MODELING THE RISK OF LUNG CANCER FROM EXPOSURE TO PLUTONIUM AT THE ROCKY FLATS ENVIRONMENTAL TECHNOLOGY SITE

by
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ABSTRACT

Past studies have shown that there is an increased risk of cancer in radiation workers. Exposure to internally deposited radionuclides increases the risk of cancer in many studies of uranium miners and in the Mayak workers in Russia . Autopsies performed on plutonium-exposed workers show accumulation of plutonium in the lung as well as other tissues in the human body. With knowledge that the risk of cancer increases with exposure to plutonium and plutonium is known to accumulate in lung tissue, it is necessary to analyze the risk of lung cancer caused by plutonium exposure to nuclear workers in this country. This case-control study attempts to better understand the relationship between mortality from lung cancer and exposure to plutonium for the employees of the Rocky Flats Environmental Technology Site. Alternative exposure metrics were created in an attempt to quantify the intensity of exposure. The new measures of internal lung exposure are average lifetime dose, maximum annual dose, and the number of years with a positive internal dose. The new metrics, along with other covariates, will be used in determining risk of mortality from lung cancer. Additionally, age-specific internal plutonium doses to the lung were analyzed in order to understand age, and its effects on the subjects at Rocky Flats, when estimating risk of mortality from lung cancer. Furthermore, this study investigated the possibility that age modifies the effects of exposure. Smoking data was not collected on one hundred-seventy two of the nine-hundred subjects in the study. A method to impute the smoking data for the missing values and using that imputed data to understand its effects on plutonium exposure and the risk of mortality from lung cancer was also studied.

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CHAPTER 1

INTRODUCTION

1.1 Background Information

Past studies have shown that there is an increased risk of cancer in radiation workers (1,16,17,18,20,25,32,34,36). Exposure to internally deposited radionuclides increases the risk of cancer in many studies of uranium miners (1,20, 32) and in the Mayak workers in Russia (18). Autopsies performed on plutonium-exposed workers show accumulation of plutonium in the lung as well as other tissues in the human body (22). With knowledge that the risk of cancer increases with exposure to plutonium and plutonium is known to accumulate in lung tissue, it is necessary to analyze the risk of lung cancer caused by plutonium exposure to nuclear workers in this country.

This case-control study attempts to better understand the relationship between mortality from lung cancer and exposure to plutonium for the employees of the Rocky Flats Environmental Technology Site. Previous studies of different cohorts (16, 17, 27) have used cumulative lifetime dose to measure exposure to plutonium. In previous studies on the Rocky Flats cohort using cumulative lifetime dose, the risk to lung cancer was not significantly elevated at certain levels of exposures and this may be because the doses are relatively small (27) or variables such as age and smoking are modifying the effects of exposure.

The measurements of plutonium exposure to the lung were calculated using dosimetry software and may be different than the true amount of plutonium received (4). Alternative exposure metrics were created in an attempt to quantify the intensity of exposure. A subject may have a different biological response if they received an intense exposure over a shorter period of time or an intense dose once in their life as compared to measuring the total dose received in a lifetime. The new measures of internal lung exposure are average lifetime dose, maximum annual dose, and the number of years with a positive internal dose. The new metrics, along with other covariates, will be used in determining risk of mortality from lung cancer.

Other risk factors such as age and smoking may contribute to the risk of mortality from lung cancer. Ruttenber et al. considered age and its effects on lung cancer by addressing it in the sampling scheme of the case-control study (27). In addition to controlling for its main-effects, age-specific cumulative lung dose categories were created to understand if age is modifying the effects of exposure. Age may have an effect on how the doses were received by the lung and studying age as a potential effect-modifier may give insight into how doses of plutonium are internalized by the human body. Using age-specific categories of internal lung dose is one way to address this issue.

Ruttenber et al. (27), when studying the Rocky Flats employees, found that smoking was not a confounder. However, the smoking data for each employee was obtained by either contacting next-of-kin or data in health files and there were several missing smoking histories. In addition to missing smoking histories, bias was introduced when collecting the histories from next-of-kin. A method to impute the missing smoking data and other analyses were attempted to understand if smoking is a confounder using all the subjects in the study. Additional analyses were performed to understand the smoking histories of the subjects and how it affects the association between exposure to radiation and the risk of mortality from lung cancer.

1.2 Research Questions

Ruttenber, A.J., et al. (27) analyzed the relationship between internal alpha-particle exposure to plutonium and death from lung cancer. This study is an extension of the above-mentioned work. Ruttenber et al. (27) used a nested case-control study of the workers at Rocky Flats to study the association of cumulative lifetime internal alpha-particle exposure to plutonium as the primary exposure covariate. This research will primarily focus upon:

1. In an attempt to understand if the intensity of internal lung exposure is related to risk of dying from lung cancer, alternate exposure metrics were created to measure dose other than cumulative lifetime dose. These exposure metrics are average annual internal dose, maximum lifetime internal dose, the number of years of internal lung exposure, and the number of fires a subject was exposed to. These additional exposure metrics, created to find a relation between exposure and death from lung cancer, are alternate measures of dose other than cumulative lifetime dose.
2. Age is a main effect when studying mortality from lung cancer. In other words, the older you are the more likely you are to die of lung cancer regardless of exposure. Age-specific internal plutonium doses to the lung were analyzed in order to understand age, and its effects on the subjects at Rocky Flats, when estimating risk of mortality from lung cancer. Furthermore, this study investigates the possibility that age modifies the effects of exposure.

3. Smoking data was not collected on one hundred-seventy two of the nine-hundred subjects in the study. A method to impute the smoking data for the missing values and using that imputed data to understand its effects on plutonium exposure and the risk of mortality from lung cancer was studied.

1.3 Previous Studies

The first series of human studies to demonstrate increased risk of mortality from lung cancer among plutonium-exposed workers were the studies conducted at the Mayak facilities in Russia and the first studies of the Mayak cohort were published in 1995. The results of these studies are based on a cohort consisting of 1,669 male workers who worked in the radiochemical processing plant from 1948-1958. These subjects were exposed to both internal alpha-particles and external gamma-ray radiation. There are additional results from a cohort of 2,172 male reactor workers who were only exposed to external gamma-ray radiation (18).

The Russian State Research Center "Biophysics Institute" studied a cohort consisting of 2,172 nuclear reactor workers, 1,059 radiochemical plant workers, and 610 plutonium production workers. Of the production plant workers, 61 (26%) died of lung cancer. The production plant workers were exposed to both internal alpha-particles and external gamma-ray radiation (17). Of the reactor workers, 74 (8.9%) died of lung cancer and of the radiochemical plant workers 56 (14.7%) died of lung cancer. The mean lifetime cumulative internal lung dose for the reactor workers and the radiochemical production plant workers are 0.15 Gy. and 0.48 Gy, respectively. The mean lifetime cumulative external gamma-ray dose for the workers at the radiochemical plant, reactor, and plutonium production plant were 2.15 Gy., 0.95 Gy, and 0.65 Gy, respectively. The average duration of work for all three facilities were 15.9 years (reactor), 22.5 years (radiochemical plant), and 27.1 years (plutonium production) (17).

