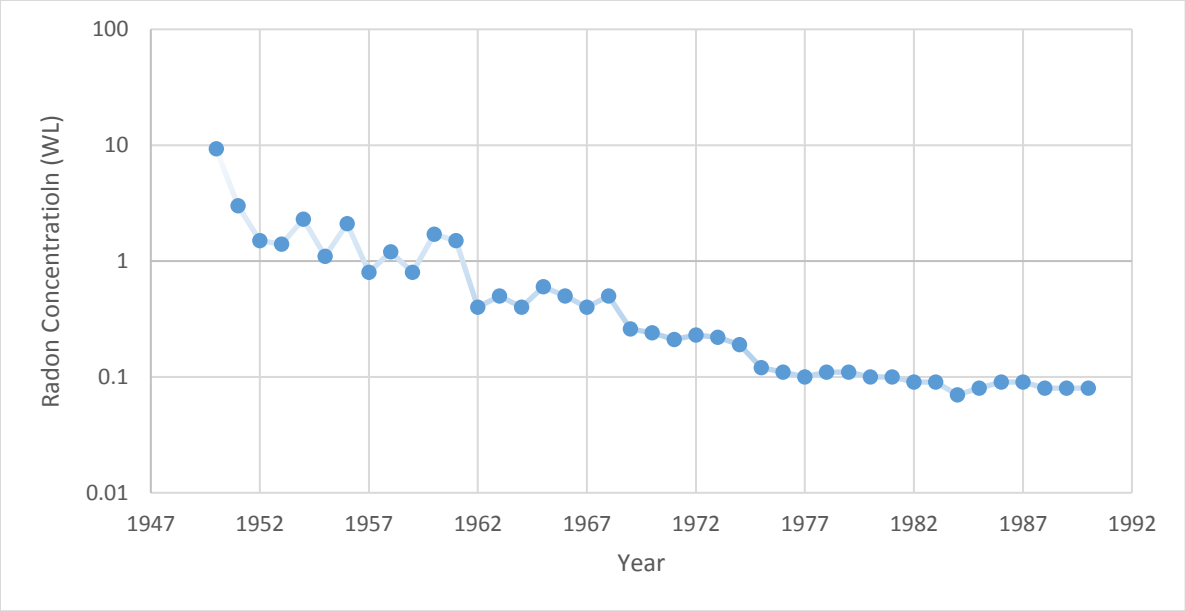



**Figure 3.1: Average radon progeny concentration per year in the Příbram mines (Adapted from Hnidzo et al 1997)**

### 3.3 Case-Cohort Study

Incident cancer cases and a subcohort were selected for inclusion in a case-cohort study with improved radon estimates (Figure 1.2). External gamma radiation, dust, and smoking were also estimated among the subcohort and cases. Subcohort members were selected based on the distribution of age of the cases at start of follow-up. All 1,807 miners with incident cancers were included as cases in the subcohort.[46] Case ascertainment is identical for the cohort and case-cohort studies, except the case-cohort was followed for cancer incidence 4 years longer than the full cohort. The case to subcohort ratio is large, and ranges between 1:4 and 1:13 depending on the outcome under study.

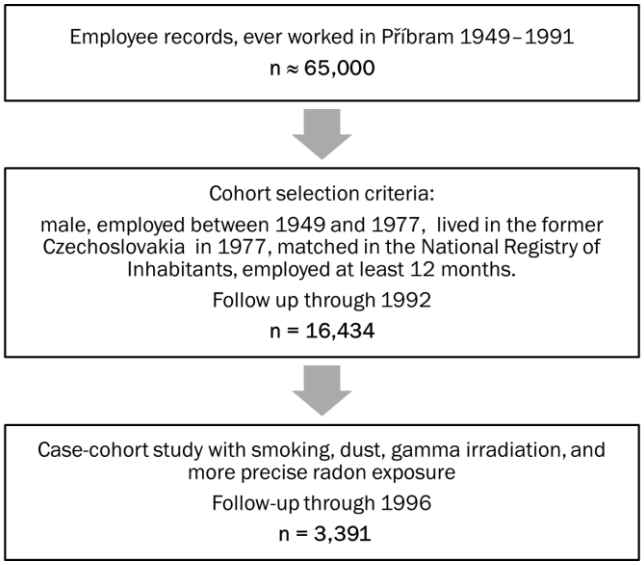



**Figure 3.2: Diagram of cohort and subcohort selection in the Příbram Czech Miner Study**

### 3.3.1 More precise radon estimates

In the case-cohort study, more detailed information from archived work histories was abstracted to calculate the locations of work within mines and entry and exit times for these locations. Exposure estimates for the case-cohort are more precise than for the full cohort. More precise estimates were assigned differently across two time periods. In the period prior to 1968, detailed employment records were abstracted by investigators to estimate the time spent underground per month. As in the cohort study, exposure is the product of duration of underground mining activity and annual radon WL averages from UI tables. In 1968, with the introduction of individual dosimetric cards, exposures were estimated by number of shifts. Radon measurements were taken in the specific workplace during each shift and recorded on dosimetric cards. In this period, radon exposure is the sum of the products of shift duration and location-specific radon estimates. Exposure estimates for each period are described in detail the sections below:

Exposure assignments were made using more detailed occupational data, obtained thorough review of worker records. Employment records before 1968 show the number of underground shifts, the mine identity and the profession. Case-cohort members' job files were reviewed and coded for this occupational history. Job activities for each year of employment were coded as full-time underground miners, part time underground miners, part-time underground technicians, specialists with occasional underground work, surface workers with no exposures (construction etc.), and ore sorting workers coded by facility.

The proportion of underground shifts was estimated based on profession. Full-time underground miners were estimated to work 100% of shifts underground. Part-time miners and technicians who worked underground part-time were estimated to work 70% of their shifts underground, specialists with occasional underground work spent an estimated 50% of time underground, and surface workers worked no shifts underground.

The exposure in WLM before 1968 was calculated as a sum of products of the average radon concentration, the relevant equilibrium factor, and the proportion of underground shifts (determined by profession), divided by 21.25 (the expected number of shifts per months based on 170 hours per month).

Starting in 1968, individual dosimetric cards were kept by the UI. Personal dosimetric cards are industry records of the number of shifts spent in a workplace and the radiation measurements (potential alpha energy concentration) taken in that workplace at least once a month.

In some instances, radon measurements were not taken at the location of work and were instead estimated from UI tables. A variable was coded to indicate whether an exposure was assigned from an actual measurement or was estimated from industry records.

### 3.3.2 Occupational co-pollutants

Dust exposure for each miner was estimated in the case-cohort study based on monthly measurements recorded in each mine.[24] Starting in 1957, law required that total airborne dust be recorded on a dosimetric card for each miner at least once a month.[43] Based on dust monitoring data and locations of work within mines and entry and exit times for these locations, monthly dust exposure was assigned to each worker in $mg/m^3$.

The average concentration of airborne dust in the mines was highest in the mid-1950s with an average concentration of 10.5 $mg/m^3$ in 1956.[43] With the introduction of a strong ventilation system in the 1970s, average concentrations fell steeply and remained around 1 $mg/m^3$ from 1973 till the end of mining operations.[43]

Dust sediments from one Příbram mine were analyzed for metal content. The dust samples contained high levels of lead (1036.7 mg/kg). The average arsenic concentration in Příbram mines is considered low (average 144.2 mg/kg among dust samples taken in one Příbram mine).[43] A load of ore was also measured for arsenic content and was found to be 25 mg/kg, 200 times lower than ore from other regional mines.[24] Chromium (264.3 mg/kg), and cadmium (19.3 mg/kg) were also present in low levels.[43]

Free crystalline silica is another component of dust which causes nonmalignant respiratory diseases, particularly silicosis, and may cause cancer. The incidence of silicosis was low among Czech uranium miners compared to other mining cohorts. This is likely because there was never extensive dry drilling in the Czechoslovakian mines.[5] The mean concentration of free crystalline silica content in the total dust in Příbram was estimated to be 15%, with measurements ranging from 10 to 35%.[43] These estimates are based on 4,406 measurements

made 1958-60, however, the concentration of silica dust in the mines appears to be constant over the course of mining operations.[43]

In 1966 most underground workers were given film badges to measure gamma exposure. A model estimating gamma exposures prior to 1966 was developed using information on annual ore production, calendar period, shifts worked, and job title.[24] Gamma radiation is measured in millisieverts (mSv).

Miners were not occupationally exposed to diesel exhaust since all vehicles in the Příbram mines were electric.[43] This provides the opportunity to study the association between radon and cancer in the absence of diesel exhaust, a common confounding occupational exposure in underground mining.

### 3.3.3 Smoking

Smoking information for the case-cohort study was abstracted from Uranium Industry job-entry medical examinations and subsequent annual checkups. Workers were classified as ever or never smokers. Based on results from a pilot study among Příbram miners, approximately 77% of all miners were smokers.[43] In the age-stratified random subcohort, 66% of miners were smokers and 5% had missing smoking information. 5% of non-smokers in the subcohort developed lung cancer, and 12% of smokers in the subcohort developed lung cancer.

The quality of smoking data among miners improved over time. In the pilot study of 124 Příbram miners, quality of smoking data was assessed as satisfactory (known start and stop of smoking and intensity), less satisfactory (smoking data only available while employed in uranium industry), and unsatisfactory (no smoking data). Among miners in this pilot study, the

proportion of satisfactory smoking data was 62.5% before 1950 but increased to 96% after 1979.[43]

### 3.4 Statistical methods

#### 3.4.1 Standardized incidence and mortality ratios

Standardized cancer incidence ratios (SIRs) and standardized mortality ratios (SMRs) were calculated, comparing the full cohort of male miners and a comparable national Czech population. The national population of males in the Czech Republic between 1977 and 1992 was the standard population used for the rate ratio calculations in Aim 1. Annual population estimates, and annual counts of cancer incidence and mortality are reported by 5-year age group in order to calculate the age-specific rate of cancer among the Czech population.

SMRs and SIRs were calculated to characterize the incidence and mortality experience the cohort in comparison to the Czech population. Cancer subtypes of *a priori* interest were examined for age, period, and cohort effects. *A priori* subtypes include lung, extrathoracic airway, kidney, liver, stomach cancers, and hematopoietic cancers. Hematopoietic cancers (ICD-9 200 -208) were further examined by subtypes of Hodgkin lymphoma (201), non-Hodgkin lymphoma (200, 202), myeloma (203) and leukemia (204–208). Ideally, ALL and CLL would be examined separately from other hematopoietic cancers due to their earlier and later and median ages of onset, respectively (Appendix Table 1). However, Czech cancer incidence and mortality data are not reported by this level of detail. Therefore, the implications of grouping such different disease were considered when interpreting SMR and SIR results.

SIRs and SMRs are ratio measures comparing the observed cancer incidence or mortality (*O*) to the expected cancers (*E*). Expected cancer is the product of cancer rates in the standard population ($\lambda$) and the person-years (*n*) in the study population. Equation 1 summarizes how these mortality ratios are the summation of each cross-classification of strata specific estimates (*k*) by age category (*i*) and calendar year (*j*). Standardized ratios were calculated using tabular methods and also modeled using a lognormal Poisson distribution with an offset representing the product of the person-time in the study population and the rate of cancer in the standard population (equation 2).[49] The 95% confidence intervals (CI) of the standardized incidence or mortality ratios were calculated as described in Rothman and Greenland, Modern Epidemiology 4th Edition for tabular calculations.[50] Wald-type 95% CIs were estimated for Poisson models.[51]

**eq 1** $$SIR_j = \frac{\sum_{i=1}^{I} O_{ij}}{\sum_{k=1}^{K} \sum_{i=1}^{I} n_{kij}\lambda_{kij}} = \frac{O_j}{E_j}$$

**eq 2** $$log(O_{ij}) = \alpha + x_j\delta_j + log(n_{ij} \times \lambda_{ij})$$

Standardized incidence and mortality ratios are typically reported by calendar period across all strata of age, which may obscure meaningful cohort effects related to population characteristics, biological properties of cancer, and the timing of carcinogenic exposures. In order to understand trends over time, several analyses were conducted which examine standardized ratio measures by different definitions of period and cohort. Cohort effects were used to evaluate possible influences of healthy worker hire effects and changing workplace hazards. One approach was to compare workers who were employed before the start of follow up to workers who were hired after the start of follow up.[52]

### 3.4.2 Random effects models

Standardized rate ratios are not comparable across calendar periods unless the underlying person-time distributions of the standardization variables are similar across those calendar periods.[53] To assess if changes in population distribution over time affect calendar period-specific rate ratios we fit a lognormal Poisson random effects model to test for heterogeneity of person-time distribution by age across calendar periods.[51] Standard SIR and SMRs, which were modeled previously, also included a random effect for age to examine the influence of heterogeneity across time, where heterogeneity is quantified by the variance of the random effect parameter, $\sigma^2$ as described in equation 3.[51]

**eq 3** $$\boldsymbol{log(O_{ij})} = \boldsymbol{\alpha} + \boldsymbol{x_j\delta_j} + \boldsymbol{log(n_{ij} \times \lambda_{ij})} + \mu \quad \mu \sim \boldsymbol{N(0, \sigma^2)}$$

### 3.4.3 Causal mortality ratios

Causal mortality ratio calculation is an approach to estimating the standardized ratio estimates using survival functions. They provide a ratio estimate which accounts for differences between the standard population mortality rate and the study population mortality rate.[54] Since miners are exposed to very hazardous conditions, the mortality rate among miners is likely higher than the standard Czech population. The elevated hazard changes the distribution of person time among the miners and biases the calculation of expected cases in typical SMR estimates. In traditional SMR analyses the expected cases are estimated as the number of deaths if the cohort had experienced the same stratum-specific rates as the reference population and occupational hazards had not affected the person-time in the cohort.[55,56] In order to estimate a counterfactual contrast that more accurately represents mortality rates in the absence of exposure, we calculated casual mortality ratios using methods described in Richardson et al.,

where the expected cases are calculated as "the number of deaths if the cohort had experienced the reference hazard rate".[54]

### 3.4.4 Internal analyses

Linear excess relative rates per 100WLM were estimated using the general model form $rate = \exp(a_0 + \sum_{j=2}^{p} a_j x_j)(1 + a_1 d)$ where $a_1$ is the excess relative rate per unit of lagged cumulative radon exposure, d and $a_j$ are parameters for effects of covariates $x_j$. To examine time since exposure and exposure rate, windows of exposure and exposure rate windows were fit, respectively, using the general model form $rate = \exp(a_0 + \sum_{i=1}^{k-1} a_j x_j)(1 + \sum_{j=k}^{p-1} a_i d_i)$ where $a_i$ represents excess relative rates per unit of lagged cumulative radon exposure in time windows or rate windows $d_i$ and $a_j$ are parameters for effects of covariates $x_j$.

Log-linear regression models were used to estimate the log relative rate (RR) (reported as RR per 100 WLM). Rate ratios were estimated using the general model form $rate = \exp(\beta_0 + \sum_{i=1}^{k-1} \beta_i d_i + \sum_{j=k}^{p-1} \beta_j x_j)$ where $\beta_1 - \beta_{k-1}$ represents the log relative rate of cancer incidence per category of lagged cumulative radon exposure, $\beta_0$ is the log rate of cancer among workers with the referent cumulative WLM, and $\beta_j$ are parameters for effects of covariates $x_j$.

In Aim 2, we analyzed mortality in the full cohort. Linear excess relative rate and log-linear rate regression models were fitted using Poisson regression methods fitted to tabulations of person-time and events; estimates of parameters for the regression models, and associated profile-type confidence intervals, were obtained using SAS PROC NLMIXED.

In Aim 3, we analyzed cancer incidence in a stratified case-cohort study. To fit the linear excess relative rate model using the stratified case-cohort data, we used the approach described by Richardson et al, where a risk-set data structure is generated and relative rate models are fit in SAS PROC NLMIXED. A weighted bootstrapping method also described by Richardson et al.,

was used to calculate confidence intervals of estimated ERRs. In this method, a random weight from an exponential distribution is assigned to each person for each weighted regression model. The weighted bootstrap approach accommodates the random stratified case-cohort design well because risk sets only need to be enumerated once, which retains the case failures from the full cohort and the observed failure times. Log-linear rate models were fitted using SAS PROC PHREG (with a robust variance estimator obtained by invoking the covsandwich option). In addition, and for comparison, log-linear RRs per 100 WLMs were also estimated using SAS PROC NLMIXED.

### 3.4.5 Risk set regression calibration

To assess the impact of radon exposure measurement error in the cohort, we used risk set regression calibration (RRC) methods which adjust radon-lung cancer associations for bias due to measurement error based on information from the subset of workers who have validated and more precise exposure estimates [57,58]. Measurement error of cumulative radon exposure was corrected using an internal validation application of the RRC approach. Results for radon-lung cancer mortality associations were compared to error-corrected results to assess the impact of measurement error on lung cancer estimates.

# CHAPTER IV: RESULTS

## 4.1 Mortality and cancer incidence among underground uranium miners in the Czech Republic (AIM 1)

### 4.1.1 Overview

Underground workers employed in the Příbram mines of the Czech Republic were exposed to low and moderate levels of radon gas and other occupational hazards. It is unknown whether these hazards increase the risk of mortality or cancer incidence when compared to the general Czech population.

A cohort of 16,434 male underground miners who were employed underground for at least one year, alive and residing in the Czech Republic on 1 January 1977, were followed for mortality and cancer incidence until 31 December 1992. We compared observed deaths and cancer incidence to expectation based on Czech mortality and cancer incidence rates. Standardized Mortality Ratios (SMRs), Standardized Incidence Ratios (SIRs) and Causal Mortality Ratios (CMRs) were calculated.

Underground workers in the Příbram mines had higher rates of death than expected due to all causes (SMR= 1.23; 95% CI: 1.20, 1.27), all cancers (SMR = 1.52; 95% CI: 1.44, 1.60), lung cancer (SMR = 2.12; 95% CI:1.96, 2.28), and extrathoracic cancer (SIR = 1.41; 95% CI: 1.15, 1.77). Similar excess was observed among cancer incidence analyses, with the addition of stomach cancer (SIR = 1.37; 95% CI: 1.11, 1.63), liver cancer (SIR = 1.70; 95% CI: 1.16, 2.25) and hematopoietic cancers including Hodgkin's lymphoma (SIR = 1.57; 95% CI: 0.77, 2.37), multiple myeloma (SIR = 1.75; 95% CI: 0.89, 2.61), lymphoid leukemia (SIR = 1.57; 95% CI:

0.90, 2.25), and myeloid leukemia (SIR = 1.58; 95% CI: 0.75, 2.42). Deaths due to hazardous mining conditions resulted in 0.33 person-years of life lost per miner.

Occupational exposure to the Příbram mines resulted in excess cancers at several sites, including sites previously linked to radon and uranium exposure. Incidence analyses resulted in the relative excess of several additional cancer subtypes.

### 4.1.2 Background

Between World War II and the Cold War, extensive uranium mining in the Příbram region was driven by demand from the former Soviet Union.[5] Czechoslovakia was the third largest supplier of uranium to the Soviet Union during this time, with a cumulative production through 1990 of 98,500 metric tons.[5] Příbram mine operations occurred between 1946 and 1991, during which over 46,000 workers were employed. By the 1960s, over 70% of all uranium production took place in Příbram.[43]

Příbram miners experienced a number of occupational hazards, including exposure to radiation, dust, accidents, and vibration. Uranium miners are routinely exposed to radiation as a result of inhalation of radon and its decay products, and also experience radiation exposure from long-lived radionuclides in uranium ore dust and external gamma radiation.[9] In Příbram, radon concentrations were highest at the start of the mining operations and gradually decreased with the improvement of ventilation practices. In the late 1940s and early 1950s, mines had mostly natural ventilation. In 1970, a strong ventilation system was introduced, and in 1975 an annual exposure limit of 3.4 working level months (WLM) of radon exposure was set. However, it is documented that many miners continued to work in environments which exceed these exposure limits.