In these earlier publications, there was a noted dependence of lung cancer mortality among those at the Mayak Facilities and exposure to internal alpha-particles. For both internal alpha-particles and external gamma-ray radiation, there were linear dose dependencies (17). These results were obtained by fitting a relative risk model. With knowledge that radiation exposure is related to cancer in radiation workers, the Rocky Flats Employee population provides an opportunity to study the effects of radiation and cancer for radiation workers in this country.

1.4 History of Rocky Flats and the Use of Plutonium

1.4.1 History of Rocky Flats

The US Atomic Energy Commission announced the approval to build Rocky Flats in March 1951 and production of nuclear weapons components began in 1952. The plant's primary objective was to increase the quantity and quality of the nation's nuclear weapon arsenal (6). Rocky Flats was chosen as the site for production of plutonium parts. It was the only site assigned to this purpose although many sites throughout the United States were chosen for plutonium production (4). Weapon components produced at Rocky Flats were created from beryllium, plutonium, uranium, and stainless steel. In addition to weapons manufacturing, research of nuclear material properties, and recycling of scrap metal and dismantled weapons were conducted at Rocky Flats.

The plant has had four contractors in its history of operation: Dow Chemical (1951-1975), Rockwell International (1975-1989), EG&G Inc. (1990-1995) and Kaiser-Hill (1995-present). During operation by Dow Chemical, plant operations were kept secret and only after a fire in 1969 did the public learn that plutonium had been released routinely and accidentally from the plant (6). In 1989 it was included on the National Priorities List for cleanup of environmental contamination and in 1994, under contract of EG&G, Rocky Flats was proposed to be a superfund site. Plutonium production ceased in 1990 and since then Rocky Flats has been in the process of decommissioning and decontaminating the site and surrounding areas. The current contractor, Kaiser-Hill estimates that the plant will be closed in 2010.

There have been roughly 23,000 employees hired since the opening of the plant in 1951. The employees at the Rocky Flats facility included administrators, engineers, health physicists, chemists, machinists, guards, and radiation protection engineers. Because of the secrecy concerning nuclear weapon production around the world, the estimate of the number of people exposed, occupationally or environmentally, is almost impossible to predict. Rocky Flats employees provide a large sub-population in which the effects of exposure to plutonium can be better understood.

1.4.2 History of Rocky Flats Plant Operations

From 1952 to 1990, Rocky Flats had two main missions: the production of "triggers" for nuclear weapons and the processing of retired weapons for plutonium recovery. There are seven phases in the life of a nuclear weapon. These are: 1) weapon conception, 2) program feasibility study, 3) development engineering, 4) production engineering, 5) first production, 6) quantity production and stockpile, and 7) retirement. Rocky Flats was involved in the fourth phase, production engineering, through the seventh phase, retirement (3). The bulk of the manufacturing work done at Rocky Flats involves the production start-up and quantity production of phases 5 and 6. Phase 5 is the first production stage where production of the weapon begins according to specifications of the design. Successful completion of this stage results in the authorization for stockpile production, phase 6. Weapons are then produced in specific quantities for stockpile. Evaluation of the weapon continues during phase 6 production to incorporate new technological advances (3).

The plutonium "triggers" manufactured at Rocky Flats were the first-stage fission bombs used to set off the second-stage fusion reaction in hydrogen bombs (6). The plutonium used in these "triggers", also called "pits", was transported from the Hanford Reservation in Washington State and from the Savannah River Plant in South Carolina. There have been only three basic "trigger" designs in the history of production at Rocky Flats. The first two designs were mostly made of uranium. They were solid units derived from the "Fat Man" and "Little Boy" dropped on Japan in World War II. The parts made at Rocky Flats had a small plutonium core surrounded by a large amount of uranium and then by high explosives (2). The concept and design of these changed in 1957 to become a sealed hollow unit which used much less uranium and much more plutonium, but was still surrounded by high explosives. The geometry of this new design and the larger amounts of plutonium made a more powerful explosion (6). Since 1958, the design has remained largely the same as have the materials used to produce them (2).

1.4.3 Plutonium Use at Rocky Flats

Plutonium is a silvery-white metal that can take on a yellow tarnish when it has been oxidized. A relatively large piece of plutonium will be warm to the touch because of the energy given off during alpha-decay and larger pieces will produce enough heat to boil water. The primary use of plutonium by man is in nuclear reactors and in nuclear weapons. The main type of plutonium used at Rocky Flats is plutonium-239, which is produced by bombarding uranium-238 with neutrons in production reactors and then chemically separating it from the irradiated fuel. In other words, plutonium-239 is produced when uranium-238 absorbs a neutron. Plutonium-239 can absorb more neutrons to form heavier isotopes, such as plutonium-240, plutonium-241 and plutonium-242. The "trigger" components produced at Rocky Flats are spheres of plutonium-239 which trigger the fission reaction used to start a thermonuclear explosion (4).

Plutonium fabrication at Rocky Flats involved casting, rolling and forming, machining, and final product assembly with the final product being the "triggers" used in nuclear weapons. Recovery of plutonium through the dismantling and recycling process involves the dissolution of plutonium metal and plutonium residues being purified and converted to metal. To recover plutonium, which started in 1959 at Rocky Flats, an incinerator was used to purify it before converting the plutonium to metal (12). Through these uses, exposure to plutonium by the employees at Rocky Flats was inevitable.

1.4.4 Radiation Terms and Units

Radioactive atoms are continuously disintegrating. In this process of change, they give off radiation. The rate of disintegration (radioactive decay) varies from one isotope to another and in the process of disintegration, energy is given up in the form of ionizing radiation. Everyone is continually exposed to ionizing radiation which has always been present in the environment, and man has lived and evolved in a background of naturally occurring radiation. The most common types of ionizing radiation are alpha-particles, beta-particles, gamma rays, X-rays, and neutrons.

Alpha-particles occur in elements heavier than lead. As the radioactive atom disintegrates and the energy is given off, an alpha-particle can be emitted. An alpha-particle is an emitted helium nucleus that consists of two neutrons and two protons. Although alpha-particles can not penetrate skin, they can travel through air. Once alpha-particles are inside the body they can cause cellular damage to unprotected tissue. Beta-particles are from decaying radionuclides that are lighter than lead. A beta-particle is an electron and is much lighter than an alpha-particle (7000 times lighter). Beta particles can travel 3 feet in air and less than 1 inch in body tissue. Often, the primary product of alpha- and beta-decay is a daughter nucleus in an excited state whose energy is higher than that of the ground state. This excess energy emitted by the excited daughter nucleus is dissipated in the form of gamma-rays. Gamma-rays are similar to X-rays, but have a higher energy. Gamma-rays can penetrate the human body which will only absorb a small part of them (33). Neutrons ionize indirectly by becoming captured by nuclei which will then become radioactive. The biological effects of alpha-particles and neutrons are generally greater than those of beta-particles, gamma-rays and X-rays because alpha-particles transfer most of their energy to a single cell increasing the likelihood of cellular damage.

Radiation dosimetry attempts to relate a quantifiable amount of radiation to biological (or chemical) changes that the radiation would produce in a target or object being irradiated. Dosimetry is essential for quantifying the incidence in biological changes as a function of the amount of radiation received. In order to understand this function between radiation and biological changes, a further explanation of radiation dosimetry is needed. The quantities and units associated with radiation exposure are complicated, but necessary in order to understand the differences between different types of radiation. The different quantities are *exposure*, *absorbed dose*, and *dose equivalent.*

The unit of *exposure* to gamma and X-rays is defined as the roentgen (R). One roentgen is defined as the amount of gamma or X-radiation that produces in air 1 electrostatic unit (esu) of charge of either sign per 0.001293 g of air. The concept of exposure applies only to electromagnetic radiation and the definition of a roentgen only applies to air. Different concepts are needed to apply to all kinds of radiation and to other materials, particularly human tissue. *Absorbed dose* is defined as the energy absorbed per unit mass from any kind of ionizing radiation in any kind of matter. The unit of absorbed dose is the rad, defined as 100 erg/g. 1 rad is equal to 1 Gray (Gy). The absorbed dose is often referred to simply as the dose. The absorbed dose needed to achieve a given level of biological damage is often different for different kinds of ionizing radiation. In order to discuss the different biological changes with different kinds of radiation, the concept of dose equivalent is used. The *dose equivalent* is defined as the product of the absorbed dose with a constant whose value depends on the kind of radiation encountered. When the absorbed dose is expressed in rad, the dose equivalent is the rem. If the absorbed dose is expressed in Gy, the dose equivalent is the sievert

(Sv.). Therefore, $1\text{Sv} = 100\text{rem}$. In routine work involving radiation, the exposure of individuals is limited to a given level of dose equivalents, independent of the type of radiation involved. In this study, external gamma-radiation and internal alpha-radiation to the lung were measured and the dose equivalent is expressed in centisieverts (cSv.) where $1\text{cSv} = 1\text{rem}$.

1.5 Measures of Increased Risk

The three most commonly used measures of increased risk of disease from exposure are the rate ratio, the risk ratio, and the odds ratio. For the sake of simplicity, assume a binary exposure. A definition of each is given below.

Let T denote the failure time (death from lung cancer) of a subject. Let P_1 denote the probability of being exposed and P_0 denote the probability of being unexposed. Let $f_1(t)$, and $f_0(t)$ be the density of T if exposed or unexposed, respectively. Also let

$\gamma_1(t) = \dfrac{f_1(t)}{P_1(T \geq t)}$ and $\gamma_0(t) = \dfrac{f_0(t)}{P_0(T \geq t)}$ be the hazard function if exposed and unexposed, respectively.

The risk ratio over the time interval $[t, t + \Delta t]$ is defined to be $\dfrac{P_1(t < T \leq t + \Delta t \mid T \geq t)}{P_0(t < T \leq t + \Delta t \mid T \geq t)}$ where T is the failure time.

The rate ratio is defined to be the limit of the risk ratio as $\Delta t \to 0$

$$= \lim_{\Delta t \to 0} \frac{P_1(t < T \leq t + \Delta t \mid T \geq t) / \Delta t}{P_0(t < T \leq t + \Delta t \mid T \geq t) / \Delta t}$$

$$= \frac{\dfrac{\lim_{\Delta t \to 0}\left(P_1(T \le t + \Delta t) - P_1(T \le t)\right)/\Delta t}{1 - P_1(T \le t)}}{\dfrac{\lim_{\Delta t \to o}\left(P_0(T \le t + \Delta t) - P_0(T \le t)\right)/\Delta t}{1 - P_0(T \le t)}}$$

$$= \frac{f_1(t)/[1 - P_1(T \le t)]}{f_0(t)/[1 - P_0(T \le t)]}$$

$$= \frac{\gamma_1(t)}{\gamma_0(t)}$$

The risk ratio over a small time interval is virtually the same as the rate ratio.

The odds ratio is the ratio of the odds of failure in exposed subjects to the odds of failure in unexposed subjects. It is defined by

$$\frac{P_1(t < T \le t + \Delta t \mid T \ge t)/[1 - P_1(t < T \le t + \Delta t \mid T \ge t)]}{P_0(t < T \le t + \Delta t \mid T \ge t)/[1 - P_0(t < T \le t + \Delta t \mid T \ge t)]}$$

Notice, as $\Delta t \to 0$, both $P_1(t < T \le t + \Delta t \mid T \ge t) = 0$ and $P_0(t < T \le t + \Delta t \mid T \ge t) = 0$ because $t < T \le t = 0$. With this, it is shown that for very small Δt, the odds ratio, the risk ratio, and the rate ratio are equivalent.

Logistic regression described later, which estimates odds ratios, was used in this study. The odds ratio (as well as the risk ratio and rate ratio) is a measure of association between the outcome, whether the subject is a case or control, and the risk factor. An odds ratio represents the risk of the outcome for the case exposed to the risk factor compared to not being exposed to the risk factor. If the odds ratio is 1 then there is no excess risk, if the odds ratio is greater than one then the subject has excess risk from exposure, and if the odds ratio is less than one the subject has decreased risk from exposure. In order to assess the fit of the logistic model and understand the results of the logistic regression that were performed, it is important to understand the variables that were included as the predictor variables. If the predictor variable is nominal-scale and dichotomous (measured at two levels), the odds ratio measures how much more likely (or unlikely) it is for the outcome to be present among the cases than the controls. If the predictor is a design variable (i.e. when a variable is measured at different levels and then categorized), then the odds ratio measures the amount of risk there is associated with the specific level of exposure as compared to the reference category (usually not having the risk factor), and if the predictor is continuous the odds ratio indicates the odds of being a case with the higher risk factor for two subjects who are 1 unit apart on the risk factor and are comparable on all other risk factors (13).

CHAPTER 2

METHODS

2.1 Study Design

In a case-control study, subjects who have developed a disease (cases) are identified and their past exposure to aetiological factors is compared to that of controls, or referents, who do not have the disease. A case-control study was designed to study the effects of exposure to plutonium and the risk of death from lung cancer. The cases are the subjects who have died of lung cancer and the controls are subjects who have not. It is important to find the proportion of the cases and controls that have been exposed because if there is an association of exposure and mortality, the prevalence of history of exposure should be higher in subjects who have died of lung cancer than in those who have not. A case-control study often defines variables to match the cases and controls in the sampling scheme. Matching is defined as the process of selecting the controls so that they are similar to the cases in certain characteristics. The reason for matching is that cases and controls might differ in characteristics or exposures other than the one that has been targeted for study; matching controls the confounding variable on which the matching is done. In this study, cases and controls were matched on age and gender. This defined the risk set of controls for every case. The risk set is the set of all controls that have the potential of dying of lung cancer at the same age as the case selected. This study is a 1:4 matched study: every case is matched to four controls in order to identify elevated risk. Cases and controls were chosen independent of exposure, and the primary exposure is exposure to plutonium; doses were not calculated until the subjects had been chosen.