Another common occupational hazard of uranium mining is inhalation of dust, which includes heavy metals and silica as components. Dust was measured in Příbram mines at least monthly, and average area measurements of airborne dust in Příbram were highest in the mid-1950s (average concentration of 10.5 $mg/m^3$ in 1956). With the introduction of a strong ventilation system in the 1970s, average concentrations fell steeply and remained around 1 $mg/m^3$ until the end of the mining operations. Dust was first measured using konimetric methods until 1960 when it was replaced by more reliable gravimetric methods. Heavy metals in dust sediments were measured in a pilot study using ore from accessible mines. Samples from Příbram mines contained higher levels of lead and lower levels of arsenic compared to the other major Czech mine in the Jáchymov region.[43] For instance, the arsenic levels averaged 144 mg/kg in Příbram and 789 mg/kg Jáchymov, and lead levels averaged 1037 mg/kg in Příbram and 112 mg/kg in Jáchymov.[43] The mean concentration of free crystalline silica in the total dust in Příbram was estimated to be 15%, lower than many other hard-rock mines because dry drilling was not common in Příbram. And, unlike many other mining operations, Příbram miners were not occupationally exposed to diesel exhaust because all vehicles in the Příbram mines were electric.[43]

Traumatic injuries and hand-arm vibration injuries are also important occupational hazards of underground mining. Hand-held pneumatic drills and, later, supported pneumatic drills were used to hammer out ore, which can cause circulatory and neural injury. The use of explosives to break rock and presence of poisonous and explosive gases underground pose major injury hazards to underground hard-rock miners.

Extensive uranium mining operations also occurred in other parts of the former Czechoslovakia, notably the Jáchymov mines of Western Bohemia. These mines operated

through World War II, but production decreased in the mid-1960s with the discovery of large uranium deposits in the Příbram region. Jáchymov working conditions were extremely harsh, and the workplace hazards were larger than those of the Příbram mines. Jáchymov miners worked very strenuously in mines with poor ventilation and few skilled explosives technicians. Many miners were German prisoners of war or Czechoslovakian convicts, and generally harsh workplace conditions existed.[43] Workers from Jáchymov may have worked in Příbram in later periods.

A cohort of Jáchymov miners has been studied extensively, and mortality relative to national rates reported a 5-fold increase in lung cancer mortality (SMR = 5.08 95%CI: 4.71, 5.47) as well as an excess of liver cancer (SMR = 1.67 95%CI: 1.04, 2.52) and gallbladder and extrahepatic bile duct cancer mortality (SMR = 2.26 95%CI: 1.16, 3.94).[59] In addition to the Czech Jáchymov cohort, several other large studies of uranium miners have demonstrated excess cancer mortality or cancer incidence in addition to lung, namely stomach and digestive cancers, kidney cancer and extrathoracic cancers.[30,38,39,60,61] Relative mortality, however, has not been previously described for this cohort of Czech Příbram miners. Our aim is to describe mortality and cancer incidence among a large cohort of uranium miners relative to national rates. This study adds to the understanding of occupational hazards experienced by a large and historically significant uranium mining cohort routinely exposed to radon and its progeny, and other occupational hazards.

### 4.1.3 Methods

**Study population.** The Příbram miner study is based on information collected from employment records for the Příbram Uranium Industry. Card records were kept for compensation purposes for each worker and subsequently computerized into an employment register containing

41,741 males and 6,106 females. Records included unique personal identification numbers, dates of birth, dates of employment, and location of employment within the mines (e.g. underground, surface, sorting ore).[24,25]

A cohort of underground miners was selected previously from the registry of Příbram Uranium Industry employees. Male employees listed in the employment card registry who worked at least 12 months underground and were alive and residing in Czechoslovakia at the establishment of the Czech cancer registry (January 1, 1977) qualified for inclusion in the cancer follow-up cohort.[24,25] Workers who emigrated after the start of follow-up were censored at the date of emigration.

**Outcome assessment.** Vital Status and emigration status for the period 1977 - 1992 were obtained for each worker from the Czech Central Register of Inhabitants using personal identification numbers listed on employment records. For workers who died in the Příbram region (approximately 30% of all deaths), underlying cause of death was coded by a nosologist. For workers who died outside this region, underlying cause of death was obtained from district death registries, or if possible, death certificates were obtained. Additional sources of vital status follow up included pensions, Uranium Industry death records and medical documentation. Last date of follow-up, and vital status at end of follow-up (dead, alive, or emigrated) were coded. Primary cause of death and contributing causes of death (such as chronic diseases) was also coded to the International Classification of Diseases, 9$^{th}$ Edition (ICD-9).[24,25]

Cancer diagnoses for the period of 1977 - 1992 was obtained for all eligible cohort members. Workers diagnosed with cancer were not allowed to work underground. Therefore, all workers alive in 1977 and still working underground were assumed to be cancer free at the start of follow-up.[24,25] Cancers were identified from 1977 through 1992 by matching the cohort

subjects with the Czech and Slovak national cancer registries using individual government identification numbers, names, and date of birth. Reporting to the cancer registry was mandatory. All cancers were coded according to the International Classification of Diseases, Ninth Revision.[24] Cancer subtypes of interest include lung, stomach, liver, kidney, extrathoracic cancers, and hematopoietic cancers. Extrathoracic cancers are reported separately and as a group based the International Commission on Radiological Protection (ICRP) dose calculations.[41] The extrathoracic group includes the nasal passages (ICD-9 160), larynx (ICD-9 161), pharynx (ICD-9 147-148), oropharynx (ICD-9 146), mouth (ICD-9 141-145).

**Statistical methods.** All statistical analyses were conducted using SAS statistical software (SAS 9.4; SAS Institute Cary, NC). SAS allows the calculation of person-time at risk contributed by each cohort member to tabulate time-dependent variables.[62] Miners contributed person-time from the start of follow-up (1/1/1977) until the earliest of the date of death among deceased miners, date of migration out of the Czech Republic, or end of the study period (12/31/1992). There were no incident hires. For each person-year at risk, we calculated the expected numbers of deaths and cancer diagnoses; these were calculated by multiplying the cohort person-time at risk by Czech mortality and cancer incidence rates specific to 5-year age group and annual calendar period. Standardized Mortality Ratios (SMRs), Standardized Incidence Ratios (SIRs), and associated 95% confidence intervals were estimated by fitting a lognormal Poisson model to calculate expected cases. This is then divided by the sum of observed cases. This modeling approach was used to allow for flexible modeling of Causal Mortality Ratios (CMRs) and random effects. Age-specific data at different calendar periods were employed to examine birth cohort effects, age effects, and period effects.[63] Categories of

duration of employment, time since exposure, and age at exposure, birth cohort and hire cohort were examined.

**Sensitivity analyses.** Hazardous conditions may shorten the amount of person-time observed in an occupational cohort. Standard SMRs, which use the observed person-time experienced by the cohort to calculate expected death rates, often lead to biased estimates in hazardous occupations such as mining.[54] To account for the reduction of person-time in the cohort, we calculated Causal Mortality Ratios (CMRs). CMRs generate counterfactual failure times for members of the occupational cohort in the absence of exposure based upon external reference mortality rates.[54] CMRs are ratios of observed deaths to expected deaths, where expected deaths are the product of death rates in the standard population and cohort person-time based on the counterfactual failure times. The difference in observed person-time and expected person-time is the years of life lost in the cohort; when this difference is divided by the number of workers in the study the resultant quantity is described as the average years of life lost per worker.

Comparisons of SMR over calendar periods or other stratifying variables (e.g., time since hire) may be impacted by the changing covariate distribution in the cohort. A condition leading to valid comparison of such SMRs is homogeneity of the rate ratio across covariates. To assess if changes in population distribution over time affected comparisons of calendar period-specific SMRs, we fit a lognormal Poisson random effects model to test for heterogeneity of person-time distribution by age across calendar periods.[51] A random effect for age was included in standard SMR lognormal Poisson models to examine the influence of heterogeneity in age distribution across time, where heterogeneity is quantified by the variance of the random effect parameter, $\sigma^2$.

### 4.1.4 Results

Eligibility for mortality and cancer incidence follow-up was met by 16,434 male underground uranium miners (Table 3.1.1). The workers contributed 231,499 person-years and 25.6% of workers died during the 16 years of follow-up period. Cause of death was available for 89.6% of deceased workers and 1,788 incident cancers were identified. Mean duration of employment was 14 years.

Overall, there was a 23% increase in deaths from all causes compared to expected rates (SMR = 1.23, 95%CI: 1.20,1.27). A number of non-malignant causes of death were higher than expected for uranium miners. SMRs for all non-malignant causes of death by major ICD-9 group and minor group when available is reported in Table 4.1.2. Deaths due to tuberculosis (SMR = 2.08, 95%CI: 0.99, 3.18) and pneumoconiosis including silicosis and asbestosis (SMR = 1.92, 95%CI: 1.11, 2.72) were two times higher than expected. Excess mortality from mental, psychoneurotic, and personality disorders was also observed (SMR = 1.88, 95%CI: 1.05, 2.71). Overall, mortality from diseases of the heart and other diseases of the circulatory system were near unity (SMR = 0.93, 95%CI: 0.89, 0.98), however, SMRs of cardiovascular subgroups varied widely. For instance, atherosclerosis mortality was in substantial excess (SMR = 3.88, 95%CI: 3.50, 4.26), while acute myocardial infarction mortality was substantially lower than expected (SMR = 0.38, 95%CI: 0.33, 0.42).

Deaths from several cancer types were elevated among the miners. There was a 52% increase in deaths from all malignant causes compared to expected rates (SMR = 1.52, 95%CI: 1.44,1.60). SMRs and SIRs for malignant causes of death with five or more cases are reported in Table 4.1.3. Lung cancer mortality was substantially elevated (SMR = 2.12, 95%CI: 1.96, 2.28). Cancer mortality among several solid cancer subtypes was elevated, notably cancers of the

stomach (SMR = 1.27, 95%CI: 1.02, 1.51), rectum (SMR = 1.33, 95%CI: 1.04, 1.62), and liver (SMR = 1.63 95%CI: 1.17, 2.10). Hematopoietic cancer subtypes were near unity for mortality estimates.

Cancer incidence was also elevated among the miners (Table 3.1.3). Lung cancer incidence was substantially elevated (SIR = 2.31, 95%CI: 2.15, 2.48). Stomach cancer (SIR = 1.37, 95%CI: 1.11, 1.63), rectal cancer (SIR = 1.41, 95%CI: 1.16, 1.66), liver cancer (SIR = 1.70, 95%CI: 1.16, 2.25), and extrathoracic cancer (SIR = 1.41, 95%CI: 1.15, 1.77) incidences were also in excess. Cancer incidence was elevated for several hematopoietic subtypes including Hodgkin's lymphoma (SIR = 1.57, 95%CI: 0.77, 2.37), multiple myeloma (SIR = 1.75, 95%CI: 0.89, 2.61), lymphoid leukemia (SIR = 1.57, 95%CI: 0.90, 2.25), and myeloid leukemia (SIR = 1.58, 95%CI: 0.75, 2.42). There was a notable deficit in non-melanoma skin cancer incidence (SIR = 0.68 (95%CI: 0.56, 0.80).

We examined all-cause mortality and lung cancer mortality by categories of duration of employment, time since hire, time since termination, and age at hire (Table 3.1.4). Lung cancer mortality increased with longer duration of employment and decreased substantially with longer time since hire and time since termination. Minimal differences were observed in lung cancer mortality by age at hire. All-cause mortality decreased with older age at hire and decreased substantially with longer time since hire and time since termination. No substantial differences were observed in all-cause mortality for duration of employment.

Because variation in incidence and mortality may result from differences in age and duration of employment, we evaluated SMRs by birth cohort and period of hire for lung cancer mortality and all-cause mortality (Table 3.1.4). Excess lung cancer mortality and all-cause mortality were observed among every birth cohort. The highest mortality occurred among miners

born between 1920 and 1929 (all-cause SMR = 1.35, 95%C:1.29, 1.42; lung cancer SMR = 2.35 95%CI: 2.10, 2.60). Earlier hiring period was associated with both an increase in all-cause and lung cancer mortality (1946-1952 hiring period all-cause SMR = 1.38, 95%CI:1.28,1.47; lung cancer SMR = 2.63, 95CI: 2.21, 3.04). All-cause mortality by hiring period was further examined using stratification by categories of employment duration (see Appendix Table 2A). For all-cause mortality, no substantial differences in mortality by duration of employment were observed in the early hiring period. In the two later hiring periods, mortality decreases with longer duration of employment.

CMRs were slightly lower than SMRs for all cancer types examined, and are reported for cancer subtypes of interest in Table 4.1.5. Lower CMRs indicate that person-time in the cohort was lower than expected across several causes of mortality. Overall expected person-time was 2.3% higher than observed person time, averaging to 0.33 person-years of life lost per miner.

Random effects were used to assess changes in standardization variables over time. SMRs from the random effects lognormal Poisson model are reported in four-year calendar periods (Table 3.1.6). The mortality ratios from the random effects model did not differ from the standard ratio estimates for all-cause mortality nor for lung cancer. All corresponding $\sigma^2$ estimates approached zero, indicating that the amount of heterogeneity in incidence ratios was minimal.

**4.1.5 Discussion**

The mortality and cancer incidence experience among the Příbram uranium miners have not been previously described relative to an external population. We have estimated SMRs, SIRs, and CMRs relative to a national population reference. We also examined trends over time in mortality ratios, evaluated comparability in standard populations using random effects models,

and evaluated possible influences of healthy-worker hire effects by stratification of employment factors, evaluated workplace hazards using CMRs, and examined cohort effects. Our results show that several cancer subtypes and non-malignant causes of death were elevated among miners. Elevated mortality rates of pneumoconiosis and tuberculosis were observed, and are plausibly related to occupational exposure to dust and its components such as silica.[10] Excess lung cancer, hematopoietic cancers, and cancers of the extrathoracic airway and stomach were observed, consistent with dosimetric models and previous studies of uranium miners.[8,11,3,37,61]

Beyond findings that were expected for uranium miners based on known hazards, a few other hazards were implicated in the current analysis. Atherosclerosis mortality was almost four times higher than expected (SMR = 3.88, 95%CI: 3.50, 4.26). Although radiation and other occupational exposures have been linked to cardiovascular disease, such a large excess of atherosclerosis is not generally associated with uranium mining activities. There are several potential reasons for this excess, namely errors in cause of death reporting or coding errors. The excess of deaths due to atherosclerosis is counter-balanced by a decrease in deaths due to myocardial infarction, which suggests the possibility of misclassification of CVD deaths among Příbram miners. Additionally, use of pneumatic drills can cause symptoms which resemble atherosclerosis.

There was also a noticeable deficit of non-melanoma skin cancer incidence in this cohort. A substantial excess of skin cancer (SMR= 5.7; 90% CI: 4.1, 7.8) has been reported among 3000 Jáchymov Czech uranium miners.[64,65] The difference in estimates may be because the Jáchymov cohort had a dermatology surveillance program, while the Příbram study relies on ICD-9 codes.[65,66] Further research on radon progeny and skin cancer incidence is needed.

Prior studies have examined associations between radon exposure and incidence of some specific cancer subtypes in this cohort of Příbram uranium miners. In a case-cohort study in which incidence of leukemia, lymphoma, and multiple myeloma was investigated among a subcohort of 2,393 workers, an elevated risk for all leukemia combined [Risk Ratio (RR) = 1.75, 95% CI: 1.10, 2.78] and for CLL (RR = 1.98, 95% CI: 1.10, 3.59) were observed when comparing high radon exposure (110 WLM) to low radon exposure (3 WLM). Suggestive associations between myeloid leukemia and Hodgkin's lymphoma with radon exposure were also reported.[24] In the present study, we found elevated risks for all leukemia combined, Hodgkin's lymphoma, multiple myeloma, myeloid leukemia, and lymphoid leukemia. We could not examine CLL alone due to availability of national rates for certain subtypes, but most lymphoid leukemias in adults are CLL.[67] The incidence of non-lung solid cancers was examined in another case-cohort study but only associations with malignant melanoma and gallbladder cancer were found.[25] The SIRs and SMRs in the present study show a higher than expected incidence of several non-lung solid cancers, namely liver, stomach, and extrathoracic airway cancers. Differences between this and prior studies are in part due to the different effect measures and comparison populations. While internal comparisons of rates yielded most estimates close to unity, external comparisons demonstrate that the rate of many cancers are higher in this uranium mining population compared to national rates.

Workers born between 1920 and 1929 had somewhat higher lung cancer mortality compared to other birth cohorts (Table 3.1.4). This pattern may reflect cohort selection criteria, since cases in the earliest birth cohorts may have occurred prior to the start of follow-up. This pattern could also reflect birth cohort trends across Europe, as smoking rates increased dramatically during and after World War II.[68] By the end of WWII, workers born 1920 to 1920

were ages 16 to 23. This birth cohort may have had a higher rate of smoking compared to other birth cohorts, which could account for the excess in all-cause mortality and substantial excess in lung cancer mortality.

Occupational hazards in the Příbram underground mines gradually declined as ventilation practices and workplace protection improved.[24,25] Miners employed at earlier periods likely experienced occupational hazards at higher exposure intensities than miners employed in later periods. This is reflected in Table 4.1.4 where the results show that the miners hired in the early period with the least ventilation and least workplace protections have the highest lung cancer mortality and highest all-cause mortality.

Earlier hires may have also been employed for longer, resulting in an increased duration of exposure to hazards. However, Table 4.1.4 shows that workers with shorter time since hire and shorter time since termination have substantially higher lung and all-cause mortality. This may be due to cohort selection criteria requiring cohort members to be alive at the start of follow-up in 1977, which excludes older workers employed in earlier time periods and more susceptible workers whose risk was higher prior to the start of follow-up. Differences in mortality by time since hire and termination may also reflect healthy-worker bias. Further internal comparisons are needed to analyze differences in these factors.

A few limitations of the analyses should be considered. Occupational exposures prior employment in the Příbram mines are unknown, and some miners transferred from the more hazardous Jáchymov to Příbram in the 1960s. This study is also limited by low numbers of some cancers, limited duration of follow-up, and uncontrolled confounding, and we did not examine disease in relation to specific exposures. Further internal analyses of cancer risks within the subcohort are needed to better evaluate radon, dust, and smoking related risks in this population.

Smoking status is only available for a subcohort of miners and not analyzed in this study. If the smoking rate among workers differs substantially from the national population, estimates may be biased. However, smoking rates appear to be high in both the cohort and national population during mining operations. Among the subcohort, 66% of workers were listed as smokers on their occupational medical records, and the proportion of male smokers in Europe was about 60% in the 1960s.[68,69] No excess COPD incidence or mortality was observed, which is another indicator that smoking rates in the cohort were similar to the Czech population.