A case-control study was selected for time and computation efficiency. Using a case-control study allowed 900 subjects in the study to have their lung doses calculated as compared to 18,000 production workers that would be needed in a cohort study design. A case-control study also allowed the previous researchers (4, 27) to collect enough cases in order to study the effects of exposure and elevated risk of the outcome. Plutonium lung doses were calculated for each of the workers in the study from exposure data in their health-physics files. First, effective plutonium intake had to be calculated and then a dose equivalent was calculated. The software CINDY (code for internal dosimetry) was used to calculate internal doses. The sources of input data for the calculations are urine bioassay and lung count data. The subject's records for accidents and exposure incidents and with records of periodic analyses of urine for plutonium and lung counting were reviewed to determine an effective intake date based on either the date of a dominant exposure incident or the midpoint of the exposure period, whichever was appropriate. Once the date was determined, the urine bioassay data and lung count data were entered into CINDY to determine the amount of effective plutonium to take. The CINDY program calculates organ doses as equivalent doses and a whole-body dose for each calendar year of employment for each subject. Many organs are considered, but inhalation is usually the major route of exposure and the dose to the lungs is typically the highest (19, 33).

In addition to calculating plutonium lung doses for each of the subjects, smoking histories were collected by contacting next-of-kin. Other factors were considered for each subject such as date of hire, date of termination, date of birth, data of death (if applicable), and external gamma radiation as well as exposure to many other chemicals. The Rocky Flats employee roster was then created and contains approximately 23,000 employees (4, 27). A subset of 900 employees was used in this analysis.

2.2 Sampling

The sampling scheme for this study was developed by Brown (4, 27) and the subjects used in her analysis were also used in this analysis. Cases had to meet the following selection criteria: a positive diagnosis of primary lung cancer as specified on a death certificate and having worked at least 6 months at Rocky Flats between January 1, 1952 and December 31, 1989. There were 180 cases identified using the above criteria.

Controls were selected using incidence density sampling. This sampling scheme identifies controls from the risk set at the time of death of each case. Age at diagnosis was used as the time variable to select controls because age is a strong risk factor for most cancers. The risk sets were defined by Brown (4, 27) as follows: Employment at Rocky Flats for at least 6 months between January 1, 1952 and December 31, 1989, gender, date of birth within 2.5 years of the case, control started work at a younger age than that of the case, and control must be alive at the age of death of the case. By setting these criteria, subjects who become cases can be included in the risk sets of other cases who died at a younger age. Seven hundred and twenty controls were matched to cases of which 66 were subjects selected more than once. This created a case-control study with 1:4 matching. (4, 27)

In incidence density sampling, incident cases are compared to controls chosen at random on times of age at diagnosis. A case-control study with incidence density sampling requires the use of all of the numerator data (cases) and takes a matched, random sample from the denominator (controls) as the cases occur. The odds ratio based on incidence density sampling is a good estimate of an incidence density rate ratio (26). A more detailed explanation follows.

Let *a* represent the number of cases in the cohort, let *c* represent the number of non-cases in the cohort, let T_1 represent the sum of the case person-time in the cohort, and let T_0 be the sum of the non-case person-time in the cohort. Person-time is the sum of the individual units of time that the persons in the study population have been exposed to the exposure of interest. The numerator data are the cases and the denominator data are the controls. The rate ratio is

$$\text{Rate ratio} = \frac{a/T_1}{c/T_0} = \frac{a/c}{T_1/T_0}$$

The numerator of the final quotient represents the odds of dying of lung cancer in the cohort and the denominator represents the ratio of case person-time to control person-time in the cohort. The rate ratio quantifies the ratio of cases to controls after adjusting for time.

2.3 Logistic Regression

Logistic regression is a technique used to model the outcome of a binary variable, e.g. failure, with one or more predictor variables. It is used to model the probability of failure in unmatched case-control studies.

Define the random variable, Y: Y=1 if a subject is a case, Y=0 if a subject is a control and the predictor variables are defined as x. In logistic regression, as in any other regression technique, the goal is to find the best fitting biologically reasonable model to describe the relationship between an outcome, the dependent variable Y and a set of independent predictor variables $\mathbf{x} = x_1, x_2, \ldots, x_p$, known as the covariates. In any regression model the important quantity is the conditional mean of the response variable given the predictors. In logistic regression, this quantity is denoted $\pi(\mathbf{x}) = E(Y \mid \mathbf{x}) = P(Y = 1 \mid \mathbf{x})$ and the specific form of the regression model is

$$\pi(\mathbf{x}) = \frac{e^{\beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p}}{1 + e^{\beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p}}$$

The quantity $g(\mathbf{x}) = \log \dfrac{\pi(\mathbf{x})}{1 - \pi(\mathbf{x})}$ is the log odds of becoming a case given the predictor variables x. It is easy to see that $g(\mathbf{x}) = \beta_0 + \ldots + \beta_p x_p$. Notice that g($x$) is linear in its parameters and has range $-\infty$ to ∞. This means that the model is estimating β_i, which is the log odds ratio and parameter in the model associated with an change in one unit of exposure.

In order to estimate the parameters, assuming a univariate exposure $\hat{\mathbf{a}}$=(β_0, β_1) suppose we have a simple random sample of n cases and a simple random sample of m controls. Let π_0= P(sampled | case) and let π_1 = P(sampled | control) and note that π_1 and π_0 do not depend on the exposure x because cases and controls were sampled independent of exposure. Let the case exposures be $x_{01}, \ldots, x_{0n}$ and the control exposures be $x_{11},\dots,x_{1m}$. The likelihood function of **â** can then be denoted

$$\prod_{i=1}^{n} P(case \mid sampled \cap x_{0i}) \prod_{j=1}^{m} P(control \mid sampled \cap x_{1j}).$$

By using Bayes' Rule it is seen that we now have

$P(case \mid sampled \cap x_{0i}) =$

$$\frac{P(sampled \mid case \cap x_{0i})P(case \cap x_{0i})}{P(sampled \mid case \cap x_{0i})P(case \cap x_{0i}) + P(sampled \mid control \cap x_{0i})P(control \cap x_{0i})}$$

$$= \frac{\pi_1 P(case \mid x_{0i})}{\pi_1 P(case \mid x_{0i}) + \pi_0 P(control \mid x_{0i})}$$

This is because $P(sampled \mid case \cap x_{0i}) = P(sampled \mid case) = \pi_1$ given that sampling is independent of exposure.

By using the logistic model:

$$P(case \mid x_{1i}) = \frac{e^{\beta_0 + \beta_1 x_{1i}}}{1 + e^{\beta_0 + \beta_1 x_{1i}}} \text{ and } P(control \mid x_{0i}) = \frac{1}{1 + e^{\beta_0 + \beta_1 x_{0i}}}$$

$$P(case \mid sampled \cap x_{1i}) = \frac{\pi_0 e^{\beta_0 + \beta_1 x_{0i}}}{\pi_1 + \pi_0 e^{\beta_0 + \beta_1 x_{0i}}} = \frac{e^{\beta_0 {*} + \beta_1 x_{0i}}}{1 + e^{\beta_0 {*} + \beta_1 x_{0i}}} \text{ where } \beta_0^{*} = \beta_0 + \log\frac{\pi_0}{\pi_1}.$$

Therefore the likelihood function is $l = \dfrac{\prod_{i=1}^{n} e^{\beta_0 {*} + \beta_1 x_{1i}}}{\prod_{i=1}^{n}(1 + e^{\beta_0 {*} + \beta_1 x_{0i}}) \prod_{j=1}^{m}(1 + e^{\beta_0 {*} + \beta_1 x_{0i}})}$