In summary, the studied population is a large, well enumerated cohort with both cancer incidence and mortality data. Despite the fact that this is a relatively modern uranium mining cohort, which experienced occupational hazards of lower intensity compared to several other uranium mining cohorts, we were still able to demonstrate excess cancers compared to the general population. We were also able to demonstrate an excess mortality and cancer incidence among the Příbram uranium miners from lung cancer, tuberculosis, pneumoconiosis, extrathoracic cancer, stomach cancer, liver cancer, and some hematopoietic cancer types. Our results support prior published findings in the cohort and other uranium mining cohorts.[8,11,3,37,61]

### 4.1.6 Tables and figures

## Table 4.1.1: Characteristics of the Příbram Czech Miners Cohort 1977-1992

| **Variable** | |
|---|---|
| Miners, n | 16,434 |
| Follow-up period | 1977–1992 |
| Person-years | 231,499 |
| Age at death among deceased subjects, mean(range) | 62 (22–102) |
| Cumulative radon in WLM, mean (range) | 53 (1.2–1121.9) |
| **Vital status, n (%)** | |
| Alive | 12,209 (74.3) |
| Deceased | 4212 (25.6) |
| Emigrated | 12 (0.07) |
| Vital Status Unknown | 1 (0.01) |
| Duration of follow-up in years, mean (range) | 14 (0.1-16) |
| Availability of cause of death | 3776 (89.6) |
| **Year of birth n (%)** | |
| 1890 - 1909 | 543 (3.3) |
| 1910 - 1919 | 1541 (9.4) |
| 1920 - 1929 | 3810 (23.2) |
| 1930 - 1939 | 3476 (21.2) |
| 1940 - 1950+ | 7064 (43.0) |
| **Year of hire n(%)** | |
| 1946 - 1952 | 1568 (9.5) |
| 1953 - 1962 | 6397 (39.0) |
| 1963 + | 8469 (51.5) |

**Table 4.1.2: Non-malignant causes of death among Příbram uranium miners**

| | Cancer Mortality | | | | |
|---|---|---|---|---|---|
| **Major groups and select ICD-9 subgroups** | **Obs** | **Exp** | **SMR** | **95%CI** | |
| (011 - 012) Respiratory Tuberculosis | 14 | 6.7 | 2.08 | (0.99 - | 3.18) |
| (250) Diabetes mellitus | 34 | 45.3 | 0.75 | (0.50 - | 1.00) |
| (280 - 289) Diseases of the Blood & Blood Forming Organs | 5 | 3.9 | 1.29 | (0.15 - | 2.42) |
| (290 - 319) Mental, Psychoneurotic, & Personality Disorders | 20 | 10.6 | 1.88 | (1.05 - | 2.71) |
| (303) Alcohol Dependence Syndrome | 7 | 9.1 | 0.77 | (0.20 - | 1.34) |
| (320 - 389) Disorders of The Nervous System & Sense Organs | 19 | 26.5 | 0.72 | (0.39 - | 1.04) |
| (390 - 459) Diseases of the Heart and Other Diseases of the Circulatory System | 1536 | 1647.6 | 0.93 | (0.89 - | 0.98) |
| (410) Acute Myocardial Infarction | 230 | 613.0 | 0.38 | (0.33 - | 0.42) |
| (410 - 414) AMI and Ischemic Heart Disease | 737 | 933.0 | 0.79 | (0.73 - | 0.85) |
| (430 - 438) Cerebrovascular Disease | 148 | 424.2 | 0.35 | (0.29 - | 0.41) |
| (440) Atherosclerosis | 403 | 103.8 | 3.88 | (3.50 - | 4.26) |
| (440 - 448) Atherosclerosis and Other Aortic Disease | 419 | 121.3 | 3.46 | (3.12 - | 3.79) |
| (460 - 519) Diseases of the Respiratory System | 166 | 187.6 | 0.89 | (0.75 - | 1.02) |
| (480 - 487) Pneumonia and Influenza | 37 | 51.6 | 0.72 | (0.48 - | 0.95) |
| (490 - 496) Respiratory Diseases: Bronchitis, COPD, Asthma, and Emphysema | 96 | 114.1 | 0.84 | (0.67 - | 1.01) |
| (500 - 505) Pneumoconiosis Including Silicosis, and Asbestosis | 22 | 11.5 | 1.92 | (1.11 - | 2.72) |
| (520 - 579) Diseases of the Digestive System | 167 | 177.0 | 0.94 | (0.80 - | 1.09) |
| (530 - 537) Diseases of the Stomach & Duodenum | 17 | 26.0 | 0.65 | (0.34 - | 0.97) |
| (571) Cirrhosis & Other Chronic Liver Disease | 89 | 95.1 | 0.94 | (0.74 - | 1.13) |
| (577) Diseases of the Pancreas | 20 | 14.8 | 1.35 | (0.76 - | 1.94) |
| (580 - 589) Diseases of the Genitourinary System | 26 | 27.8 | 0.94 | (0.58 - | 1.30) |
| (580 - 629) Diseases of the Genitourinary System | 55 | 75.4 | 0.73 | (0.54 - | 0.92) |
| (590) Infections of the Kidney | 21 | 25.3 | 0.83 | (0.47 - | 1.19) |
| (800 - 999) Transportation Injuries, Falls and Violence | 101 | 277.5 | 0.36 | (0.29 - | 0.44) |
| (E800 - E949) Transportation Injuries, Falls and Accidents | 95 | 163.8 | 0.58 | (0.46 - | 0.70) |
| (E950 - E959) Suicide and Self-Inflicted | 86 | 97.2 | 0.89 | (0.70 - | 1.07) |
| (E960 - E969) Assault | 4 | 3.3 | 1.20 | (0.02 - | 2.38) |
| (001 -139) Other Causes | 19 | 15.3 | 1.25 | (0.68 - | 1.81) |
| (001-E999) All-Cause mortality* | 4211 | 3419.0 | 1.23 | (1.20 - | 1.27) |

*437 miners are missing cause of death codes, and 12 have undetermined external causes of injury (ICD-9 E970- E999)

## Table 4.1.3: Cancer mortality and incidence for select ICD-9 groups

| | Cancer Mortality | | | | Cancer Incidence | | | |
|---|---|---|---|---|---|---|---|---|
| **(ICD) Cancer Subtype** | **Obs** | **Exp** | **SMR** | **95%CI** | **Obs** | **Exp** | **SIR** | **95%CI** |
| (140) Malignant neoplasm of lip | 0 | - | - | - | 6 | 8.6 | 0.70 | 0.14 - 1.26 |
| (141) Malignant neoplasm of tongue | 9 | 6.4 | 1.41 | 0.48 - 2.33 | 12 | 7.6 | 1.58 | 0.68 - 2.48 |
| (146) Malignant neoplasm of oropharynx | 3 | 4.5 | 0.66 | 0.00 - 1.41 | 6 | 7.7 | 0.78 | 0.15 - 1.40 |
| (140 - 149) Lip, Oral Cavity, and Pharynx | 25 | 21.8 | 1.14 | 0.75 - 1.65 | 41 | 42.1 | 0.98 | 0.71 - 1.31 |
| (150) Malignant neoplasm of esophagus | 23 | 15.0 | 1.53 | 0.90 - 2.16 | 19 | 14.0 | 1.36 | 0.74 - 1.97 |
| (151) Malignant neoplasm of stomach | 102 | 80.6 | 1.27 | 1.02 - 1.51 | 108 | 78.9 | 1.37 | 1.11 - 1.63 |
| (152) Malignant neoplasm of small intestine, including duodenum | 6 | 2.1 | 2.91 | 0.57 - 5.25 | 7 | 2.1 | 3.26 | 0.83 - 5.69 |
| (153) Malignant neoplasm colon | 54 | 59.7 | 0.90 | 0.66 - 1.15 | 80 | 75.7 | 1.06 | 0.82 - 1.29 |
| (154) Malignant neoplasm of rectum, rectosigmoid junction, and anus | 80 | 60.2 | 1.33 | 1.04 - 1.62 | 119 | 84.4 | 1.41 | 1.16 - 1.66 |
| (155) Malignant neoplasm of liver and intrahepatic bile ducts | 48 | 29.4 | 1.63 | 1.17 - 2.10 | 38 | 22.3 | 1.70 | 1.16 - 2.25 |
| (156) Malignant neoplasm of gallbladder and extrahepatic bile ducts | 13 | 14.7 | 0.88 | 0.40 - 1.37 | 9 | 14.8 | 0.61 | 0.21 - 1.00 |
| (157) Malignant neoplasm of pancreas | 53 | 44.6 | 1.19 | 0.87 - 1.51 | 54 | 41.3 | 1.31 | 0.96 - 1.66 |
| (159) Malignant neoplasm of other and ill-defined sites | 14 | 7.7 | 1.82 | 0.86 - 2.77 | 16 | 4.9 | 3.29 | 1.67 - 4.91 |
| (140-148, 160, 161) Extrathoracic airway* | 59 | 41.8 | 1.41 | 1.15 - 1.77 | 80 | 68.9 | 1.16 | 0.95 - 1.39 |
| (150 - 159) Digestive organs and peritoneum | 396 | 316.7 | 1.25 | 1.13 - 1.38 | 453 | 340.8 | 1.33 | 1.21 - 1.46 |
| (161) Malignant neoplasm of larynx | 33 | 19.8 | 1.67 | 1.10 - 2.24 | 45 | 33.6 | 1.34 | 0.95 - 1.73 |
| (162) Malignant neoplasm of trachea, bronchus, and lung | 705 | 332.3 | 2.12 | 1.96 - 2.28 | 755 | 326.2 | 2.31 | 2.15 - 2.48 |
| (163) Malignant neoplasm of pleura | 5 | 2.4 | 2.06 | 0.25 - 3.87 | 5 | 2.5 | 1.97 | 0.24 - 3.71 |
| (160 - 165) Respiratory and Intrathoracic | 749 | 358.5 | 2.09 | 1.95 - 2.25 | 808 | 367.0 | 2.20 | 2.05 - 2.36 |
| (171) Malignant neoplasm of connective and other soft tissue | 3 | 2.8 | 1.07 | 0.00 - 2.28 | 5 | 6.9 | 0.72 | 0.09 - 1.36 |
| (172) Malignant melanoma of skin | 14 | 11.9 | 1.18 | 0.56 - 1.80 | 18 | 23.3 | 0.77 | 0.41 - 1.13 |
| (173) Other malignant neoplasm of skin | 1 | 2.6 | 0.39 | 0.00 - 1.16 | 129 | 190.3 | 0.68 | 0.56 - 0.80 |
| ICD 170 - 175: Bone, Connective tissue, Skin, and Breast | 22 | 21.8 | 1.00 | 0.64 - 1.49 | 157 | 224.9 | 0.70 | 0.59 - 0.81 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (185) Malignant neoplasm of prostate | 30 | 45.1 | 0.67 | 0.43 - 0.90 | 57 | 65.9 | 0.86 | 0.64 - 1.09 |
| (186) Malignant neoplasm of testis | 4 | 3.8 | 1.05 | 0.02 - 2.09 | 10 | 11.7 | 0.85 | 0.32 - 1.38 |
| (187) Malignant neoplasm of penis and other male genital organs | 4 | 1.4 | 2.81 | 0.04 - 5.57 | 6 | 3.4 | 1.76 | 0.35 - 3.18 |
| (188) Malignant neoplasm of bladder | 29 | 27.7 | 1.05 | 0.67 - 1.43 | 54 | 50.8 | 1.06 | 0.78 - 1.35 |
| (189) Malignant neoplasm of kidney and other and unspecified urinary organs | 41 | 40.9 | 1.00 | 0.69 - 1.31 | 49 | 55.9 | 0.88 | 0.63 - 1.12 |
| ICD 185 - 189: Genitourinary Organs | 108 | 118.9 | 0.91 | 0.75 - 1.09 | 176 | 187.8 | 0.94 | 0.81 - 1.08 |
| (191) Malignant neoplasm of brain | 13 | 17.0 | 0.76 | 0.35 - 1.18 | 13 | 15.6 | 0.83 | 0.38 - 1.29 |
| (193) Malignant neoplasm of thyroid gland | 2 | 2.2 | 0.91 | 0.00 - 2.19 | 5 | 4.3 | 1.17 | 0.14 - 2.20 |
| (195) Malignant neoplasm of other and ill-defined sites | 5 | 4.3 | 1.17 | 0.14 - 2.19 | 3 | 3.4 | 0.87 | 0.00 - 1.86 |
| (197) Secondary malignant neoplasm of respiratory and digestive systems | 8 | 0.1 | 71.70 | 21.81 - 121.60 | 7 | 5.4 | 1.29 | 0.33 - 2.25 |
| (198) Secondary malignant neoplasm of other specified sites | 6 | 0.1 | 52.86 | 10.39 - 95.33 | 13 | 4.5 | 2.86 | 1.30 - 4.42 |
| (199) Malignant neoplasm without specification of site | 14 | 13.8 | 1.02 | 0.48 - 1.55 | 19 | 8.0 | 2.36 | 1.30 - 3.43 |
| (190 - 199) Other and unspecified sites | 53 | 39.2 | 1.36 | 1.03 - 1.76 | 68 | 49.1 | 1.38 | 1.09 - 1.75 |
| (200) Lymphosarcoma and reticulosarcoma | 7 | 4.5 | 1.57 | 0.40 - 2.73 | 7 | 7.4 | 0.94 | 0.24 - 1.64 |
| (201) Hodgkin's disease | 8 | 6.8 | 1.18 | 0.36 - 2.00 | 15 | 9.5 | 1.57 | 0.77 - 2.37 |
| (202) Other malignant neoplasms of lymphoid and histiocytic tissue | 10 | 10.2 | 0.98 | 0.37 - 1.58 | 10 | 14.1 | 0.71 | 0.27 - 1.15 |
| (203) Multiple myeloma and immunoproliferative neoplasms | 8 | 7.5 | 1.07 | 0.33 - 1.82 | 16 | 9.2 | 1.75 | 0.89 - 2.61 |
| (204) Lymphoid leukemia | 11 | 10.6 | 1.03 | 0.42 - 1.65 | 21 | 13.3 | 1.57 | 0.90 - 2.25 |
| (205) Myeloid leukemia | 12 | 8.8 | 1.36 | 0.59 - 2.14 | 14 | 8.8 | 1.58 | 0.75 - 2.42 |
| (204-208) All Leukemia^ | 25 | 24.0 | 1.05 | 0.69 - 1.52 | 37 | 24.0 | 1.51 | 1.08 - 2.07 |
| (200 - 208) Lymphatic and Hematopoietic | 58 | 52.8 | 1.09 | 0.84 - 1.41 | 85 | 64.7 | 1.31 | 1.05 - 1.61 |
| (140 - 232) All cancer types | 1411 | 929.6 | 1.52 | 1.44 - 1.60 | 1788 | 1276.5 | 1.40 | 1.34 - 1.47 |

*Extrathoracic airway includes cancers of the oral cavity and pharynx (141 - 148), nasal cavities (160) and larynx (161)

^ Lymphoid, Myeloid, other and unspecified leukemia

**Table 4.1.4: All-cause mortality and lung cancer mortality by duration of employment, time since hire, time since termination, age at hire, birth cohort and hiring period**

| | All-cause mortality | | | Lung Cancer Mortality | | |
|---|---|---|---|---|---|---|
| | Obs | SMR | 95%CI | Obs | SMR | 95%CI |
| **Duration of Employment** | | | | | | |
| < 2 years | 1181 | 1.27 | 1.20 - 1.34 | 149 | 1.69 | 1.42 - 1.97 |
| 2 - <10 years | 1579 | 1.30 | 1.24 - 1.37 | 247 | 2.15 | 1.88 - 2.42 |
| ≥ 10 years | 1451 | 1.14 | 1.08 - 1.20 | 309 | 2.39 | 2.12 - 2.65 |
| **Time since hire** | | | | | | |
| < 15 years | 238 | 52.11 | 45.46 - 58.76 | 18 | 46.62 | 24.99 - 68.25 |
| 15 - < 25 years | 1096 | 2.39 | 2.24 - 2.53 | 187 | 5.09 | 4.36 - 5.83 |
| 25 - < 35 years | 2162 | 1.92 | 1.83 - 2.00 | 350 | 3.22 | 2.88 - 3.56 |
| ≥ 35 years | 715 | 0.39 | 0.36 - 0.42 | 150 | 0.80 | 0.67 - 0.93 |
| **Time since termination** | | | | | | |
| < 15 years | 1124 | 3.30 | 3.11 - 3.49 | 189 | 5.68 | 4.86 - 6.49 |
| 15 - < 25 years | 1750 | 1.31 | 1.25 - 1.37 | 310 | 2.40 | 2.14 - 2.67 |
| ≥ 25 years | 1337 | 0.77 | 0.73 - 0.81 | 206 | 1.21 | 1.05 - 1.38 |
| **Age at hire** | | | | | | |
| < 25 years | 825 | 1.24 | 1.15 - 1.32 | 134 | 2.04 | 1.70 - 2.39 |
| 25 - < 35 years | 1554 | 1.36 | 1.29 - 1.42 | 310 | 2.29 | 2.03 - 2.54 |
| ≥ 35 years | 1832 | 1.14 | 1.09 - 1.19 | 261 | 1.99 | 1.75 - 2.23 |
| **Birth Cohort** | | | | | | |
| 1940 - 1950+ | 481 | 1.09 | 1.00 - 1.19 | 28 | 1.47 | 1.02 - 2.13 |
| 1930 - 1939 | 1049 | 1.16 | 1.09 - 1.23 | 141 | 2.01 | 1.68 - 2.35 |
| 1920 - 1929 | 1610 | 1.35 | 1.29 - 1.42 | 342 | 2.35 | 2.10 - 2.60 |
| 1910 - 1919 | 680 | 1.23 | 1.13 - 1.32 | 155 | 2.10 | 1.77 - 2.43 |
| 1890 - 1909 | 391 | 1.19 | 1.07 - 1.31 | 39 | 1.63 | 1.19 - 2.22 |
| **Hiring period** | | | | | | |
| 1946 - 1952 | 821 | 1.38 | 1.28 - 1.47 | 154 | 2.63 | 2.21 - 3.04 |
| 1953 - 1962 | 2579 | 1.20 | 1.15 - 1.25 | 435 | 2.02 | 1.83 - 2.21 |
| 1963 + | 811 | 1.20 | 1.12 - 1.29 | 116 | 1.98 | 1.62 - 2.34 |

**Table 4.1.5: Classical standardized mortality ratio calculations and causal mortality ratio calculations**

| | | Classical SMR calculation | | CMR calculation | |
|---|---|---|---|---|---|
| Outcome | Observed | Expected | SMR | Expected | CMR |
| All-cause mortality | 4211 | 3419.0 | 1.23 | 3623.0 | 1.16 |
| Lung Cancer | 705 | 332.3 | 2.12 | 350.7 | 2.01 |
| Extrathoracic Airway Cancer | 59 | 41.8 | 1.41 | 43.7 | 1.35 |
| Kidney Cancer | 41 | 40.9 | 1.00 | 43.2 | 0.95 |
| Liver Cancer | 48 | 29.4 | 1.63 | 31.2 | 1.54 |
| Stomach Cancer | 102 | 80.6 | 1.27 | 85.3 | 1.20 |
| Hematopoietic Cancer | 58 | 52.7 | 1.10 | 55.6 | 1.03 |

**Table 4.1.6. All-cause mortality and lung cancer mortality, standard and hierarchical estimates**

**All-cause mortality**

| | | Standard | | | Hierarchical | | | |
|---|---|---|---|---|---|---|---|---|
| Study Period | Obs | SMR | 95% CI | | SMR | 95% CI | | $\sigma^2$ |
| 1977 - 1980 | 268 | 1.51 | 1.33 - | 1.70 | 1.51 | 1.32 - | 1.71 | 5.4E-09 |
| 1981 - 1984 | 312 | 1.43 | 1.27 - | 1.59 | 1.43 | 1.25 - | 1.60 | 1.3E-05 |
| 1985 - 1988 | 386 | 1.52 | 1.36 - | 1.67 | 1.52 | 1.35 - | 1.68 | 9.1E-08 |
| 1989 - 1992 | 453 | 1.60 | 1.45 - | 1.75 | 1.60 | 1.43 - | 1.77 | 1.7E-04 |

**Lung cancer mortality**

| | | Standard | | | Hierarchical | | | |
|---|---|---|---|---|---|---|---|---|
| Study Period | Obs | SMR | 95% CI | | SMR | 95% CI | | $\sigma^2$ |
| 1977 - 1980 | 144 | 2.22 | 1.85 - | 2.59 | 2.22 | 1.83 - | 2.61 | 1.5E-09 |
| 1981 - 1984 | 147 | 1.86 | 1.56 - | 2.17 | 1.86 | 1.54 - | 2.19 | 2.6E-09 |
| 1985 - 1988 | 197 | 2.15 | 1.84 - | 2.45 | 2.15 | 1.83 - | 2.47 | 1.7E-08 |
| 1989 - 1992 | 217 | 2.24 | 1.93 - | 2.54 | 2.24 | 1.92 - | 2.56 | 5.6E-08 |

## 4.2 Radon and cancer mortality among underground uranium miners in the Příbram region of the Czech Republic (AIM 2)

### 4.2.1 Overview

Miners exposed to radon and its progeny experience higher rates of lung cancer. Positive associations between radon and malignancies other than lung have also been reported, but estimates vary across studies.

Cancer mortality over the period 1977-1992 was ascertained for a cohort of 16,434 underground uranium miners employed in the Czech Republic between 1946 and 1992. Poisson regression was used to estimate relationships between cumulative radiation exposure (in working level months, WLM) and cancer mortality.

Radon is positively associated with lung cancer mortality (Excess relative rate (ERR) per 100WLM = 0.23: 95%CI: 0.10, 0.37). The best fit of the dose-response relationship between radon and lung cancer mortality was linear and varied with time since start of exposure. Positive but statistically imprecise associations between radon and several other cancer types were identified, including extrathoracic cancer (ERR/100WLM = 0.12; 95%CI: -0.25, 0.48) and Chronic Lymphocytic Leukemia (CLL) (ERR/100WLM = 0.24; 95%CI: -0.80, 1.27).

This study confirms the established radon-lung cancer association and suggests that radon may be associated with other non-lung cancer mortality. Further investigations of extrathoracic and CLL cancer, with the aim of obtaining more precise estimates, are warranted to understand associations between radon and cancers other than lung

### 4.2.2 Introduction

It is well established that underground miners exposed to radon progeny experience higher rates of lung cancer (Lubin et al., 1995; National Research Council, 1999a; Tirmarche et

al., 2012). Several cohort studies of underground uranium miners have confirmed the association between radon exposure and lung cancer, although magnitudes of associations vary somewhat between studies. Three North American cohorts (Hornung et al., 1998, 1995; Lane et al., 2010; Navaranjan et al., 2016; Samet et al., 1991; Schubauer-Berigan et al., 2009), a cohort of Czech miners in Western Bohemia (Tomásek and Zárská, 2004; Tomásek, 2002; Tomasek et al., 2008), a cohort of French uranium miners with extended follow-up (Laurier et al., 2004; Rogel et al., 2002; Vacquier et al., 2008), and a large cohort study of German uranium miners, which is similar in size to the pooled Committee on the Biological Effects of Ionizing Radiation (BEIR VI) analysis (Grosche et al., 2006; National Research Council, 1999a) have all found positive and statistically significant associations between radon and lung cancer. Radon and its progeny is classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC, 1988).

Epidemiological studies and dosimetric models suggest that radon progeny may be associated with cancer types other than lung (National Research Council, 1999a). Animal models have demonstrated that inhaled radon results in radon activity in blood, adipose tissue, and organs (Ishimori et al., 2017; National Research Council, 1999b; Nussbaum and Hursh, 1957). Radon gas is soluble in water, so inhaled radon progeny can enter the bloodstream. In the bloodstream, radon progeny may cause leukemias through irradiation of T lymphocyte blood cells close to the airway. Radon gas is also soluble in fat, so radon progeny can reach organs through proximity to adipose tissue. For instance, the liver and kidney may receive higher doses of radon progeny because they are surrounded by visceral fat (Harley and Robbins, 1992). Prior uranium miner studies have examined cancer subtypes other than lung and reported excess mortality from leukemia among miners in a Czech cohort (Rericha et al., 2006), stomach cancer

among German and US miners (Darby et al., 1995; Kreuzer et al., 2008; Schubauer-Berigan et al., 2009) and kidney cancer among French miners (E Rage et al., 2015).

When radon and its progeny are inhaled, the tissues of the extrathoracic respiratory system also receive radiation doses (ICRP, 1994). The association between cumulative radon exposure and rates of extrathoracic airway cancers is not well characterized. Recent studies of the Ontario and German uranium miners reported on the association between radon and extrathoracic cancer. The German study found a positive but statistically imprecise association between radon and extrathoracic cancer mortality (ERR/100 WLM= 0.036 95%CI: -0.009, 0.080) while the Ontario study found a negative but statistically imprecise association with extrathoracic cancer incidence (ERR/100 WLM = −0.29; 95%CI: −0.57, 0.0034) and mortality (ERR/100 WLM = −0.17; 95%CI: −0.64, 0.30).

Aside from respiratory cancers, several studies suggest radon progeny exposure is associated with other cancer subtypes among uranium miners, but many of these positive findings are based on standardized mortality ratios that use external comparison populations. We report on radon exposure-mortality analyses for lung cancer and other types of cancer among a cohort of workers from the Příbram region of Central Bohemia, Czech Republic. Compared to many other uranium miner cohorts, the Příbram cohort has a lower average radon exposure and a higher proportion of workers with low cumulative exposures (Table 3.2.1). This allows us to further examine radon-cancer associations at lower levels and at lower exposure rates that are more representative of modern occupational radon exposures. Příbram miners also have lower average exposures to other co-pollutants such as no diesel exhaust exposure and low silica exposure (Hu et al., 2000; Kulich et al., 2011; Rericha et al., 2006), reducing bias from unmeasured confounding. This study adds to the understanding of cancer mortality by analyzing

a large and historically significant uranium mining cohort routinely exposed to low and moderate levels of radon and its progeny, and examining extrathoracic cancers as a group.

### 4.2.3 Methods

**Study setting.** The Příbram mines are located 60 kilometers southwest of Prague, in a region of the Czech Republic known historically for lead, silver and zinc mining. Příbram uranium mine operations occurred between 1946 and 1991, during which time over 46,000 workers were employed, producing over 98,500 metric tons of uranium (Hu et al., 2000). Workers produced most of the country's uranium through the collapse of the Soviet Union; and by the 1960s over 70% of all uranium production took place in Příbram (Hnidzo et al., n.d.).

**Cohort definition.** The Příbram miner study is based on information collected from employment records for the Příbram Uranium Industry. Card records were kept for compensation purposes for each worker and subsequently computerized into an employment register containing 41,741 males and 6,106 females. Records included unique personal identification numbers, dates of birth, dates of employment, and location of employment within the mines (e.g., underground, surface, sorting ore) (Kulich et al., 2011; Rericha et al., 2006). Male employees who worked at least 12 months underground between 1946 and 1991, and were alive and residing in Czechoslovakia on January 1, 1977 are included in the follow-up cohort (Kulich et al., 2011; Rericha et al., 2006).

**Exposure assessment.** An annual estimate of exposure to radon progeny, expressed in Working Level Months (WLM), was assigned to each miner based on their duration of underground mining and estimates of potential alpha energy of radon progeny in their location of work. Duration of time spent underground was derived from the Czech Uranium Industry (UI) employment records. Annual radon exposure concentration estimates, expressed in working

levels, were based on measurements by the Czech UI using area monitors. Prior to 1968, potential alpha energy was estimated from > 50,000 radon gas measurements throughout the mines (Rericha et al., 2006). Radon gas measurements were converted to working levels using an equilibrium factor based mainly on mine ventilation practices (Hnidzo et al., n.d.). From 1968 onwards, direct measurements of the potential alpha energy of radon progeny were measured in the UI. Over  direct measurements were taken through the mines between 1968 and 1992 (Rericha et al., 2006). Cumulative WLM of radon exposure was calculated for each miner by summing annual estimates for each year since the start of exposure.

**Other exposures.** Diesel fumes and dust are a concern among miners. . Unlike many other mining operations, Příbram miners were not occupationally exposed to diesel exhaust because all vehicles in the Příbram mines were electric (Hnidzo et al., n.d.). Dust was measured in Příbram mines at least monthly and is described in detail in prior studies (Kelly-Reif et al., 2018). Average area measurements of airborne dust in Příbram were highest in the mid-1950s (but decreased in the 170s with the introduction of a strong ventilation system. Heavy metals in dust sediments were measured in a pilot study and contained higher levels of lead and lower levels of arsenic compared to the other major Czech mine in the Jáchymov region (Hnidzo et al., n.d.). The mean concentration of free crystalline silica in the total dust in Příbram was estimated to be 15%, lower than many other hard-rock mines; dry drilling was not common in Czech mines

**Outcome assessment.** Vital Status for the period 1977 - 1992 was obtained for each worker from the Czech Central Register of Inhabitants using personal identification numbers listed on employment records. Workers who emigrated after the start of follow-up were censored at the date of emigration. For workers who died in the Příbram region (approximately 30% of all deaths), underlying cause of death was coded by a nosologist. For workers who died outside this

region, underlying cause of death was obtained from district death registries, and if possible, hard copy death certificates were obtained. Additional sources of vital status follow up included pensions, Uranium Industry death records and medical documentation. Last date of follow-up, and vital status at end of follow-up (dead, alive, or emigrated) were coded. Primary cause of death and contributing causes of death (such as chronic diseases) were also coded to the International Classification of Diseases, 9th Edition (ICD-9) (Kulich et al., 2011; Rericha et al., 2006).

Outcomes of interest in the current analysis, chosen based on prior epidemiological and dosimetric studies of uranium miners, include lung, stomach, kidney, and liver cancer as well as hematopoietic cancers (non-Hodgkin's lymphoma, Hodgkin's lymphoma, myeloma, chronic lymphocytic leukemia, and myeloid leukemia). The category of extrathoracic cancers, defined as all respiratory tissues other than lung and bronchus, is grouped based on the International Commission on Radiological Protection (ICRP) dose calculations (ICRP, 1994) and includes the nasal passages (ICD-9 160), larynx (ICD-9 161), pharynx (ICD-9 147-148), oropharynx (ICD-9 146), and mouth (ICD-9 141-145).

**Statistical analyses.** Miners contributed person-time from the start of follow-up (1/1/1977) until the earliest of the date of death among deceased miners, date of migration out of the Czech Republic, or end of the study period (12/31/1992). Workers diagnosed with cancer were not allowed to work underground. Therefore, all workers alive in 1977 and still working underground were assumed to be cancer free at the start of follow-up (Kulich et al., 2011; Rericha et al., 2006). Person-years and events were enumerated and analyzed using Poisson regression analyses with single units of person-time, without grouping (Loomis et al., 2005).

The relationship between cumulative radon exposure (in k categories) and cancer deaths of interest was modeled using the general model form $rate = \exp(\beta_0 + \sum_{i=1}^{k-1} \beta_i d_i + \sum_{j=k}^{p-1} \beta_j x_j)$. $\beta_1 - \beta_{k-1}$ represents the log relative rate of cancer mortality per category of lagged cumulative radon exposure in k groups (relative to the referent group). $\beta_0$ is the log rate of cancer among workers with the referent level of cumulative WLM, and $\beta_j$ are parameters for effects of the *p* covariates $x_j$. Cumulative WLM was categorized as <25, 25 - <50, 50 - <150, and 150+ WLM for subtypes of interest except lung cancer. Due to the larger number of deaths, lung cancer rates were modeled with more exposure categories (<15, 15-<25, 25-<50, 50-<75, 75-<100, 100-<150, 150-<200, 200-<250, and 250+ WLM). A log-linear model was fit for continuous dose, $rate = \exp(\beta_0 + \beta_1 d + \sum_{j=2}^{p} \beta_j x_j)$ where $\beta_1$ represents the log relative rate of cancer mortality per unit of lagged cumulative radon exposure and $\beta_j$ are parameters for effects of the covariates $x_j$. To account for an induction and latency times, 2-year, 5-year, and 10-year lags were applied to cumulative radon exposures. Model fit and precision were used to determine final lag-time choice.

Linear excess relative rate (ERR) estimates and 95% CIs were estimated by fitting a model for the association between a continuous measure of cumulative WLM and deaths by cancer types of interest. Excess relative rate estimates were obtained using a model form $rate = \exp(a_0 + \sum_{j=2}^{p} a_j x_j)(1 + a_1 d)$ where $a_1$ is the excess relative rate per unit of lagged cumulative radon exposure d, and $a_j$ are parameters for effects of the covariates $x_j$. Variation in the radon exposure-cancer mortality association with time-since-exposure was examined in analyses of lung cancer mortality; three windows of exposure (10-20 years, 20-30 years, and 30+ years) were modeled using a model form $rate = \exp(a_0 + \sum_{j=4}^{p+2} a_j x_j)(1 + \sum_{i=1}^{3} a_i d_i)$ where $a_i$ represents

excess relative rates per unit of lagged cumulative radon exposure in time windows $d_i$ and $a_j$ are parameters for effects of the covariates $x_j$.

Potential adjustment variables included age, year of follow-up, birth cohort groups (by decade of employment starting in 1890), duration of employment, and time since exposure. Model fit was assessed using Akaike information criterion (AIC). Due to the small number of potential confounders, the final adjustment set was mainly informed by a Directed Acyclical Graph (DAG) with the aim of selecting the most parsimonious model. For most cancer outcomes, a model with log age and birth cohort terms was the best fit; some cancer outcomes with few deaths had improved fit when excluding birth cohort terms or including interaction terms between birth cohort and age.

In sensitivity analyses of the lung cancer models, cumulative WLM was restricted to workers with <250 WLM to evaluate the impact of a small proportion of workers with very high exposure estimates. All statistical analyses were conducted using SAS statistical software (SAS 9.4; SAS Institute Cary, NC) and procedures GENMOD, NLMIXED; PROC NLP was used to obtain profile likelihood confidence intervals (CIs).

### 4.2.4 Results

16,434 male underground uranium miners met cohort inclusion criteria. The workers contributed 231,499 person-years during the 16 years of follow-up. During follow up, 25.6% of workers died. Cause of death was available for 89.6% of deceased workers. Mean duration of employment was 7 years, and mean cumulative radon exposure was 53 WLM. During the follow-up period 1977 – 1992, 1,416 malignant causes of death were identified (Table 3.2.1). This included 705 lung cancer deaths, 102 stomach cancer deaths, and 58 hematopoietic cancer deaths (Table 3.2.2).

Figure 3.2.1 shows rate ratios and 95% CIs for the association between cumulative radon exposure under a five-year lagged exposure assumption and lung cancer mortality using log-linear RR models and linear ERR models. Statistically significant estimates in the exposure category 75 to <100WLM (RR = 1.46 95%CI: 1.04, 2.03) and all exposure categories with WLM greater than 150. The highest relative rate was observed in the 200 to <250 WLM category (RR =1.88 95%CI: 1.23, 2.87). A log-linear relative rate model with continuous exposure was best fit with a quadratic term for WLM (Table 3.2.2, RR at 100WLM = 1.31; 95%CI: 1.17, 1.48). The linear model of ERR is also plotted in Figure 3.2.1. Lung cancer mortality increased with higher cumulative radon exposure (ERR/100WLM = 0.22 95%CI: 0.10, 0.37). Lung cancer results were not sensitive to exposure lag assumptions, such that 2, 5 and 10 year exposure lag assumptions yielded comparable estimates of association. Estimates with five-year lag assumptions were reported in order to be more directly comparable to estimates of association from other uranium miner studies.

Restricting the model to workers with less than 250 cumulative WLM increased the ERR (Table 3.2.3, ERR/100WLM = 0.32; 95%CI: 0.11, 0.53). Windows of exposure, where only exposures within specific time intervals are considered relevant (Checkoway et al., 1990), showed substantial variations in rates across windows, with the highest ERR in the 15 to 30-year window (ERR/100WLM = 0.44; 95%CI: 0.21, 0.67) and the lowest in the 30+ year window (ERR/100WLM = 0.05; 95%CI:-0.11, 0.20).

We examined cancer subtypes other than lung in linear and log-linear models. Linear excess relative rates for other outcomes of interest are shown in Table 4.2.2. Positive but statistically imprecise associations were observed between cumulative radon exposure and extrathoracic airway (ERR/100 WLM = 0.12; 95%CIL -0.25, 0.48), liver (ERR/100 WLM =

0.06; 95%CI: -0.23, 0.35), kidney cancers (ERR/100 WLM = 0.02; 95%CI: -0.39, 0.43), chronic lymphocytic leukemia (CLL) (ERR/100 WLM = 0.24; 95%CI: -0.80, 1.27) and myeloma (ERR/100 WLM = 0.25; 95%CI: -1.51, 2.01). Log-linear rate ratios were similarly positive but statistically imprecise for these subtypes with the exception of myeloma, which showed no association (Table 3.2.2).

Relative rates for subtypes other than lung were assessed by categories of cumulative radon exposure, reported in Appendix Table A.3. Although RRs were very imprecise, there is suggestion of a linear dose response between cumulative radon exposure and CLL (RR 150+ WLM vs <25 WLM = 1.23; 95%CI: 0.20, 7.56). There was also a positive but imprecise association between radon and extrathoracic cancer mortality when comparing the highest and lowest categories of exposure (RR 150+ WLM vs <25 WLM = 1.27; 95%CI 0.60, 2.72)

**4.2.5 Discussion**

This study identified suggestive associations between radon and cancer mortality other than lung, namely extrathoracic cancers and CLL. Extended follow-up of this cohort may provide a more complete assessment of the association between prolonged exposure to low and moderate levels of radon and death these cancer types. This study also provides additional evidence regarding the positive exposure-response relationship between radon and lung cancer mortality. While the association between radon and lung cancer mortality has been observed in several other cohorts of underground uranium miners, estimates vary across studies as cohorts have different levels of radon exposure, rates of exposure, co-exposures, and smoking rates. This study provides lung cancer mortality estimates among a cohort of miners with low radon exposures and relatively few co-pollutants. Lung cancer mortality persisted in this cohort despite having lower average radon exposure than several other uranium miner studies.

Similar to other studies of uranium miner cohorts, a positive exposure–response relationship was observed between cumulative radon exposure and lung cancer mortality. Characteristics of several recently updated cohorts and the BEIR VI report are shown in Table 5.2.1, which illustrates the variation in estimates between cohorts. The BEIR VI analysis of 11 cohorts of underground miners included a total of 60,606 workers and a mean cumulative radon exposure of 164.4 WLM and reported a combined ERR/100WLM of 0.76 (Standard Error = 1.86) (National Research Council, 1999a). The French, German, and Ontario uranium mining cohorts reported analyses updated since the BEIR VI report.(Kreuzer et al., 2010; Navaranjan et al., 2016; E. Rage et al., 2015) An study of 1,785 French uranium miners with a mean 71.3 cumulative WLM radon exposure found an ERR/100WLM of 0.6 (95%CI: 0.1, 1.2) (Laurier et al., 2004). In the study of 58,987 German uranium miners with a mean 5-year lagged exposure of 280 cumulative WLM among the exposed, an ERR/100 WLM of 0.19 (95% CI: 0.17, 0.22) was reported (Kreuzer et al., 2010). Among the Ontario miners, an ERR/ 100WLM of 0.66 (95% CI 0.44 to 0.87) was reported in the cohort of 28,546 workers with a mean 21 cumulative WLM lagged 5 years (Navaranjan et al., 2016). This study, the BEIR VI pooled analysis, and recent studies of the French, German and Ontario cohorts all support a positive association between radon exposure and lung cancer mortality although this study estimated a relatively low ERR/100WLM.