The principle of maximum likelihood states that we use as the estimate of **â** the value which maximizes the above expression. To estimate the parameters **â** it is easier to use the log of this expression, which is called the log likelihood function and is defined as

$$L = \ln[l(\beta)] = \sum_{i=1}^{n} \ln(e^{\beta_0 {*} + \beta_1 x_{1i}}) - \sum_{i=1}^{n} \ln(1 + e^{\beta_0 {*} + \beta_1 x_{1i}}) - \sum_{j=1}^{m} \ln(1 + e^{\beta_0 {*} + \beta_1 x_{0i}})$$

$$= \sum_{i=1}^{n} \beta_0^* + \beta_1 x_{1i} - \sum_{i=1}^{n} \ln(1 + e^{\beta_0^* + \beta_1 x_{1i}}) - \sum_{j=1}^{m} \ln(1 + e^{\beta_0^* + \beta_1 x_{0i}}).$$

From this, there will be likelihood equations that are obtained by differentiating the log likelihood function with respect to the coefficients and setting the partial derivatives equal to zero.

2.4 Conditional Logistic Regression

Conditional logistic regression is used to estimate risk in matched case-control studies. Think of each case to be in a stratum, so that there are i strata, with m controls matched to each case.

To begin the discussion, let x_1 be the case exposure and let $x_{01},\ldots,x_{0m}$ be the control exposure in the i^{th} stratum. The likelihood contribution to the likelihood function from the i^{th} stratum is

$$l_i = \frac{P(case \mid x_1)}{P(case \mid x_1) + \sum_{j=1}^{m} P(case \mid x_{0j})}$$ and using the logistic model from earlier,

$$P(case \mid x_1) = \frac{e^{\beta_0 + \beta_1 x}}{1 + e^{\beta_0 + \beta_1 x}}$$ and the likelihood function is seen to be

$$l_i \approx \frac{e^{\beta_0 + \beta_1 x}}{e^{\beta_0 + \beta_1 x} + \sum_{j=1}^{m} e^{\beta_0 + \beta_1 x_{0j}}} = \frac{1}{1 + \sum_{j=1}^{m} e^{\beta_1 (x_{0j} - x_1)}}.$$

The model coefficients and resulting odds ratios have the same interpretation as unconditional logistic regression. The conditional regression model was used to determine if there is a higher risk of mortality from lung cancer from being exposed to plutonium and other risk factors for all subjects in the 1:4 matched case-control study.

2.5 Definition of Exposure Metrics

The four routes by which plutonium enters the human body are ingestion, inhalation, absorption through unbroken skin, and direct injection into body tissue. The second method, inhalation and subsequent absorption into the lung will be the main focus of exposure. The Rocky Flats roster, containing exposure records on all employees, has been used in analyzing the risk of lung cancer from plutonium where cumulative lifetime dose was used as the main exposure metric (4, 27). Because the cumulative dose received by the employees at Rocky Flats is generally small (compared, for example, to Mayak facility workers (18)), it seems reasonable to look at other measures of internal lung dose to understand the relationship of plutonium exposure and the risk of dying from lung cancer. It is also reasonable to investigate the intensity of exposure; an intense dose may have different effects on the lung as compared to small doses over a period of time. The new exposure metrics aim to quantify intensity and identify increased risk of dying from lung cancer. These include the average lifetime dose, maximum annual dose, and number of years with an above zero dose.

The average lifetime dose is equal to the lifetime cumulative dose divided by the number of years employed at Rocky Flats. This metric quantifies a measure of intensity by looking at the dose and the duration of employment. A larger average dose can indicate that the subject worked for a shorter period of time and received an elevated exposure. The maximum annual dose attempts to determine the intensity of the doses received by a subject because it quantifies the one-time maximum dose that was received during employment at Rocky Flats. If the maximum dose is large, then it can be concluded that it was an intense dose and may increase the risk of dying from lung cancer. If the number of years with an above zero dose is large then it can be a way to understand how long they were exposed to plutonium and the intensity of the dose can be determined by studying the amount of plutonium to which they were exposed. A low number of years with an above zero dose and a large cumulative lung dose might indicate the subject had an intense dose of plutonium to the lung. Another method of measuring intensity of exposure is the number of fires to which an employee was exposed. There were many fires and explosions at Rocky Flats during its operation which can contribute to the intensity of exposure (12).

2.5.1 Cumulative Internal Lung Dose

Brown (4, 27) used the cumulative lifetime dose as a measure of dose to the lung. First, effective plutonium intake had to be calculated and then a dose equivalent was calculated. To calculate internal doses, the software CINDY (code for internal dosimetry), developed at Rocky Flats, was used. The CINDY program calculates organ doses as equivalent doses and a whole-body dose for each calendar year of employment for each subject. Many organs are considered, but inhalation is usually the major route of exposure and the dose to the lungs is typically the highest (19, 33). To calculate the cumulative lifetime dose, the exposures were lagged by 10 years. Since the effects of radiation cannot be seen immediately, the dose was lagged by a certain number of years preceding the case's death. The doses were lagged by 10 years prior to the case's death and were calculated by finding the age of the case 10 years prior to death and then excluding the doses in that age period for the controls matched to the case. The cumulative lifetime dose is then calculated by adding all of the annual internal lung doses calculated using the CINDY software until the age of the subject at the time of the case's death the subject is matched to minus 10 years. This can be described mathematically as weighting the exposures received in the lag period by zero, while weighting other exposures by unity (23). A cumulative measure of exposure is commonly used in studies to evaluate the effects of long-term exposures (17,18, 25). Usually, larger cumulative exposures are associated with larger observed effects. With this knowledge, a measure of cumulative exposure offers a way to simplify a potentially complicated exposure history (23).

2.5.2 Average Lifetime Internal Lung Dose

Internal lung doses received by the subjects during their employment may have happened all at once giving a large one-time exposure, over a long period of time, or for only a portion of their employment. If receiving an internal dose increases a subject's risk of lung cancer, the average dose over the subject's employment could be studied to see if the risk increases as the average internal dose increases. As the average dose increases it could mean that duration of employment was shorter, indicating a more intense dose. The average internal lung dose used in the analysis was calculated as the cumulative dose divided by the number of years with a positive dose.

All annual doses were recorded for each subject throughout the study. Also recorded was the year in which a subject was hired and a year for which each subject was terminated. These were used to calculate the number of years employed at Rocky Flats. After that was determined, the number of years a subject had a positive annual internal lung dose was used to measure the amount of time a subject was exposed. The average dose was then computed by taking the total lifetime internal lung dose divided by the number of years with a positive dose. The total lifetime dose was lagged by 10 years which means that the doses obtained from exposure 10 years prior to the matched case's death are not included in the total lifetime dose. Since the total lifetime dose is lagged by 10 years, the total number of years with a positive dose may be shorter than the true amount of time they were exposed and the lifetime dose used may be smaller than the actual total dose they received in their lifetime.

2.5.3 Maximum Annual Internal Lung Dose

The maximum annual dose was used in this analysis because it is thought that the intensity of the lung dose may be an important factor as well as the duration of dose throughout employment. Since it is a one-time dose measurement, a very high dose indicates that a subject was exposed to a large amount of plutonium at one time. Being exposed to a large amount of plutonium at one time could affect the subject's health in a different way than being exposed to a small amount of plutonium over a long period of time.