Estimates in this study may be lower than other cohorts because the Příbram cohort follow-up starts long after the start of mining operations, meaning lung cancer deaths prior to the start of follow up are unobserved. On average, the French, German and Ontario cohorts have 3-times longer follow up periods that begin about 20 years prior to this study. In this study the start of follow up was 30 years after the start of mining operations (1977), which has several

implications for the interpretation of results. Workers who were employed at the start of mining operations had higher average radon exposures. Workers in earlier periods had higher exposures prior to the implementation of a strong ventilation system in the 1970s. The older workers who were still alive at the start of follow-up may have been less susceptible to lung cancer or experienced more competing risks due to advanced age, and/or the peak epidemic of lung cancer occurred prior to the start of follow up. Birth cohort and interactions between age and birth cohort were important adjustment variables in linear lung cancer models. This may reflect missed deaths in the early birth cohorts that occurred prior to the start of follow-up. Thus cohort selection criteria and limited duration of follow up may have contributed to lower lung cancer mortality estimates than in other recent studies. Additionally cause of death was missing for 10.4% of deceased workers, which reduces power and may bias results if cause of death is missing not at random.

While overall ERRs were somewhat lower than in other uranium miner studies, estimates were higher when adjusted for time since exposure and when restricted to workers with less than 250 WLM. ERR estimates varied substantially by time since exposure with the highest estimate in the 15-30 year window. Variation in time since exposure has been observed in other uranium mining cohorts, including the West Bohemian Czech cohort, which reported substantial variations in estimates by time since exposure, with a decrease in ERR/WLM with increasing time since exposure (Tomásek and Darby, 1995; Tomasek, 2012). Decreasing estimates as a function of time since exposure has also been reported in the Colorado Plateau uranium miner cohort (Hornung et al., 1995). We observed a higher ERR for lung cancer when we restricted the cohort to miners with lower cumulative exposures, which has also been observed in studies of

sub cohorts of miners who worked in periods of lower exposures (Kreuzer et al., 2015; E Rage et al., 2015).

Cancers other than lung have been investigated in several other uranium mining cohorts, as well as among Příbram miners. Two analyses of cancer incidence among the Příbram miners have been published to date (Kulich et al., 2011; Rericha et al., 2006). One report examined incidence of leukemia, lymphoma, and multiple myeloma in a case-cohort study with a stratified random subcohort of 2,393 workers and 177 incident hematopoietic cancer cases, of which 53 were CLL cases. This study found an elevated rate of leukemia, including CLL. Authors reported a rate ratio (RR) of 1.75 (95% CI: 1.10–2.78) for all leukemia combined and an RR of 1.98 (95% CI: 1.10–3.59) for CLL comparing high radon exposure (110 working level months (WLM)) to low radon exposure (3 WLM). Suggestive associations of radon exposure with myeloid leukemia and Hodgkin lymphoma were also found (Rericha et al., 2006). The present study supports the CLL incidence findings from the incidence study of Příbram miners, although several differences exist. CLL has a high relative survival (National Cancer Institute, 2017); there are 42 fewer CLL fatalities than incident cases. Also, the case-cohort study has more detailed radon exposure estimates and may have bias from exposure misclassification. Extended follow up will be important for understanding radon-CLL associations in this cohort because median age at diagnosis of CLL is 70 years, and average age at end of follow up among Příbram miners is 58.

Extrathoracic cancer is another area of concern since inhalation of radon and its progeny delivers radiation doses to the respiratory tract (ICRP, 1994). Two other uranium miner cohorts have recently studied extrathoracic cancers as a group with conflicting results. A study of extrathoracic cancer among Ontario uranium miners found negative but imprecise associations with both incidence (ERR/100 WLM = −0.29; 95%CI: −0.57, 0.0034) and mortality (ERR/100

WLM = −0.17; 95%CI: −0.64, 0.30) (Navaranjan et al., 2016). Another recent study of extrathoracic cancer mortality among German uranium miners showed a small but imprecise increase (ERR/100 WLM = 0.036; 95%CI: -0.009, 0.080) (Kreuzer et al., 2014). Another case-cohort study of Příbram miners found no association between radon exposure and the incidence of non-lung solid cancers except for malignant melanoma and gallbladder cancer, but examined extrathoracic cancers by individual subtypes (Kulich et al., 2011). The present study also did not identify any statistically significant positive associations with non-lung solid cancers. However, there are several suggestive associations, particularly for the group of extrathoracic cancers. The combined study of extrathoracic cancer incidence in the case cohort study of Příbram miners will be an important direction for future research, as more incident cases and more detailed exposure estimates should improve the precision of estimates.

In this cohort of miners exposed to relatively low radon levels and with less occupational co-pollutants compared other uranium mining cohorts, we see that the associations between radon and lung cancer persist. This study supports other findings that low-level, protracted radon exposure causes lung cancer. We also examined other cancer sites associated with radon inhalation in the epidemiologic and dosimetric literature, and identified extrathoracic cancers and CLL as a possible areas of concern. Extended follow-up of this cohort may improve the precision of these findings, and illustrates the importance of the continuing to monitor both historical and contemporary populations of underground workers.

### 4.2.6 Tables and figures

## Table 4.2.1. Characteristics of the Příbram uranium miner cohort

| Variable | |
|---|---|
| Miners, n | 16,434 |
| Follow-up period | 1977–1992 |
| Person-years | 231,499 |
| **Employment Factors, mean (range)** | |
| Duration of employment, years | 7.0 (1.1–37.9) |
| Year of birth | 1935 (1886–1957) |
| Year of hire | 1963 (1946–1975) |
| Age at hire | 27.8 (18.0–69.7) |
| Age at death | 62 (22–102) |
| **Vital status, n (%)** | |
| Alive | 12,209 (74.3) |
| Deceased | 4212 (25.6) |
| Emigrated | 12 (0.07) |
| Vital Status Unknown | 1 (0.01) |
| Availability of cause of death | 3776 (89.6) |
| Duration of follow-up in years, mean (range) | 14 (0.1-16) |
| **Radon** | |
| Cumulative radon in WLM, mean (range) | 53.2 (1.2–1121.9) |
| < 10 WLM radon exposure, n (%) | 4883 (30) |
| < 50 WLM, n (%) | 11678 (71) |
| <100 WLM, n (%) | 13502 (82) |

**Table 4.2.2: Excess relative risk and relative hazards of cancer types by cumulative working level month radon exposure among Příbram uranium miners^**

| Cancer Site (ICD-9) | Number of Deaths | Crude Death Rate per 1000 person years | Linear ERR (95%CI) per 100 WLM* | Log-linear Rate Ratio at 100 WLM (95%CI) |
|---|---|---|---|---|
| Extrathoracic airway (140-148, 160, 161) | 59 | 0.25 | 0.12 (-0.25 , 0.48) | 1.10 (0.87 , 1.39) |
| Stomach (151) | 102 | 0.44 | 0.00 (-0.21 , 0.20) | 1.00 (0.82 , 1.21) |
| Liver (155) | 48 | 0.21 | 0.06 (-0.23 , 0.35) | 1.08 (0.85 , 1.37) |
| Lung (162)± | 705 | 3.02 | 0.22 (0.10 , 0.37) | 1.31± (1.17 , 1.48) |
| Kidney (189) | 41 | 0.18 | 0.01 (-0.39 , 0.41) | 1.01 (0.74 , 1.37) |
| Non-Hodgkin lymphoma (200, 202) | 17 | 0.07 | -0.09 (-0.84 , 0.67) | 0.99 (0.57 , 1.72) |
| Hodgkin lymphoma (201) | 8 | 0.03 | -0.09 (-4.12 , 3.95) | 0.52 (0.12 , 2.21) |
| Myeloma (203)¨ | 8 | 0.03 | 0.25 (-1.51 , 2.01) | 0.98 (0.52 , 1.86) |
| CLL (204.1) | 11 | 0.05 | 0.24 (-0.80 , 1.27) | 1.15 (0.72 , 1.82) |
| Myeloid leukemia (205.0, 205.1)¨ | 12 | 0.05 | -0.09 (-0.76 , 0.58) | 0.75 (0.33 , 1.67) |
| All Hematopoietic (200 - 208) | 58 | 0.25 | -0.09 (-0.36 , 0.18) | 0.91 (0.67 , 1.23) |

*5-year exposure lag assumption= Lung, kidney, extrathoracic airway, stomach, liver, all hematopoietic, myeloma, and CLL. 2-year exposure lag assumption = NHL, HL, Myeloid leukemia.

^Adjusted for age and birth cohort, ¨Adjusted for age , ±Adjusted for age, birth cohort, and age-birth cohort interaction.
±Log-linear rate ratio model includes quadratic term for WLM

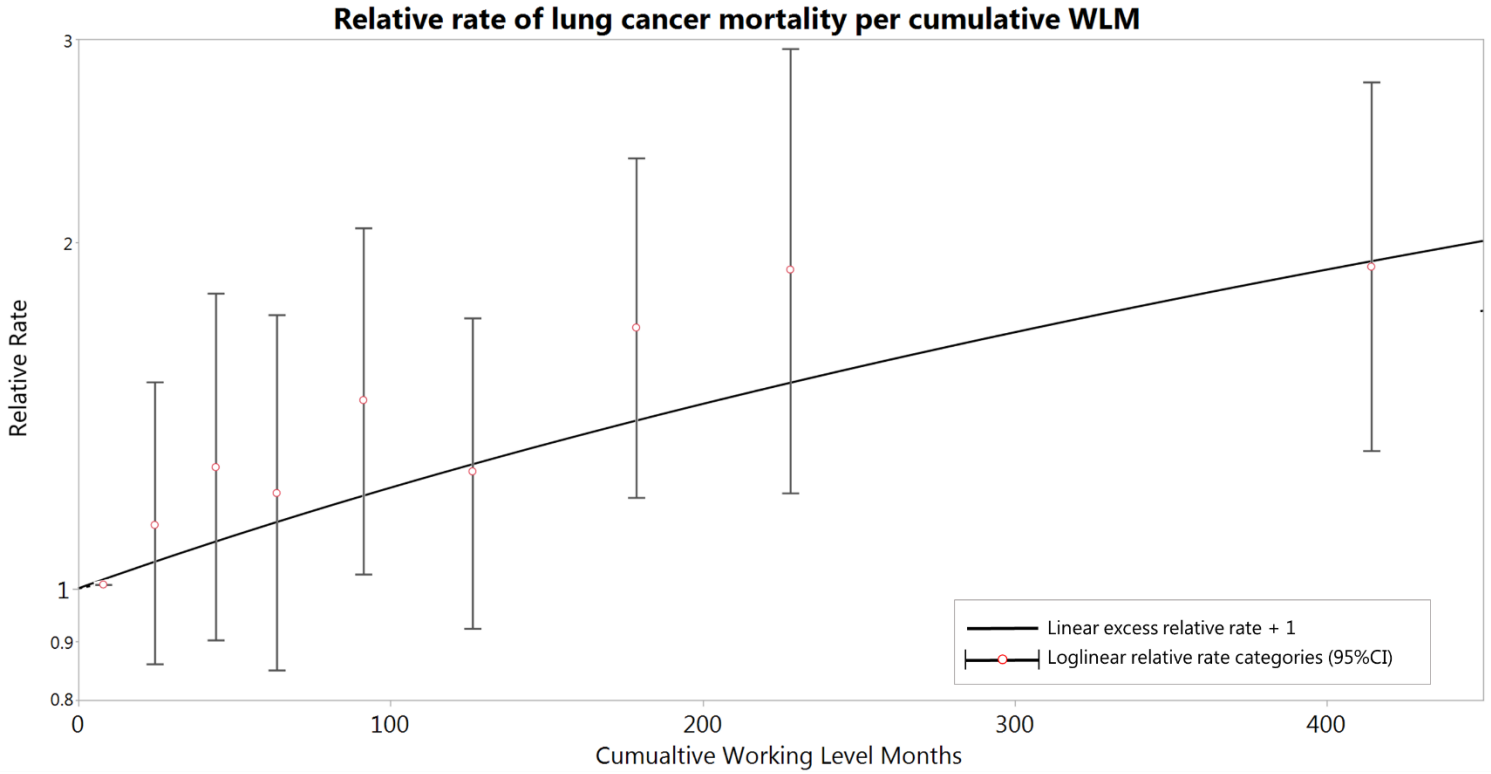
**Table 4.2.3: Lung cancer mortality by cumulative working level month (WLM) radon exposure by windows of time since exposure and by exposure less than 250 WLM, among male Příbram uranium miners 1977-1992**

| Cumulative Radon Exposure (WLM) | | Excess Relative Rate/100WLM (95% CI) | | |
|---|---|---|---|---|
| Windows of exposure^ | 5-15 yrs: | 0.21 | (-0.96 , | 1.37) |
| | 15-30 yrs: | 0.44 | (0.21 , | 0.67) |
| | 30+ yrs: | 0.05 | (-0.11 , | 0.20) |
| Restricted to < 250 WLM* | | 0.32 | (0.11 , | 0.53) |

^Adjusted for age and birth cohort

*Cumulative working level months under a five-year lag assumption

**Figure 4.2.1 Relative rate of lung cancer mortality per cumulative WLM lagged 10 years among male underground uranium miners in the Příbram region of the Czech Republic, 1977-1992**



## 4.3 Lung and extrathoracic cancer incidence among underground uranium miners exposed to radon progeny in the Příbram region of the Czech Republic: a case-cohort study (AIM 3)

### 4.3.1 Overview

Background: Uranium miners are occupationally exposed to radon and its progeny. It has been established that radon is carcinogenic, but more studies are needed to understand radon exposure-response relationships for lung and extrathoracic cancers at low and moderate levels, differences between cancer incidence and mortality, and the modifying effect of smoking.

Methods: We conducted a case-cohort study with 16,434 underground uranium miners with cancer incidence follow-up between 1977 and 1996 in the Příbram region of the Czech Republic. Associations between radon exposure and lung cancer as well as extrathoracic cancer were estimated with log-linear rate and linear excess relative rate models. We also examined smoking, birth cohorts, exposure rate, and time since exposure.

Results: Compared to those with cumulative radon exposure <3 WLM, the relative rate of extrathoracic cancer was elevated among those with cumulative radon exposure 3 to <5 WLM and 5 to <10 WLM (RR = 3.85; 95%CI: 1.58, 9.39 and RR = 2.42; 95%CI: 1.19, 4.93, respectively), but not at higher levels. The estimated linear excess relative rate of extrathoracic cancer per 100 WLM was positive but imprecise (ERR/100 WLM= 0.07; 95%CI: -0.17, 0.72). Relative rates of lung cancer by categories of WLM compared to the reference category of <10 WLM were elevated among smokers. The estimated linear excess relative rate of lung cancer per 100 WLM was modified by smoking status. The estimated ERR/100 WLM among non-smokers was 0.12 (95%CI: -0.09, 0.33) and among smokers 1.34 (95%CI: 0.88, 1.80). Also, ERRs among smokers decreased with later windows of exposure and decreased at higher radon exposure rates.

Conclusions: This study is consistent with prior studies of uranium miners, which reported positive associations between radon and lung cancer. We found that the joint effects of radon and smoking were multiplicative or super-multiplicative. Furthermore, this study suggests an association between radon exposure and extrathoracic cancer.

### 4.3.2 Background

Inhalation of radon and its decay products (henceforth referred to as radon) are the leading cause of occupational lung cancer. Globally, inhalation exposure to radon is the second leading cause of lung cancer deaths after smoking.[11] Uranium miners are occupationally exposed to radon and several cohort studies of underground uranium miners have provided strong evidence of the exposure-response relationship between radon and lung cancer mortality.[4,8,26,33,73] While it is established that radon is carcinogenic[1], more studies are needed to understand exposure-response relationships that reflect modern occupational and environmental radon exposures, the differences between cancer incidence and mortality, the effect of smoking, and associations with cancers other than lung, particularly extrathoracic cancers.

Several studies of underground miners have demonstrated strong exposure–response relationships with cumulative radon exposure and lung cancer mortality [8,15,23,29,33,61,74], but more information is needed about lung cancer incidence. Incidence estimates are less frequently studied but are preferable because they increase statistical precision, are less subject to outcome misclassification. Additionally, the modifying effect of smoking has been characterized among several studies[11,17,36] but more information is needed to understand the modifying effect of smoking at low exposure levels. Modification by smoking has been studied in several populations of uranium miners, namely in analyses from the Committee on Health Risks of Exposure to Radon (BEIR VI) report, a pooled case control study of three European uranium

mining studies, and the Colorado Plateau cohort. All concluded that there is sub-multiplicative interaction between radon and smoking.[11,17,36] However, the mean estimated cumulative radon exposures in these studies were much higher than levels experienced in modern occupational settings. More research is needed to understand the effect of smoking at low cumulative radon exposures and at low exposure rates (<4 WLM per year).

It is unclear if radon exposure causes cancers of the extrathoracic respiratory system (the upper airway, including the tongue, mouth, pharynx, nasal cavity, and larynx). Dosimetric models indicate that α-radiation doses to the extrathoracic airway occur upon inhalation.[41] Although the magnitude of these dose estimates are smaller than lung dose estimates, they may still be substantial. Extrathoracic cancer subtypes were historically examined as separate groups, which led to very small numbers of deaths among subgroups, but two recent studies of uranium miners examined rates of extrathoracic cancer as a group based on the International Commission on Radiological Protection (ICRP) models for energy deposition following radon inhalation.[8,39] One study reported a positive imprecise association between radon and extrathoracic cancer mortality while the other found a negative imprecise association with both incidence and mortality.[8,39] Smoking is an important risk factor for extrathoracic cancer and was not accounted for in either of these prior studies examining radon-extrathoracic cancer associations.[8,39]

In order to investigate associations between radon exposure and lung and extrathoracic cancer incidence in an occupational cohort with individual information on smoking status, we analyzed a case-cohort study of uranium miners in the Czech Republic. In 1996, the National Institute of Environmental Health Sciences (NIEHS), in collaboration with the Health Institute of the Uranium Industry (HIUI) of the Czech Republic, created a study of underground uranium miners in the Příbram region of the Czech Republic to better understand the health effects caused

by radon exposure.[24,25,43] This is a large cohort with 20 years of follow-up with exposures comparable to modern occupational exposures with exposures comparable to modern occupational exposures. The study contains both mortality and incidence data, as well as smoking estimates within the case-cohort study.

The main objective of this study were to estimate the exposure-response relationships between radon exposure and lung incidence, as well as extrathoracic cancer incidence, within a case-cohort of underground uranium miners in the Příbram region of the Czech Republic. We also examined exposure rates, windows of exposure, and the effects of cigarette smoking.

### 4.3.3 Methods

**Study population.** Between World War II and the Cold War, extensive uranium mining activities occurred in the Příbram region of the Czech Republic.[43] The Příbram mines are 60 kilometers southwest of Prague, in Central Bohemian region which is historically known for lead, silver and zinc mining. Příbram mine operations occurred between 1946 and 1991, during which over 46,000 workers were employed. By the 1960s, over 70% of Czechoslovakian uranium production took place in Příbram.[43] Czechoslovakia was the third largest supplier of uranium to the Soviet Union during this time, with a cumulative production through 1990 of 98,500 metric tons.[5]

The Příbram Uranium Industry (UI) kept a card register for each employee that contained a personal identification number and occupational history. The card register was computerized and a cohort study was developed from these records. The cohort included male workers who were listed in the employment registry between January 1, 1949 and December 31, 1975, worked underground for at least 1 year, and were alive and living in the former Czechoslovakia on

January 1, 1977. 16,434 workers satisfied cohort selection criteria and were followed for cancer incidence and mortality outcomes from 1977 through 1996.[24,25]

**Case-cohort study.** In the late 1990's a case-cohort study was developed with the goal to investigate radon-cancer associations using more precise radon exposure estimates than those in the full cohort, and to collect additional data on smoking and co-pollutants. A sub-cohort of 1,826 workers was selected by stratified random sampling based on the age of cases at start of follow-up (1977) in 5-year intervals.

**Exposure estimates.** Cumulative exposure to radon progeny in Working Level Months (WLM) was first estimated for each worker in the full cohort. WLMs were estimated based on the duration of underground mining in a calendar year and annual radon concentration estimates, derived from industry records. Duration of underground mining was based on start and end of employment and annual radon exposure concentration estimates were based on measurements from area monitors.

Subcohort members and non-subcohort cases were assigned more precise WLM estimates than the full cohort by combining the radon exposure measurements recorded in the original hygiene records with a detailed archive of employee work histories that contained locations of work within mines and entry and exit times for these locations. Estimates were assigned differently across two time periods. In the period prior to 1968, detailed employment records were abstracted by investigators to estimate the time spent underground per month. In 1968, with the introduction of individual dosimetric cards, exposures were estimated by number of shifts. Area radon measurements were taken in each specific workplace during each shift and recorded on dosimetric cards.

Smoking information was derived mainly from job-entry medical records and annual check-ups conducted by the UI. Cigarette smoking status was categorized as a fixed variable as ever smoker and never smoker.

Diesel exhaust exposure is a potential confounder of concern in some studies of underground miners. However, in Příbram, diesel was never used in mining operations because all vehicles were electric.

**Outcome assessment.** Incident cancer cases were identified among the miners between 1977 and 1996 by matching individual government identification numbers, names, and date of birth with the Czech and Slovak national cancer registries. Reporting to the cancer registry was mandatory. All cancers were coded according to the International Classification of Diseases, Ninth Revision.[24] Workers diagnosed with cancer were not allowed to work underground. Therefore, all workers alive in 1977 and still working underground were assumed to be cancer free at the start of follow-up.[24,25] Cancer subtypes of interest include lung and extrathoracic cancers. Extrathoracic cancers are reported as a group based on the International Commission on Radiological Protection (ICRP) models for energy deposition following radon inhalation.[41] The extrathoracic group includes the nasal passages (ICD-9 160), larynx (ICD-9 161), pharynx (ICD-9 147-148), oropharynx (ICD-9 146), mouth (ICD-9 141-145).

**Statistical analyses.** To estimate the association between cumulative WLMs of radon exposure and cancer incidence, linear and log-linear models with age at the start of follow up as the underlying time scale were fit to the case-cohort data. In addition to cumulative working level months, windows of exposure (5-15, 15-25, and 25+ years) and exposure-rate windows (<5 and ≥5 WL) were modeled to investigate timing and rate of radon exposure.[75] Birth cohort, duration of employment, and active *vs.* inactive employment were investigated for potential

confounding. Smoking was investigated both as a potential confounder and effect measure modifier. Due to a small set of measured covariates, the final adjustment set was mainly informed by a Directed Acyclical Graph (DAG) with the aim of selecting the most parsimonious model. Potential confounders were also systematically evaluated for changes in the WLM parameter estimate compared to a model with all covariates, and assessed for change in model fit based on Akaike's information criterion. The interaction terms for smoking were tested with LRT tests (*a priori* $\chi^2 < 0.1$).

**Linear relative rates.** Linear excess relative rates per 100 WLM were estimated using the general model form $rate = \exp(a_0 + \sum_{j=2}^{p} a_j x_j)(1 + a_1 d)$ where $a_1$ is the excess relative rate per unit of lagged cumulative radon exposure, d and $a_j$ are parameters for effects of covariates $x_j$. To examine time since exposure and exposure rate, windows of exposure and exposure-rate windows were fit, respectively, using the general model form $rate = \exp(a_0 + \sum_{i=1}^{k-1} a_j x_j)(1 + \sum_{j=k}^{p-1} a_i d_i)$ where $a_i$ represents excess relative rates per unit of lagged cumulative radon exposure in time windows or rate windows, and $d_i$ and $a_j$ are parameters for effects of covariates $x_j$.

To model relative rates with a linear exposure in the random stratified case-cohort design, we used the approach described by Richardson et al, where a risk-set data structure is generated and relative rate models are fit in SAS PROC NLMIXED.[76] A weighted bootstrapping method also described by Richardson et al., is used to calculate confidence intervals of ERRs.[76] In this method, a random weight from an exponential distribution is assigned to each person for each weighted regression model. The weighted bootstrap approach accommodates the random stratified case-cohort design well because risk sets only need to be enumerated once, which retains the case failures from the full cohort and the observed failure times.

**Log-linear models.** Proportional hazards regression models were used to estimate the log relative rate (RR) per 100 WLM using SAS PROC PHREG with a robust variance estimator (covsandwich option). For comparison to hazard ratio estimates, log-linear RRs per 100 WLMs were also estimated using SAS PROC NLMIXED using the approach outlined by Richardson et al., described above.[76] Rate ratios were estimated using the general model form $rate = \exp(\beta_0 + \sum_{i=1}^{k-1} \beta_i d_i + \sum_{j=k}^{p-1} \beta_j x_j)$ where $\beta_1 - \beta_{k-1}$ represents the log relative rate of cancer incidence per category of lagged cumulative radon exposure, $\beta_0$ is the log rate of cancer among workers with the referent cumulative WLM, and $\beta_j$ are parameters for effects of covariates $x_j$. A model with a quadratic term for radon exposure was also examined and assessed for model fit using AIC and LRT tests.

The joint effects of radon exposure and smoking were evaluated formally in a mixture model that allows for model forms intermediate between the linear excess relative rate model and the log-linear (i.e., exponential rate) model. A mixture model if the form $rate = \exp(\beta_i d + \beta_j s)^{\alpha}(1 + \beta_i d + \beta_j s)^{1-\alpha}$ was fitted, where $\beta_j$ and $\beta_i$ are parameters for the effects of smoking and radon exposure, respectively, and $\alpha = 1$ indicates a strictly multiplicative model and $\alpha = 0$ indicates a strictly additive model.

### 4.3.4 Results

During follow up, 890 lung cancer cases (190 subcohort cases and 700 non-subcohort cases), and 127 extrathoracic cancer cases (13 subcohort cases and 114 non-subcohort cases) were identified, as well as 1621 non-case subcohort members (Table 3.3.1). Among extrathoracic cancers, the most common subtype was cancer of the larynx (ICD = 161, 63 cases). The mean duration of follow up was 13.6 years. The mean and standard deviations of age at start of follow up was 50.7 ± 10 years. The members of the case-cohort study were on average older than in the

full cohort due to the age-stratified subcohort sampling based on the age distribution of cases.[24] Mean cumulative exposures to radon among the lung cancer cases was higher than in the subcohort or among the extrathoracic cancer cases. For all models, 5-year and 10-year lagged exposures were compared for changes in effect estimates and statistical precision of estimates. Estimates with 10-year lags were marginally higher than estimates with 5-year lags, but for comparability with other studies of radon among uranium miners, a 5-year lag was chosen.

Tables 3.3.2 and 3.3.3 present relative rates of lung and extrathoracic cancer incidence among smokers and non-smokers by category of cumulative radon exposure. Among categories of exposure, adjusting for smoking improved model fit but was a statistically insignificant effect measure modifier for both outcomes of interest, so smoking was included in the models as a main effect but without a product term between smoking status and cumulative radon exposure. Birth cohort is an important covariate identified in DAG analyses and substantially improved model fit; it was adjusted for in all models. Because smoking was missing for 40 lung cancer cases and 8 extrathoracic cases, 850 lung cancer cases and 119 extrathoracic cases were included in the analyses.

For lung cancer, modification by smoking was observed on both the linear and log-linear scales. In log-linear models, statistically significant RRs above the null were observed in each exposure category only among smokers. Although there was not a strictly monotonic increase across categories, rates of lung cancer generally increased with higher radon exposures among smokers. Compared to the reference category (<10WLM), the relative rate at cumulative exposures 10-<50 WLM was 1.67 (95%CI: 1.24, 2.26) among smokers. Among non-smokers, the relative rate at cumulative exposures 10-<50 WLM was 1.27 (95%CI: 0.71, 2.27). On the log-linear scale with continuous WLM, smoking was observed to be a modifier and RRs are

reported separately among smokers (RR/100 WLM= 2.88; 95%CI: 1.93, 4.30) and non-smokers (RR/100 WLM = 1.11; 95%CI: 0.94, 1.31)).

Estimates of the exposure-response association between radon exposure and extrathoracic cancer did not increase monotonically. When analyzed by categories, the highest and most precise relative rates appear in the 3 to <5 and the 5 to <10 WLM categories (RR = 3.85; 95%CI: 1.58, 9.39 and RR = 2.42; 95%CI: 1.19, 4.93, respectively). Exposure categories above 10 WLM have lower and statistically imprecise estimates. We estimated the relative rate of extrathoracic cancer with a quadratic term for radon exposure. The addition of the quadratic term improved model fit, and the observed positive associations at low WLMs decreased (RR at 100 WLM = 0.73 (95%CI: 0.50 - 1.07). Smoking was not a modifier of the radon-extrathoracic cancer association.

Excess relative rates of lung cancer by continuous WLM, windows of exposure, and exposure rate windows, adjusted for age, birth cohort, and smoking are shown in Table 4.3.4. Smoking was a modifier of the radon-lung cancer association in linear excess relative rate models, and estimates are reported separately among smokers and non-smokers. The ERR per 100 WLM among non-smokers was 0.12 (95%CI: -0.09, 0.33) and among smokers 1.34 (95%CI: 0.88, 1.80). The estimate from our mixture model approached 1, which indicates that the interaction is multiplicative.

Among smokers, we observed variations between exposure time windows, where ERRs/100 WLM were lower in windows of exposure that occurred further in the past. Among non-smokers, ERRs/100 WLM for all exposure time windows were highly imprecise. We also fitted a model that partitioned cumulative radon exposure by two categories of radon exposure rate, and lower exposure rates were associated with higher ERR/100 WLM among both smokers

and non-smokers, although estimated associations were imprecise. Adjustment for active employment and duration of employment did not change model estimates or improve model fit.

An elevated but imprecise estimate of the association between cumulative radon exposure (5 year lag) and extrathoracic cancers was observed [ERR/100 WLM = 0.07 (95%CI: -0.17, 0.31)] in a model of continuous exposure adjusted for age, birth cohort, and smoking. Models adjusting for smoking interaction, windows of exposure, exposure rate, active employment, and duration of employment did not improve model fit.

**4.3.5 Discussion**

This is the first study conducted on lung cancer incidence among the Příbram uranium miners. The positive exposure-response relationship between cumulative radon exposure and lung cancer incidence is consistent with conclusions published from prior mortality studies.[4,8,26,33,73] This study also provides evidence of radon-lung cancer associations at levels reflective of modern occupational exposures. A positive ERR was observed at exposure rate levels less than 5 WL, and modification by smoking was also observed at this level. This study provides additional evidence of the radon-lung cancer association based upon incidence rather than mortality. To our knowledge, only one other uranium miner cohort study conducted in Ontario, Canada has described lung cancer incidence.[8] Among the Ontario uranium mining cohort, the ERR/100 WLM for lung cancer incidence was 0.64 (95%CI: 0.43, 0.85).[8] Although smoking was an important modifier in our study, the overall ERR/100 WLM estimate without a smoking interaction was 0.53 (95%CI: 0.35, 0.71), which is similar to the Ontario estimate and estimates from the analysis of lung cancer mortality among the full cohort of Příbram miners.

Two other studies of uranium miners have examined associations between radon exposure and extrathoracic cancer as a group, a category of interest given ICRP models for

energy deposition following radon inhalation. A positive but imprecise association between radon and extrathoracic cancer mortality (ERR/100 WLM= 0.036 95%CI: -0.009, 0.080) was observed in the German miner study.[40] In this study, long-lived radionuclides, external gamma radiation and silica dust, were examined but none were associated with increased extrathoracic mortality. A negative but imprecise association with extrathoracic cancer incidence (ERR/100 WLM = −0.29; 95%CI: −0.57, 0.0034) and mortality (ERR/100 WLM = −0.17; 95%CI: −0.64, 0.30) was observed in the study of Ontario miners.[8] Neither the German nor the Canadian study included smoking information. In several other miner studies individual subtypes of extrathoracic cancer were investigated, but in all of them statistically imprecise results were obtained.[25,30,3,38,39,59]

We report here a modification of the radon-lung cancer association by smoking when both linear and log-linear rate models were fitted. Presence of modification on both the linear and log-linear scales, and results from the mixture model suggest that the joint effects of radon exposure and smoking is greater than additive. In several other uranium miner studies interaction between radon and smoking was observed to be less than multiplicative.[11,17,36] The BEIR VI report concluded that there is a sub-multiplicative interaction between radon exposure and smoking.[11] Also, a combined analysis of three case- control studies from three European uranium mining cohorts suggests a sub-multiplicative interaction between radon and smoking.[36] The Colorado Plateau cohort of uranium miner study included time-varying smoking information and an interaction intermediate between additive and multiplicative was observed.[77] While the presence of modification is consistent with other studies, our results are more consistent with a multiplicative or super-multiplicative interaction. This may be due to differences in quality of information on smoking status. In the European pooled case-cohort and the Colorado Plateau

studies, smoking information was more detailed and included information on duration of smoking whereas our study only included information on smoking status (typically recorded at the start of employment). Another reason for difference in modification scale may be because our study population experienced lower average exposures to radon than the BEIR VI, European and Colorado studies.

In this current study, adjustment for birth cohort improved both lung and extrathoracic model fit substantially. This was observed in the mortality analyses for this cohort as well, and may be related to a cohort selection criterion that workers be alive at the start of follow-up in 1977. This is unlike most other uranium mining cohorts, where follow-up usually begins at the start of mining operations. Workers who were employed at the start of mining operations had higher average radon exposures until a strong ventilation system was installed in the 1970s. Many of the earlier workers may have died of lung cancer prior to the start of follow up. Additionally, the older workers who were still alive at the start of follow-up had higher exposures but may have had less lung cancer than other birth cohorts due to competing risks associated with advanced age.

A strength of this study is the availability of cancer incidence data. Incidence data is less prone to outcome misclassification and has higher sensitivity than mortality estimates because cases are ascertained through national cancer registries while mortality data is abstracted from cause of death listed on death certificates. Extrathoracic cancers are rare, and incidence follow-up allows for the analysis of several additional cancers. But, even with incidence information, there were relatively few extrathoracic cancers in this cohort and the statistical power to estimate associations between radon exposure and extrathoracic cancers, even as a group, was low.

Another strength of this study is the validation of radon exposure estimates and availability of smoking information. In this study, smoking was an important effect measure modifier which is consistent with lung cancer mortality studies, although the interaction scales differ. It should be noted that smoking data are crude, incomplete, and time invariant. There may also be additional unmeasured confounding. For instance, alcohol consumption is a major risk factor for extrathoracic airway cancer and was not measured in this study. The German extrathoracic study looked at alcohol abuse on death records and saw a slight bias towards the null [39].

Linear excess relative rates were estimated using the approach outlined by Richardson et al., where case-cohort data was restructured into risk-set data and weighted bootstraps were used to calculate confidence intervals.[76] Richardson et al. demonstrated this method using a case-cohort sample drawn from the cohort of Colorado Plateau uranium miners. The application of this method was particularly advantageous in the present study because it allowed for the estimation of linear relative rate models from the case-cohort data derived from a stratified random sample.[76] Other approaches are constrained to either log-linear model forms or data derived from a simple random samples. The method developed by Richardson et al. leads to a more flexible modeling approach and better specified models, thus, more accurately representing the exposure-response association between radon exposure and lung or extrathoracic cancer.

The results obtained from this study are consistent with results of prior studies indicating that uranium miners exposed to radon experience an increased rate of lung cancer, and there is a positive exposure-response relationship between cumulative WLM of radon and lung cancer.[4,8,26,33,73] The results are also consistent with prior findings that smoking modifies the association between radon exposure and development of lung cancer.[11,17,36] Extrathoracic cancer

analyses were less precise and more variable depending on the model scale and model selection. However, the results suggests that miners may experience an elevated rate of extrathoracic cancers even at low levels of cumulative radon exposure (<5WLM). In order to obtain more precise estimates of extrathoracic cancer rates and determine exposure-response relationships, more studies are of radon-extrathoracic cancer are needed. Specifically, studies with individual dosimetric estimates of radon to the extrathoracic tissues, and larger studies with more cases and extended follow up would improve understanding of radon-extrathoracic cancer associations.