In order to understand how this metric was calculated, it is important to understand how the plutonium doses were recorded for each subject wile employed at Rocky Flats. Each subject had a recorded monthly dose (calculated by CINDY). The doses were then added to create a yearly dose for each subject. The maximum annual dose was taken to be the maximum annual cumulative dose while the employee was in the dose period. The number of years a subject was exposed not including the years that were 10 years prior to the matched case's death is referred to as the "dose period." The maximum annual dose is a one-time annual dose that each subject received while employed at Rocky Flats.

2.5.4 Number of Years with a Positive Internal Lung Dose

When looking at the relationship between the exposure to plutonium and the risk of mortality from lung cancer in the Rocky Flats cohort, it is important to notice that the doses received by the subjects in the case-control analysis are lower than previous studies (Mayak workers) reporting a higher risk if exposed to plutonium. Since the doses are so small, as compared to other occupational studies (18), this may contribute to the results obtained when using the cumulative internal lung dose as a measure of exposure. It is reasonable to believe that if a subject received a dose spread out over a long period of time, this could increase their risk of lung cancer as compared to people who did not receive an internal lung dose while employed at Rocky Flats.

All annual doses were recorded (or created using dosimetry techniques) for each subject throughout the study. Since the effects of plutonium are not seen immediately, the doses received 10 years prior to the case's death are not counted in identifying how many years each subject had a positive dose. The number of years a subject was exposed not including the years that were 10 years prior to the matched case's death was found and is referred to as the "dose period." After identifying the years each subject was in the "dose-period", the number of years each subject had a positive dose were counted and became another measure of exposure.

2.5.5 Exposure to Fires

Plutonium is pyrophoric (ignites in the presence of oxygen) and plutonium workers have to take extra precautions when handling the substance. While Rocky Flats was in operation, there were two documented fires (12, 29). It is believed that the inhalation of hot alpha-particles may have a greater effect on the lungs than other alpha-particles (33). Since Rocky Flats workers were exposed to these hot particles, their risk of mortality from lung cancer may be increased.

The fires were in 1957 and 1969. The 1957 fire is well documented and workers' dose data was recorded to be used to see if the risk of mortality of lung cancer is evident. The 1957 fire occurred in building 771 on the Rocky Flats property. Though the 1969 fire was not documented as well (workers in that fire were not studied), it is known that the fire occurred in building 776.

The building that each subject worked in while employed at Rocky Flats was recorded. If employees worked at multiple buildings during their employment, each building was recorded for the year that they worked in the building. Since it is believed that plutonium's effect on the tissue of the lung does not happen instantaneously, each subject's building was only looked at 10 years prior to the case's death.

The variable was created by looking at the employment history and seeing if they were employed in 1957 or 1969. If they were, the building(s) where they worked were studied. If an employee worked in 1957 in building 771 or worked in building 776 in 1969, they were recorded as being in a fire. Either a worker was in no fires, one fire, or two fires. There were no cases exposed to fires, so no analysis was done. The numbers of cases and controls exposed to fires is shown in table 2.6.1.

Table 2.6.1 Number of cases and controls exposed to fires

Model Variables	Cases (n=180)	Controls (n=720)
	n	n
Number of fires exposed to (categorical)		
One	0	4
Two	0	1

2.6 Age and Its Effects on Exposure

2.6.1 Age as a Main Effect

Stewart and Kneale (16) have stressed the importance of analyses that examine the effects of age at exposure in occupational studies of the effects of radiation. People experience physiological changes with age which may lead to changes in sensitivity to many kinds of radiation exposure. In situations of prolonged, low-level exposure, differences in the effects of exposures received at different ages require examination of the effects of different age patterns of exposure (23). Age has been used to understand several relationships and to match the subjects when sampling in this study. It was also analyzed to understand the effects it might have on exposure.

As a main effect, age was used as one of the criteria to match cases and controls when sampling subjects for the case-control study. This is because the risk of cancer increases with age regardless of exposure and to estimate excess risk, one does not want the analysis to reflect the presence or absence of the disease and have it be attributable to a difference in age when a difference in exposure is what is of interest. The sampling scheme of this study addresses these concerns and was used in the models in the analysis of excess risk. Prior case-control studies of radiation workers have matched on age to control its effects on the outcome (4). The subjects were matched on age, in an attempt to control for its main effect, and age-specific lung dose categories modeled exposure to control for age as an effect-modifier.

2.6.2 Age as an Effect Modifier

When using the annual lung dose for employees at Rocky Flats as a measure of exposure to determine if exposure to plutonium increases the risk of mortality from lung cancer, it is important to take into consideration when the doses were received. The human body changes as it gets older and understanding the effect of age and the exposure to plutonium becomes of interest. The human body may not be able to defend itself against foreign bodies as it ages. Consequently, aging may be an important modifier of the effects of exposure and it is interesting to examine the cumulative exposure and the different effects when received at different ages. Using age-specific categories to determine at what age and how much plutonium was received can determine the relationship between the subject's exposure and their risk of cancer.

As adults age, they experience declines in lung function and have decreased physical and cellular repair processes (16, 23). Knowing the amount of plutonium subjects were exposed to in specific stages of life will give insight as to whether or not there is increased risk as a person ages. Being exposed earlier in life might have a different effect on the exposure compared to being exposed later in life. Prior research suggests understanding the effects of age for employees with prolonged, low level exposure to radiation controlling for age with age-specific dose categories and examining the effects on age (23). The age-specific-lung dose categories for the Rocky Flats employees will address this.

All annual doses were recorded in addition to the year in which the dose was received. By knowing the year in which each exposure was received, the age at which each exposure was received can be determined by subtracting the year of birth. This was done to get all subjects' ages when they were exposed to plutonium. The total lung dose at each age was recorded and then used to calculate how much each subject received in their twenties, thirties, forties, and fifties. The doses received in their twenties and thirties were included in one group. This created three categories for the age-specific internal lung doses. After age was categorized, the doses were added together to create a total for each subject in the above-mentioned, age-specific categories. This method was introduced by Richardson and Wing (23) and can be explained mathematically using a step function. The following equation describes a weighting function in which exposures received before a critical age c are set equal to zero and exposures received after that age are weighted by unity.

$$\text{Weight} = 0 \quad \text{if age} < c;$$

$$\text{Weight} = 1 \quad \text{if age} \geq c$$

The cumulative exposure at any age is the sum of the weighted exposure received up to that age. To study a dose response relationship in each of the age-specific categories, the age categories were divided into dose categories for each age group based on the quartiles for each age group and can be seen in table A1.

CHAPTER 3

ANALYSIS

3.1 Exposure Metrics

Three alternative exposure metrics were created to better understand the risk of internal lung exposure and mortality from lung cancer. These are: average annual internal lung dose, maximum annual internal lung dose, and the number of years each subject had an internal lung dose above zero. In S. Brown's study (4), two control subjects were deleted from the analysis due to their increased cumulative dose. The two control outliers had high cumulative lifetime doses of 2693.207 cSv and 4270 cSv. In this study they were included, which can be seen with 180 cases and 720 controls included in the analysis. Descriptive statistics reported in table 1 report the medians as well as the means and it is seen that the doses are skewed. Each of these exposure metrics was modeled in its continuous form and then broken into categories based on quartiles. The highest average annual dose category was split into two categories later in the analysis and that is what is reported in table A1. Controls have a higher cumulative dose than that of cases. A similar result is seen for the average and maximum dose. Controls also have a greater average number of years with an above zero dose.