### 4.3.6 Tables and figures

**Table 4.3.1: Characteristics of a case-cohort study of male underground uranium miners in the Příbram region of the Czech Republic 1977-1996**

| | Subcohort non-cases | Lung cancer cases | Extrathoracic cancer cases |
|---|---|---|---|
| Total cases, n | 1621 | 890 | 127 |
| Year of birth, n (%) | | | |
| < 1910 | 87 (5) | 30 (3) | 4 (3) |
| 1910 - 1919 | 342 (21) | 185 (21) | 17 (13) |
| 1920 - 1929 | 677 (42) | 403 (45) | 39 (31) |
| 1930 - 1939 | 367 (23) | 212 (24) | 33 (26) |
| ≥1940 | 148 (9) | 60 (7) | 34 (27) |
| Age at start of employment (years), n(%) | | | |
| <20 | 99 (6) | 59 (7) | 12 (9) |
| 20-<30 | 677 (42) | 379 (43) | 63 (50) |
| 30-<40 | 528 (33) | 313 (35) | 36 (28) |
| ≥40 | 317 (20) | 139 (16) | 16 (13) |
| Duration of employment (years) | | | |
| 1-<3 | 632 (39) | 250 (28) | 61 (48) |
| 3-<10 | 351 (22) | 190 (21) | 24 (19) |
| ≥10 | 638 (39) | 450 (51) | 42 (33) |
| Cumulative exposure, mean (range) | | | |
| Radon (WLM) | 78 (0- 959) | 115 (0- 1022) | 69 (0- 866) |
| Gamma irradiation (mGy) | 13 (0- 227) | 48 (0- 208) | 16 (0- 134) |
| Dust (mg/m$^3$) | 41 (0- 155) | 49 (0- 179) | 32 (0- 120) |
| Smoking Status | | | |
| Smoker | 1027 (63) | 729 (82) | 95 (75) |
| Non-Smoker | 506 (31) | 121 (14) | 24 (19) |
| Missing | 88 (5) | 40 (4) | 8 (6) |

**Table 4.3.2: Relative rates (RR) of lung cancer incidence among smokers and non-smokers by categories of cumulative radon exposure (5 year lag) among male uranium miners in the Příbram region of the Czech Republic, 1977-1996**

| | | Smokers | | | Non-smokers | | |
|---|---|---|---|---|---|---|---|
| WLM Categories | Total lung cancer cases (n) | Smoking cases (n) | Log-linear Relative Rate (RR) | 95%CI | Non- Smoking cases(n) | Log-linear Relative Rate (RR) | 95%CI |
| 0 - <10 | 112 | 92 | 1 (ref) | | 20 | 1 (ref) | |
| 10 - <50 | 227 | 186 | 1.67 | 1.24, 2.26 | 41 | 1.27 | 0.71, 2.27 |
| 50 - <100 | 139 | 121 | 1.60 | 1.15, 2.23 | 18 | 0.93 | 0.47, 1.85 |
| 100 - <150 | 117 | 104 | 1.86 | 1.30, 2.66 | 13 | 0.88 | 0.42, 1.86 |
| 150 - <200 | 93 | 85 | 3.41 | 2.28, 5.09 | 8 | 1.55 | 0.61, 3.92 |
| 200+ | 164 | 143 | 3.56 | 2.50, 5.09 | 21 | 1.79 | 0.90, 3.57 |

*All models are adjusted for age, birth cohort, and smoking interaction. WLM = Working Level Months



**Table 4.3.3: Relative rates (RR) of extrathoracic cancer incidence by categories of cumulative radon exposure (5 year lag) among male uranium miners in the Příbram region of the Czech Republic, 1977-1996**

| WLM Categories | | RR | 95%CI |
|---|---|---|---|
| 0 - <3 | 15 | 1 (ref) | |
| 3 - <5 | 10 | 3.85 | 1.58 , 9.39 |
| 5 - <10 | 21 | 2.42 | 1.19 , 4.93 |
| 10 - <50 | 32 | 1.26 | 0.66 , 2.41 |
| 50 - <100 | 15 | 1.05 | 0.50 , 2.24 |
| 100+ | 26 | 1.30 | 0.64 , 2.65 |

*All models are adjusted for age, birth cohort, and smoking. WLM = Working Level Months

**Table 4.3.4: Excess relative rates of lung cancer incidence per 100 working level months (ERR/100 WLM)^ among male uranium miners in the Příbram region of the Czech Republic, 1977-1996**

| | Non Smokers | | Smokers | | Overall | |
|---|---|---|---|---|---|---|
| | ERR/100 WLM | 95%CI | ERR/100 WLM | 95%CI | ERR/100 WLM | 95%CI |
| Continuous WLM | 0.12 | -0.09 , 0.33 | 1.34 | 0.88 , 1.80 | 0.53 | 0.35 , 0.71 |
| Windows of exposure | | | | | | |
| 5-15 | -1.39 | -4.00 , 1.21 | 4.78 | 0.18 , 9.37 | 1.76 | -0.20 , 3.71 |
| 15-25 | 0.26 | -0.37 , 0.90 | 2.18 | 1.02 , 3.34 | 0.91 | 0.42 , 1.40 |
| 25+ | 0.11 | -0.14 , 0.36 | 1.04 | 0.59 , 1.50 | 0.42 | 0.23 , 0.62 |
| Exposure rate | | | | | | |
| <5 WL | 0.31 | -0.07 , 0.69 | 1.70 | 1.06 , 2.34 | 0.87 | 0.57 , 1.17 |
| ≥ 5 WL | -0.13 | -0.44 , 0.18 | 0.73 | ### , 1.56 | 0.08 | -0.17 , 0.33 |

^All models adjusted for age and birth cohort. Nonsmoker and smoker estimates are adjusted for smoking product terms. Radon exposure is lagged 5 years

## 4.4 Additional results: risk set regression calibration, exploration of gamma and dust exposure models (AIM 2A and 3A)

This section presents additional analyses that were not included in the main three results sections. Results from the risk set regression calibration corrections and adjustment for gamma and dust exposure in the case-cohort study and reported in the following sections.

### 4.4.1 Risk set regression calibration

We used a risk set regression calibration approach to account for measurement error in annual estimates of radon exposure in the cohort analysis, leveraging more precise estimates by treating radon estimates from the case-cohort study as an internal validation study of a subset of workers. When radon estimates were calibrated to the radon estimates available for the internal validation subset, the adjusted hazard ratio was higher (HR/100WLM = 1.20 95%CI: 1.11, 1.30) than the standard hazard ratio (HR/100WLM =1.14 95%CI: 1.08, 1.20). Precision of the RRC estimate is slightly lower than the un-calibrated estimates.

**Table 4.4.1: Lung cancer mortality uncorrected and corrected estimated hazard ratios (per 100 working level months), 10-yr lagged radon exposures**

| Model Description | Estimate | Standard Error | Hazard Ratio | (95% CI) |
|---|---|---|---|---|
| Uncorrected | 0.13 | 0.03 | 1.14 | (1.08, 1.21) |
| Corrected for measurement error | 0.18 | 0.04 | 1.20 | (1.11, 1.30) |

We used RRC as an approach to evaluate bias arising from exposure misclassification; results of our sensitivity analysis suggest that with improvements in the quality of radon estimates a larger magnitude exposure-response coefficient is obtained, suggesting that exposure measurement errors are a cause of slight bias towards the null.

### 4.4.2 Gamma radiation and dust exposure models

**Background.** Uranium miners are also occupationally exposed to other potential carcinogens including dust, diesel exhaust, long-lived radionuclides from uranium ore dust, and external gamma radiation.[9] Exposures to these pollutants are often unaccounted, but have been analyzed in some studies of underground uranium miners. Generally, the measurements of these co-pollutants are poorly characterized and subject to exposure misclassification, especially during early periods of mining operations. Their impact on the association between radon and cancer is not well understood.

**Exposure estimates.** The case-cohort study included covariate information on gamma and dust; occupational exposure to diesel exhaust was believed to be absent for all miners because diesel engines were not used at these mines. Annual dust exposures were assigned to each worker based on dust monitoring data starting in 1966, and locations of work and entry and exit times from employment records. Concentrations of silica and heavy metals within dust were sometimes measured but not assigned to individual workers Annual estimates of gamma radiation (in millisievert, mSv) were assigned to each worker based on monitoring data starting in 1966. At this time most underground workers were given film badges to measure gamma exposure. A model estimating gamma and dust exposures prior to 1966 was developed to estimate pre 1966 measures using information on annual ore productivity, calendar period, shifts worked, and job title.[24]

**Statistical analysis.** In addition to the models reported in Aim 3, we also modeled radon-lung cancer associations with adjustments for gamma and dust as potential confounders. Models were develop and final models were selected using the same approach described in the methods of section 3.3.

**Results.** Mean cumulative exposures to gamma radiation among the lung cancer cases was higher than in the subcohort or among the extrathoracic cancer cases. Adjusting for gamma and dust exposures increases the estimated association between radon and lung cancer as well as the association between radon and extrathoracic cancers, though estimates are less precise.

**Table 4.4.2: Excess relative rates of lung and extrathoracic cancer incidence per 100 working level months (ERR/100WLM)^ among male uranium miners in the Příbram region of the Czech Republic, 1977-1996, additional adjustment for gamma and dust**

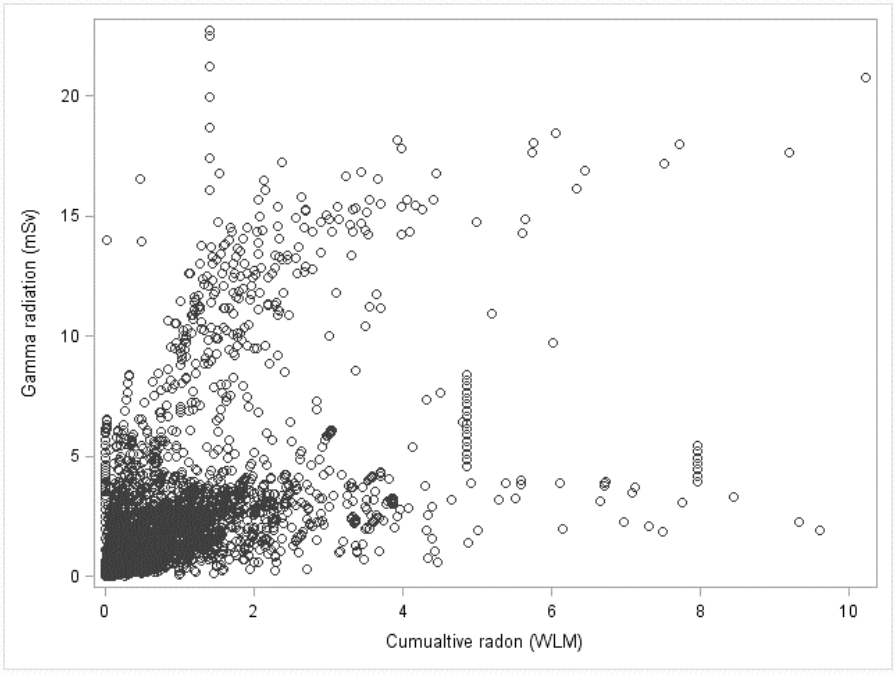
| | Non Smokers | | Smokers | |
|---|---|---|---|---|
| **Lung Cancer** | | | | |
| | ERR/100WLM | 95%CI | ERR/100WLM | 95%CI |
| Continuous WLM | 1.89 | 0.44,3.34 | 6.54 | 2.96,10.13 |
| Windows of exposure | | | | |
| 5-15 | -2.26 | -8.25,3.73 | 12.28 | 1.75,22.81 |
| 15-25 | 2.00 | -0.10,4.10 | 10.03 | 4.53,15.53 |
| 25+ | 1.76 | 0.31,3.21 | 4.39 | 1.74, 7.04 |
| Dose rate | | | | |
| <5 WL | 2.47 | 0.41,4.52 | 8.96 | 4.04,13.87 |
| ≥ 5 WL | 1.02 | -1.17,3.22 | 1.92 | -0.47, 4.31 |
| **Extrathoracic Cancer** | | | | |
| | ERR/100WLM | 95%CI | | |
| Continuous WLM (Smokers and nonsmokers) | 0.25 | -0.23,0.72 | | |

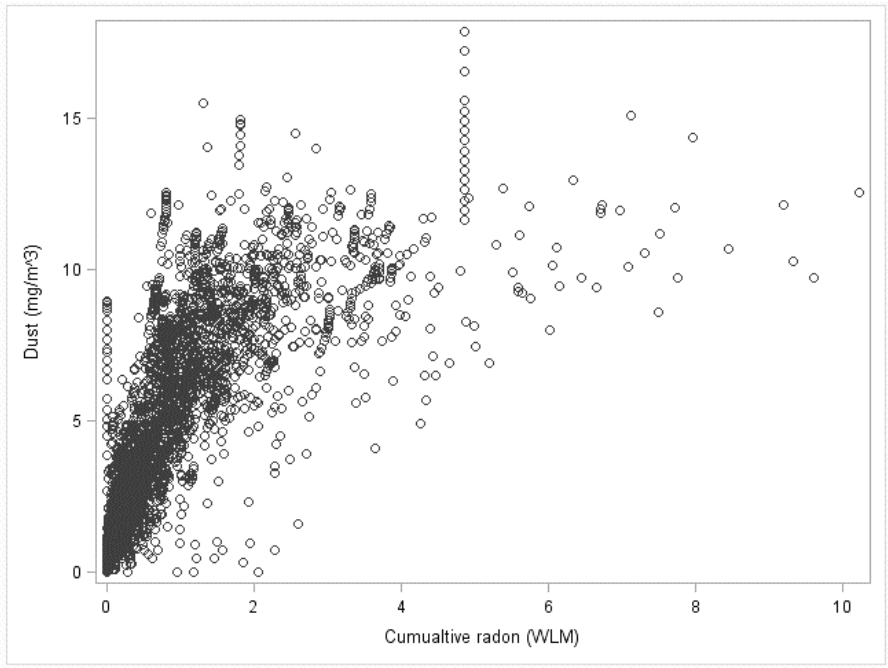
^All models adjusted for birth cohort, smoking, gamma, and dust. Lung cancer includes an interaction term between WLM and smoking

**Discussion.** Adjusting for gamma radiation and dust caused substantial changes in dose response estimates. This may be due to exposure misclassification, or due to the high correlation between radon and gamma exposures or misclassification of the model used to estimate pre-1966 gamma exposures.[24] One prior study of the association between radon and non-solid cancer types noted a high overall correlation between radon and gamma estimates, when they observed large changes in rate estimates when adjusting for gamma.[24] In the case-cohort risk set data structure, we did not observe a strong correlation between cumulative radon and cumulative gamma (correlation = 0.58), however we did observe a strong correlation between radon and cumulative dust (correlation = 0.74). We tested the effect of removing workers who had both low radon

estimates and high gamma estimates (because low radon and high gamma is implausible), but this did not alter main effect estimates. Figure 4.3.1 presents scatterplots of radon compared to gamma and dust. Several of the very high measures or linearly correlated measures belong to the same worker but at different ages depending on the risk set. Gamma and dust estimates require further investigation and possibly a reevaluation of imputed estimates.

**Figure 4.4.1: Scatterplots of cumulative radon and gamma, and cumulative radon and dust**



# CHAPTER V: DISCUSSION

## 5.1 Overview

Over 46,000 people were employed in the Příbram mines from WWII through the Cold War, many of whom were exposed to radon and its progeny, dust, gamma radiation, and other occupational hazards such as traumatic injury, vibration, heat, and noise. It was said that 40% of lung cancers in the Czech Republic could be attributed to work in the Příbram mines due mainly to the extremely large scale of mining operations.[43] We investigated the association between radon exposure and cancer incidence and mortality among Příbram miners. We also addressed research priorities identified in the introduction (Section 1.5) because we evaluated cancer incidence in addition to mortality, smoking, and other occupational co-pollutants among a population of workers exposed to levels of radon at exposure rates reflective of modern occupational exposure scenarios.

## 5.2 Summary of results

We compared the mortality and cancer incidence rates of male Příbram underground miners with a comparable Czech population. While this is a relatively modern uranium mining cohort, which experienced occupational hazards of lower intensity than several other uranium mining cohorts, we were still able to demonstrate excess cancer mortality and incidence compared to the general population. We concluded that all-cause mortality and total cancer incidence were substantially higher among Příbram miners than the Czech male population. We demonstrated an excess mortality from lung cancer, extrathoracic cancer, tuberculosis, and

pneumoconiosis. We demonstrated and excess incidence from lung cancer, extrathoracic cancer, stomach cancer, liver cancer, and some hematopoietic cancer types.

We also estimated relationships between radon exposure and deaths from cancer subtypes of interest, namely lung cancer, extrathoracic cancer, and chronic lymphocytic leukemia. Primarily, this study provides additional evidence regarding the positive dose-response relationship between radon exposure and lung cancer mortality. Positive but imprecise associations were identified among other outcomes of interest, including extrathoracic cancers, myeloma, and CLL.

Finally, we estimated associations between radon exposure and lung and extrathoracic cancer incidences. A positive exposure-response relationship was observed between cumulative WLMs of radon exposure and lung cancer. Our results are consistent with prior findings that smoking modifies the association between radon exposure and rate of lung cancer. Extrathoracic cancer analyses were also positive but less precise.

Overall, our results support prior published findings in this cohort and other uranium mining cohorts.[8,11,3,37,61] Table 5.2.1 shows the comparison of the time period, number of cases, mean WLM, and ERR/100 WLM observed in this study and in other major studies of underground uranium miners in which updates on rates of lung cancer incidence and mortality were recently reported. Both the incidence and mortality estimates derived in this study fall within the range of the other previously published estimates. Mortality estimates fall within the lower range of the previously published estimates, which may be due to a delayed start of follow-up compared to the other cohorts. Table 5.2.1 also illustrates that to our knowledge we conducted the second study of lung cancer incidence among uranium miners, the first incidence

study with smoking information, and that that average WLM exposures in this cohort are lower than several other major cohorts.

**Table 5.2.1: Recent updates of several major underground uranium mining cohorts, compared to the current study**

| Study (publication) | Follow-up period | Lung Cancer Deaths | Mean cumulative WLM | ERR/100WLM (95%CI) |
|---|---|---|---|---|
| **BEIR VI** (NRC, 1999) | Various cohorts | 2,674 | 164.4 | Overall: 0.59 (SE = 1.32)<br>Non-smokers: 1.02 (0.15, 7.18)<br>Smokers: 0.48 (0.18, 1.27) |
| **Ontario, Canada** (Navaranjan et al, 2016) | 1954–2007 | 1,230 | 21 | 0.66 (0.44, 0.87) |
| **WISMUT, Germany** (Kreuzer et al, 2010) | 1946-2003 | 3,016 | 280 | 0.19 (0.17, 0.22) |
| **CEA-COGEMA, France** (Rage et al, 2015) | 1946 - 2007 | 211 | 36.6 | 0.71 (0.31, 1.30) |
| **Western Bohemia, Czech Republic** (Tomasek et al, 2012) | 1952-2010 | 1141 | 73 | 0.97 (0.74-1.27) |
| **Příbram, Czech Republic** (Present study) | 1977-1992 | 705 | 53 | 0.23 (0.09, 0.36) |

| Study (publication) | Follow-up period | Lung Cancer Incidence | Mean cumulative WLM | ERR/100WLM (95%CI) |
|---|---|---|---|---|
| **Ontario uranium miners** (Navaranjan et al, 2016) | 1969–2005 | 1,291 | 21 WLM | 0.64 (0.43, 0.85) |
| **Příbram, Czech Republic** (Present study) | 1977 - 1996 | 892 | 78 WLM | Non-smokers: 0.12 (-0.09, 0.33)<br>Smokers: 1.34 (0.88, 1.80) |

Ultimately, more research is needed on prolonged exposure to low and moderate levels of radon and death from cancers other than lung, especially among extrathoracic cancer. The current literature presents conflicting results and imprecise estimates.[8,40] The results from this present study and the German cohort suggest that miners may experience an elevated rate of extrathoracic cancer incidence, even at low levels of radon exposure (<5 WLM). More studies

are needed to obtain more precise estimates of extrathoracic cancer rates and exposure-response relationships. Finally, we have identified several opportunities for future research we believe is important to the continued study of this cohort, described in the next section.

### 5.3 Future directions

There are several areas for future work with the Příbram uranium miner cohort and case-cohort data. They include updating mortality and cancer incidence records, obtaining death records from the start of mining operations, investigating worker overlap with other Czech mines, assessing the validity of the gamma and dust exposure estimates, developing more refined measures of smoking, and further improving radon estimates in the full cohort with new applications of RRC methods. Updating cancer incidence and mortality to 2016 would extend follow-up to 30 years. Extending follow-up would increase case and death counts which would improve precision of estimates. This would be particularly useful in the investigation of extrathoracic cancer incidence, which has a positive but imprecise association with radon exposure. Extending follow-up would also allow researchers to observe the occurrence of more cancers with protracted induction and latency periods, several of which are of interest in the study radon. A longer follow-up would also improve comparability with other notable uranium mining cohorts, many of which have updated their follow-up through the early 2000s.

Obtaining death records from the start of mining operations through the start of follow up is another important future direction and is necessary to understand the impacts of cohort selection criteria. To meet cohort selection criteria, workers must have been alive at the start of follow up in 1977. While this criterion is useful in creating a left-truncated cohort, it introduces other methodological issues. Namely, workers who survived to the start of follow-up may be different than workers who died prior to the start of follow-up. We observed evidence of this

phenomenon when adjusting for birth cohort in internal analyses. Starting follow-up 32 years after the start of mining operations also reduces comparability with other uranium miner studies, most of which began follow-up at the start of mining operations. Obtaining death records prior to the start of follow-up could be conducted in conjunction with extending incidence and mortality follow-up through 2016.