Ninety-three cases and 386 controls had a cumulative lung dose of zero. Therefore, these same subjects had a maximum internal lung dose of zero, an average dose of zero and the number of years with an above zero dose equal to zero. Two controls had an unknown hire date and the variable created using that information, the average annual internal lung dose and the number of years with an above zero dose, were affected. The age at which that subject was first exposed was used to help determine the number of years in which they were exposed. Therefore, using the age at first exposure, the year of first exposure could be determined. With that, the number of years a subject had a positive dose could be determined for every subject as well as the average dose for every subject.

3.2 Age and Age-Specific Cumulative Internal Lung Dose

The age-specific categories measuring cumulative internal dose for that age period for each subject were first looked at for each subject to measure the amount of internal lung dose received in their twenties, thirties, forties, and fifties. There were relatively few subjects who were exposed in their twenties, so the doses received in their twenties and thirties were grouped together. The categories, with means and medians, can be seen in table A1. In each of the age-specific categories, internal lung dose was divided into groups and categorized into three categories. The dose categories with in the age-specific categories are reported in table A1 and it is seen that the categories of dose are not the same in each of the age-specific categories. This is because there were an unequal number of subjects in the age-specific categories and dose was divided making somewhat equal groups in each of the dose categories. Controls had a higher average than cases in each of the age-specific categories and the averages increased, for both cases and controls, as age increased. Exposures were greater when the subjects were older and categorizing the doses aids in determining if there is an increasing trend in risk associated with an increase in dose and age.

3.3 Smoking Data

Smoking has been known to increase the risk of mortality from lung cancer and it is necessary to use the number of years each subject smoked and how much each subject smoked as one of the covariates in determining the risk. Smoking was measured in pack-years where 1 pack-year is defined as smoking 1 pack of cigarettes per day per year. Smoking histories were collected on 123 cases and 605 controls. The other subjects had missing smoking histories and the analysis including smoking as a risk factor might not be accurate since subjects had missing data. A matched analysis on the data only uses the subjects in the stratums where all subjects have data and the missing smoking data poses a problem because not all subjects are used in the analysis. Breaking the matching in a case-control study results in an underestimation of risk because age, a well-known risk factor for cancer, is no longer controlled for in the analysis. An effort was made to impute smoking status for these subjects to be able to use all of the subjects in the full 1:4 matched study where age is controlled for. Additionally, smoking may modify exposure and the subjects who were smokers were analyzed to understand the relationship between smoking and exposure.

3.4 Additional Risk Factors

Several other variables were considered to be potential confounders in understanding the risk of mortality of lung cancer and exposure to plutonium. Previous studies on the Rocky Flats employees have determined these variables and can be seen in table A2. These variables are age at first internal plutonium lung dose, period of first hire, external penetrating radiation, and smoking. Only subjects that had an above zero lung dose had the age at first exposure variable defined. Period of first hire was also included in the models because as time has progressed, knowledge of the hurtful aspects of exposure to radiation became more apparent. This variable was then broken into categories to understand risk for employees hired early in the plant's history. External penetrating radiation is used to determine excess risk because gamma-rays are known to cause biological damage (18).

Variables were first analyzed with univariate comparisons to test for any significant associations with the outcome, and were modeled as continuous and categorical. Age at first exposure was modeled as continuous as was duration of employment. The continuous form of these variables was determined to be the best fit in previous studies (4). Period of hire was modeled as categorical with the fourth period of hire as the reference group because the data indicate that the risk of lung cancer drops significantly for workers hired after that time (4). The categories were determined by using the quartiles of the variable. External penetrating radiation was also modeled as a categorical variable in order to see if there was a positive dose-response relationship. After the subjects who did not have any external penetrating radiation were determined, the remainder of the subjects were split into two groups. These categories were used in other epidemiological studies (4). Having no external penetrating radiation was used as the reference group to determine if there was increased risk with increased radiation. Variables for the final models were chosen based on either significant odds ratios and p-values or changed the main effect (plutonium lung dose) by more than 10%.

CHAPTER 4

RESULTS

4.1 Average Lifetime Exposure

When using lifetime average exposure as the exposure metric, the univariate analysis shows that exposure, when modeled as continuous or categorical, is not associated with elevated risk of lung cancer. The results are presented in table A3.

Using the different variables to measure internal lung dose, models were defined using other covariates associated with death from lung cancer and are as follows: external penetrating dose (cSv), duration of employment (years), age at first exposure (years), year of hire (years), and smoking (pack-years). Conditional logistic regression in SAS produced the output associated with average lifetime internal dose and the outcome, death from lung cancer.

The conditional logistic regression model showed that the average lifetime internal lung dose, when modeled as continuous or categorical, was not significantly associated with the outcome. When using the average lifetime internal lung dose as a measure of exposure, with additional risk factors in the model, having an average internal dose in the 4th category significantly increases risk by a factor of 2.8 compared to having a zero average dose of plutonium. Being hired in the period between 1960 and 1967 increased the risk by a factor of 2 as compared to someone hired in the period 1968-1989. Duration of employment was protective against death from lung cancer. The above results can be seen in table A4.

In table A5, the results of the multivariate analysis with the average lifetime exposure metric and smoking data are reported. Some of the subject's smoking data is missing and not all of the subjects in the study were included in the matched analysis. Having an average dose in the third category significantly increased the subject's risk by a factor of 2.7. The third period of hire increased the risk and duration of employment is protective. Having a pack-years value in the highest category, increased the subject's risk by a factor of 2.2.

There is a positive dose response relationship and the highest odds ratio occurs in the fourth category (2.257-4.415 cSv/yr) and then decreases if the average is higher than that. This can be seen in the univariate (table A3) and multivariate analysis (tables A4 and A5). Alone, the average lifetime cumulative dose cannot statistically predict death from lung cancer, but when used with other risk factors, having an average dose between 2.257 and 4.415 cSv/yr. significantly increases risk. Having a dose larger than that does not significantly increase risk and a negative trend is observed. This can be due to the fact that if the average is higher, they might have been employed longer and a reasonable conclusion is that the non-linear relationship may be the result of the "healthy worker" effect.

4.2 Maximum Lifetime Exposure

The maximum lifetime internal lung dose was modeled as a categorical variable using five categories, one of which is having a maximum of zero cSv which is considered the baseline because these subjects were not exposed to plutonium. In table A6, it is seen that when modeled continuous or categorical, the maximum lifetime internal lung dose of plutonium is not associated with mortality from lung cancer. Several models with additional risk factors were used to determine the associated risk of exposure to plutonium. The first model (table A7 that includes the maximum lifetime dose, external penetrating radiation, period of first hire, and duration of employment) was significantly associated with the outcome. Being hired between 1960 and 1967 increased the risk by a factor of 2 as compared to being hired between 1968-1989. Duration of employment was shown to be protective. When adding age at first exposure and dropping external penetrating radiation to the model, it is seen in table A8 that the third period of hire increased the risk by a factor of 3 and duration of employment was protective. When dropping age at first exposure from the model as seen in table A9, the third period of hire increased risk by a factor of 1.9 and duration was again protective. In table A10, using the maximum internal dose and duration of employment as covariates, it can be seen that the fourth category for maximum annual dose increases the risk by a factor of 1.8 and duration of employment is protective.