Another important future direction for this cohort is to identify workers with prior employment in the Jachymov mines of Western Bohemia, Czech Republic. Currently, prior employment status is unknown. It is known that many Jachymov workers moved to Příbram in the 1970's as mining operations in Jachymov declined. Since working conditions in Jachymov mines were poorer (e.g. poor ventilation and higher dust concentrations) than Příbram working conditions, exposure to radon and other co-pollutants among prior Jachymov employees may have been substantial. Prior employment status could be obtained through linking personal identification numbers of Příbram miners to the Western Bohemia cohort of uranium miners.

An additional direction for future work is to review the additional smoking data collected and develop more refined smoking covariate information. In current analyses, smoking is coded as ever/never. At least for some cohort members, there is more detailed smoking information which includes duration and intensity of smoking, as well as information of tobacco use other than cigarettes, but this has not been developed into variables for analysis. We observed a multiplicative or super-multiplicative interaction between smoking and radon exposure on the rate of lung cancer, whereas most other uranium miner studies have concluded that smoking is sub-multiplicative. Because smoking information in this study is crude and only reflects smoking at baseline, developing more detailed indicators of smoking will be useful in further examining smoking as a modifier of the radon-lung cancer association.

Another future approach should be to revisit gamma and dust exposure models. When we modeled radon-lung cancer associations that included dust and gamma parameters, the effects were extremely large. These estimated associations per unit gamma dose, and per unit dust did not represent plausible magnitudes of effects given the low exposure estimated, and suggest that there may be issues with the modeled gamma and dust estimates. All gamma and dust exposure estimates are imputed prior to 1966, and half of the sub-cohort has imputed estimates for all years of work. Even when restricting models to 1966+ workers with exact exposure estimates, we still observed these issues. One reason this issue may persist is due to the strong birth cohort effects created by initiating cohort follow-up 30+ years after the start of mining operations. Revisiting the original gamma and dust models, and re-analyzing data with pre-1977 mortality estimates may reveal the reasons for these issues.

One final future direction (which is currently in progress) is the risk set regression calibration of radon estimates with software updated to handle time-varying cumulative measures and internal validation. Current analyses only use cumulative radon estimates at the time each case occurs in each risk set. But recently, new applications of RRC software have been developed to incorporate all measures prior to the event as well. In the context of the Příbram exposure measurement error in the uranium miners study, we expect these updated estimates to reflect similar results to those presented in this dissertation as most workers accumulated radon exposures at low dose rates.

# APPENDIX: ADDITIONAL TABLES

The following  pages contain additional tables not presented in the main text.

## Table A.1: Cancer mortality and incidence for all ICD-9 groups

| | Cancer Mortality | | | | Cancer Incidence | | | |
|---|---|---|---|---|---|---|---|---|
| **(ICD) Cancer Subtype** | **Obs** | **Exp** | **SMR** | **95%CI** | **Obs** | **Exp** | **SIR** | **95%CI** |
| (140) Malignant neoplasm of lip | 0 | - | - | - | 6 | 8.6 | 0.70 | 0.14 - 1.26 |
| (141) Malignant neoplasm of tongue | 9 | 6.4 | 1.41 | 0.48 - 2.33 | 12 | 7.6 | 1.58 | 0.68 - 2.48 |
| (142) Malignant neoplasm of major salivary glands | 2 | 1.8 | 1.14 | 0.00 - 2.73 | 2 | 3.1 | 0.64 | 0.00 - 1.53 |
| (143) Malignant neoplasm of gum | 0 | | - | - | 2 | 1.6 | 1.21 | 0.00 - 2.90 |
| (144) Malignant neoplasm of floor of mouth | 3 | 2.4 | 1.27 | 0.00 - 2.72 | 3 | 4.1 | 0.73 | 0.00 - 1.57 |
| (145) Malignant neoplasm of other and unspecified parts of mouth | 1 | 1.2 | 0.81 | 0.00 - 2.40 | 4 | 2.8 | 1.43 | 0.02 - 2.83 |
| (146) Malignant neoplasm of oropharynx | 3 | 4.5 | 0.66 | 0.00 - 1.41 | 6 | 7.7 | 0.78 | 0.15 - 1.40 |
| (147) Malignant neoplasm of nasopharynx | 4 | 1.6 | 2.55 | 0.04 - 5.05 | 4 | 2.4 | 1.66 | 0.03 - 3.29 |
| (148) Malignant neoplasm of hypopharynx | 2 | 2.8 | 0.73 | 0.00 - 1.73 | 1 | 3.8 | 0.26 | 0.00 - 0.78 |
| (149) Malignant neoplasm of other and ill-defined sites within the lip | 1 | 1.2 | 0.83 | 0.00 - 2.47 | 1 | 0.3 | 3.29 | 0.00 - 9.76 |
| (140 - 149) Lip, Oral Cavity, and Pharynx | 25 | 21.8 | 1.14 | 0.75 - 1.65 | 41 | 42.1 | 0.98 | 0.71 - 1.31 |
| (150) Malignant neoplasm of esophagus | 23 | 15.0 | 1.53 | 0.90 - 2.16 | 19 | 14.0 | 1.36 | 0.74 - 1.97 |
| (151) Malignant neoplasm of stomach | 102 | 80.6 | 1.27 | 1.02 - 1.51 | 108 | 78.9 | 1.37 | 1.11 - 1.63 |
| (152) Malignant neoplasm of small intestine, including duodenum | 6 | 2.1 | 2.91 | 0.57 - 5.25 | 7 | 2.1 | 3.26 | 0.83 - 5.69 |
| (153) Malignant neoplasm colon | 54 | 59.7 | 0.90 | 0.66 - 1.15 | 80 | 75.7 | 1.06 | 0.82 - 1.29 |
| (154) Malignant neoplasm of rectum, rectosigmoid junction, and anus | 80 | 60.2 | 1.33 | 1.04 - 1.62 | 119 | 84.4 | 1.41 | 1.16 - 1.66 |
| (155) Malignant neoplasm of liver and intrahepatic bile ducts | 48 | 29.4 | 1.63 | 1.17 - 2.10 | 38 | 22.3 | 1.70 | 1.16 - 2.25 |
| (156) Malignant neoplasm of gallbladder and extrahepatic bile ducts | 13 | 14.7 | 0.88 | 0.40 - 1.37 | 9 | 14.8 | 0.61 | 0.21 - 1.00 |
| (157) Malignant neoplasm of pancreas | 53 | 44.6 | 1.19 | 0.87 - 1.51 | 54 | 41.3 | 1.31 | 0.96 - 1.66 |
| (158) Malignant neoplasm of retroperitoneum and peritoneum | 3 | 2.7 | 1.11 | 0.00 - 2.38 | 3 | 2.3 | 1.30 | 0.00 - 2.77 |
| (159) Malignant neoplasm of other and ill-defined sites | 14 | 7.7 | 1.82 | 0.86 - 2.77 | 16 | 4.9 | 3.29 | 1.67 - 4.91 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (150 - 159) Digestive organs and peritoneum | 396 | 316.7 | 1.25 | 1.13 - | 1.38 | 453 | 340.8 | 1.33 | 1.21 - | 1.46 |
| (160) Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses | 2 | 1.4 | 1.41 | 0.00 - | 3.38 | 1 | 2.2 | 0.46 | 0.00 - | 1.38 |
| (161) Malignant neoplasm of larynx | 33 | 19.8 | 1.67 | 1.10 - | 2.24 | 45 | 33.6 | 1.34 | 0.95 - | 1.73 |
| (162) Malignant neoplasm of trachea, bronchus, and lung | 705 | 332.3 | 2.12 | 1.96 - | 2.28 | 755 | 326.2 | 2.31 | 2.15 - | 2.48 |
| (163) Malignant neoplasm of pleura | 5 | 2.4 | 2.06 | 0.25 - | 3.87 | 5 | 2.5 | 1.97 | 0.24 - | 3.71 |
| (164) Malignant neoplasm of thymus, heart, and mediastinum | 2 | 1.9 | 1.03 | 0.00 - | 2.46 | 2 | 2.6 | 0.78 | 0.00 - | 1.87 |
| (165) Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs | 2 | 0.6 | 3.22 | 0.00 - | 7.71 | 0 | - | - | - | |
| (160 - 165) Respiratory and Intrathoracic | 749 | 358.5 | 2.09 | 1.95 - | 2.25 | 808 | 367.0 | 2.20 | 2.05 - | 2.36 |
| (170) Malignant neoplasm of bone and articular cartilage | 4 | 4.5 | 0.88 | 0.01 - | 1.74 | 4 | 2.8 | 1.44 | 0.02 - | 2.87 |
| (171) Malignant neoplasm of connective and other soft tissue | 3 | 2.8 | 1.07 | 0.00 - | 2.28 | 5 | 6.9 | 0.72 | 0.09 - | 1.36 |
| (172) Malignant melanoma of skin | 14 | 11.9 | 1.18 | 0.56 - | 1.80 | 18 | 23.3 | 0.77 | 0.41 - | 1.13 |
| (173) Other malignant neoplasm of skin | 1 | 2.6 | 0.39 | 0.00 - | 1.16 | 129 | 190.3 | 0.68 | 0.56 - | 0.80 |
| (175) Malignant neoplasm of male breast | 0 | - | - | - | | 1 | 1.7 | 0.60 | 0.00 - | 1.78 |
| ICD 170 - 175: Bone, Connective tissue, Skin, and Breast | 22 | 21.8 | 1.00 | 0.64 - | 1.49 | 157 | 224.9 | 0.70 | 0.59 - | 0.81 |
| (185) Malignant neoplasm of prostate | 30 | 45.1 | 0.67 | 0.43 - | 0.90 | 57 | 65.9 | 0.86 | 0.64 - | 1.09 |
| (186) Malignant neoplasm of testis | 4 | 3.8 | 1.05 | 0.02 - | 2.09 | 10 | 11.7 | 0.85 | 0.32 - | 1.38 |
| (187) Malignant neoplasm of penis and other male genital organs | 4 | 1.4 | 2.81 | 0.04 - | 5.57 | 6 | 3.4 | 1.76 | 0.35 - | 3.18 |
| (188) Malignant neoplasm of bladder | 29 | 27.7 | 1.05 | 0.67 - | 1.43 | 54 | 50.8 | 1.06 | 0.78 - | 1.35 |
| (189) Malignant neoplasm of kidney and other and unspecified urinary organs | 41 | 40.9 | 1.00 | 0.69 - | 1.31 | 49 | 55.9 | 0.88 | 0.63 - | 1.12 |
| ICD 185 - 189: Genitourinary Organs | 108 | 118.9 | 0.91 | 0.75 - | 1.09 | 176 | 187.8 | 0.94 | 0.81 - | 1.08 |
| (190) Malignant neoplasm of eye | 1 | 0.7 | 1.49 | 0.00 - | 4.42 | 1 | 2.7 | 0.37 | 0.00 - | 1.09 |
| (191) Malignant neoplasm of brain | 13 | 17.0 | 0.76 | 0.35 - | 1.18 | 13 | 15.6 | 0.83 | 0.38 - | 1.29 |
| (192) Malignant neoplasm of other and unspecified parts of nervous system | 1 | 0.9 | 1.07 | 0.00 - | 3.18 | 0 | - | - | - | |
| (193) Malignant neoplasm of thyroid gland | 2 | 2.2 | 0.91 | 0.00 - | 2.19 | 5 | 4.3 | 1.17 | 0.14 - | 2.20 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (194) Malignant neoplasm of other endocrine glands and related structures | 0 | - | - | - | | 3 | 1.3 | 2.35 | 0.00 - | 5.02 |
| (195) Malignant neoplasm of other and ill-defined sites | 5 | 4.3 | 1.17 | 0.14 - | 2.19 | 3 | 3.4 | 0.87 | 0.00 - | 1.86 |
| (196) Secondary and unspecified malignant neoplasm of lymph nodes | 3 | 0.1 | 21.39 | 0.00 - | 45.70 | 4 | 3.8 | 1.06 | 0.02 - | 2.10 |
| (197) Secondary malignant neoplasm of respiratory and digestive systems | 8 | 0.1 | 71.70 | 21.81 - | 121.60 | 7 | 5.4 | 1.29 | 0.33 - | 2.25 |
| (198) Secondary malignant neoplasm of other specified sites | 6 | 0.1 | 52.86 | 10.39 - | 95.33 | 13 | 4.5 | 2.86 | 1.30 - | 4.42 |
| (199) Malignant neoplasm without specification of site | 14 | 13.8 | 1.02 | 0.48 - | 1.55 | 19 | 8.0 | 2.36 | 1.30 - | 3.43 |
| (190 - 199) Other and unspecified sites | 53 | 39.2 | 1.36 | 1.03 - | 1.76 | 68 | 49.1 | 1.38 | 1.09 - | 1.75 |
| (200) Lymphosarcoma and reticulosarcoma | 7 | 4.5 | 1.57 | 0.40 - | 2.73 | 7 | 7.4 | 0.94 | 0.24 - | 1.64 |
| (201) Hodgkin's disease | 8 | 6.8 | 1.18 | 0.36 - | 2.00 | 15 | 9.5 | 1.57 | 0.77 - | 2.37 |
| (202) Other malignant neoplasms of lymphoid and histiocytic tissue | 10 | 10.2 | 0.98 | 0.37 - | 1.58 | 10 | 14.1 | 0.71 | 0.27 - | 1.15 |
| (203) Multiple myeloma and immunoproliferative neoplasms | 8 | 7.5 | 1.07 | 0.33 - | 1.82 | 16 | 9.2 | 1.75 | 0.89 - | 2.61 |
| (204) Lymphoid leukemia | 11 | 10.6 | 1.03 | 0.42 - | 1.65 | 21 | 13.3 | 1.57 | 0.90 - | 2.25 |
| (205) Myeloid leukemia | 12 | 8.8 | 1.36 | 0.59 - | 2.14 | 14 | 8.8 | 1.58 | 0.75 - | 2.42 |
| (207) Other specified leukemia | 1 | 1.4 | 0.70 | 0.00 - | 2.07 | 1 | 0.8 | 1.31 | 0.00 - | 3.88 |
| (208) Leukemia of unspecified cell type | 1 | 2.9 | 0.34 | 0.00 - | 1.02 | 1 | 1.5 | 0.67 | 0.00 - | 1.98 |
| ICD 200 - 208: Lymphatic and Hematopoietic | 58 | 52.8 | 1.09 | 0.84 - | 1.41 | 85 | 64.7 | 1.31 | 1.05 - | 1.61 |
| (230) Carcinoma in situ of digestive organs | 0 | - | - | - | | 3 | 1.7 | 1.76 | 0.00 - | 3.76 |
| (231) Carcinoma in situ of respiratory system | 0 | - | - | - | | 1 | 0.6 | 1.71 | 0.00 - | 5.06 |
| (232) Carcinoma in situ of skin | 0 | - | - | - | | 2 | 3.1 | 0.64 | 0.00 - | 1.54 |
| (140 - 232) All cancer types | 1411 | 929.6 | 1.52 | 1.44 - | 1.60 | 1788 | 1276.5 | 1.40 | 1.34 - | 1.47 |

## Table A.2: Mortality by hiring period and duration of employment

| | All-cause mortality | | |
|---|---|---|---|
| 1946 - 1952 Hiring Period | Obs | SMR | 95%CI |
| < 2 years | 157 | 1.37 | 1.16 - 1.59 |
| 2 - <10 years | 274 | 1.43 | 1.26 - 1.60 |
| ≥ 10 years | 390 | 1.34 | 1.21 - 1.48 |
| 1953 - 1962 Hiring Period | Obs | SMR | 95%CI |
| < 2 years | 745 | 1.24 | 1.15 - 1.33 |
| 2 - <10 years | 971 | 1.25 | 1.17 - 1.33 |
| ≥ 10 years | 863 | 1.12 | 1.04 - 1.10 |
| 1963+ Hiring Period | Obs | SMR | 95%CI |
| < 2 years | 279 | 1.30 | 1.14 - 1.45 |
| 2 - <10 years | 334 | 1.37 | 1.22 - 1.52 |
| ≥ 10 years | 198 | 0.92 | 0.79 - 1.05 |

## Table A.3: Cancer mortality other than lung by cumulative working level month radon exposure among male Příbram uranium miners 1977-1992*

| Cancer Site | Cumulative Radon Exposure (WLM) | n | Relative Risks (95%CI) | |
|---|---|---|---|---|
| Extrathoracic airway (140-148, 160, 161) | <25 WLM | 22 | 1 | |
| | 25 - <50 WLM | 11 | 0.93 | (0.43 - 2.00) |
| | 50 - <150 WLM | 15 | 0.83 | (0.42 - 1.65) |
| | 150+ | 11 | 1.27 | (0.60 - 2.72) |
| Stomach (151) | <25 WLM | 30 | 1 | |
| | 25 - <50 WLM | 22 | 1.18 | (0.68 - 2.05) |
| | 50 - <150 WLM | 33 | 0.95 | (0.57 - 1.57) |
| | 150+ | 17 | 1.05 | (0.57 - 1.91) |
| Liver (155) | <25 WLM | 12 | 1 | |
| | 25 - <50 WLM | 11 | 1.43 | (0.63 - 3.27) |
| | 50 - <150 WLM | 18 | 1.27 | (0.60 - 2.68) |
| | 150+ | 7 | 1.04 | (0.40 - 2.66) |
| Kidney (189) | <25 WLM | 8 | 1 | |
| | 25 - <50 WLM | 14 | 3.56 | (1.45 - 8.72) |
| | 50 - <150 WLM | 12 | 1.78 | (0.70 - 4.55) |
| | 150+ | 7 | 2.18 | (0.76 - 6.26) |
| Non-Hodgkin lymphoma (200, 202) | <25 WLM | 7 | 1 | |
| | 25 - <50 WLM | 1 | 0.47 | (0.05 - 4.07) |
| | 50 - <150 WLM | 7 | 2.16 | (0.64 - 7.36) |
| | 150+ | 2 | 1.36 | (0.24 - 7.63) |
| Hodgkin lymphoma (201) | <25 WLM | 5 | 1 | |
| | 25 - <50 WLM | 1 | 0.51 | (0.06 - 4.65) |
| | 50 - <150 WLM | 1 | 0.31 | (0.03 - 2.98) |
| | 150+ | 1 | 0.67 | (0.07 - 6.49) |
| Myeloma^ (203) | <50 WLM | 3 | 1 | |
| | 50 - <150 WLM | 3 | 1.41 | (0.28 - 7.15) |
| | 150+ | 2 | 1.95 | (0.32 - 11.84) |
| CLL (204.1) | <25 WLM | 3 | 1 | |
| | 25 - <50 WLM | 2 | 1.08 | (0.18 - 6.55) |
| | 50 - <150 WLM | 4 | 1.18 | (0.25 - 5.45) |
| | 150+ | 2 | 1.23 | (0.20 - 7.56) |
| Myeloid leukemia (205.0, 205.1) | <25 WLM | 5 | 1.00 | |
| | 25 - <50 WLM | 2 | 0.67 | (0.13 - 3.50) |
| | 50 - <150 WLM | 4 | 0.76 | (0.20 - 2.95) |
| | 150+ | 1 | 0.39 | (0.04 - 3.44) |
| All Hematopoietic (200 - 208) | <25 WLM | 23 | 1 | |
| | 25 - <50 WLM | 8 | 0.72 | (0.31 - 1.63) |
| | 50 - <150 WLM | 19 | 1.00 | (0.52 - 1.90) |
| | 150+ | 8 | 0.88 | (0.38 - 2.04) |

*Adjusted for age

^<25 WLM and 25 - <50 WLM categories collapsed

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