In table A11, the results of using the maximum annual dose as the exposure metric and including pack-years are reported. Exposure is not related to the outcome, but the third period of hire increased risk by a factor of 2, duration of employment is protective, and the highest category of smoking increased the risk by a factor of 2.2.

The risk of death from lung cancer is elevated when using the maximum dose as the predictor, though it is not statistically significant. This can be seen in tables A6-A11. In table A6, the exposure is modeled in a univariate analysis and exposure is not related to risk. In table A7, a nonlinear trend is present in the maximum annual dose categories. When controlling for age, an increasing trend is observed in table A8. No category of this exposure metric was statistically associated with risk, except in the model only using the maximum annual lung dose and duration of employment as the covariates. In this model, table A10, the highest maximum value significantly increased risk by a factor of 1.8. A reason for this could be due to the fact that the employees were not exposed to very high amounts of plutonium and that their maximum dose was not large either having only the highest category increase risk. The doses received by the employees at Rocky Flats were smaller than other radiation workers exposed to plutonium and would not give a large maximum dose (17). Therefore, very intense doses were not seen and it would be difficult to quantify significant risk.

4.3 Number of Years of Positive Exposure

Table A12 presents the univariate analysis using the number of years with a positive dose as the exposure metric. When modeled continuously, the exposure is protective and not associated with the outcome when modeled categorically.

Using the number of years with a positive dose as a measure of internal lung dose the age at first exposure was used to create the exposure metric so it is not in the models used to understand the relationship between the number of years a subject had a positive dose and the risk of mortality from lung cancer. When modeled as categorical, two models are significantly associated with the outcome. Table A13 presents the first model using the five categories, and including external penetrating dose, period of first hire and duration of employment, showed that having one to five years with a positive lung dose increased the subject's risk by a factor of 1.6 compared to not having any years with a positive dose and having a positive dose between 11 and 14 years increased risk by a factor of 2. Being hired between 1960 and 1967 increased the risk by a factor of 1.9 compared to those hired between 1968-1989. Duration was found to be protective.

When dropping external penetrating dose from the model having a positive dose between one and five years significantly increased the risk by a factor of 1.6 and having a positive dose for ten to fourteen years increased the risk by a factor of 2.1. Again, being hired between 1960 and 1967 increased the risk by almost a factor of 2 and duration of employment was protective. These results can be seen in table A14.

Table A15 presents the results of using number of years with a positive dose as the exposure metric and including period of first hire, duration of employment, and smoking data. In this model the third category, having a positive dose from 10-14 years increased the risk by a factor of 1.9, duration of employment was protective and smoking the most increased the risk by a factor of 2.2.

An interesting non-linear trend in the odds ratios for the exposure metric is presented in tables A12-A15. A subject who is in the highest category (more than 14 years) has a decreased odds ratio than a subject in the third category (11-14 years). Another interesting finding is that the first category (1-5 years) has a higher odds ratio than the second category (6-10 years). This might indicate that subjects had an intense dose early on in their employment and then decided to change jobs where there was no risk of radiation.

Dose was added to the model to investigate the effect of dose and the number of years with a positive dose. It can be seen in tables A16-A18 that controlling for dose in the model did change the odds ratios for number of years with a positive dose. In table A16 and A17, the number of years with a positive dose is no longer significantly related to mortality from lung cancer. However, a non-linear trend in the odds ratios is still present. This research primarily focused on alternative exposure metrics and further investigation of dose modifiers including duration of exposure is important and is recommended.

4.4 Age-Specific Exposure

By focusing on the second research question, age was looked at to see if the age of the subject was correlated with exposure. The matched variable, though matched to control for main effects, can have an association with exposure. The correlation coefficient between age and the exposure metrics were calculated, and age was not significantly correlated with any of the exposure metrics, including cumulative lifetime dose. The only significant correlation was with the number of years a subject had an above zero dose (ρ =0.21, p=0.0001). This is a reasonable result because the exposure metric, number of years with an above zero dose, was created using the age of the subject and the older you are the more years you have to collect exposures.

Using the age-specific categories in a univariate model showed no risk associated with the outcome. These results can be seen in table A19. Additionally, several multivariate models were created including one with cumulative external penetrating dose, period of first hire, and duration of employment. In this model (table A20), it can be seen that none of the dose covariates increased the risk of lung cancer. However, the third period of hire increased risk by a factor of 2 and duration of employment was found to be protective. Including smoking data in the model along with using the age-specific categories gave the results in table A21. It can be seen that the third period of hire increased risk by a factor of 2.2 and the highest category of smoking increased risk by a factor of 2.2. Duration of employment significantly decreased the risk of mortality from lung cancer. The models indicate that age does not interact with exposure and the age at which a dose was received is not an important factor to consider when understanding the risk of lung cancer in this case control study.

4.5 Smoking

In order to predict whether or not a subject smoked, a logistic model was used in an attempt to predict smoking (either did or didn't) based on several covariates to determine whether or not a subject smoked. However, using gender, job (either blue collar or white collar), chemical carcinogen exposures, exposure to plutonium, exposure to external gamma radiation, age at first exposure, and duration of employment, no model was found to find the probability of a subject being a smoker. It was then attempted to impute the number of pack-years in subjects with missing smoking data.

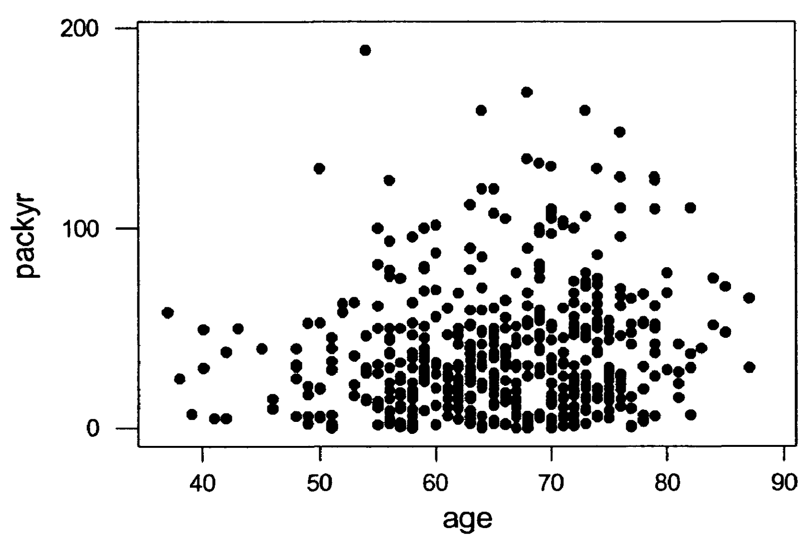
The primary interest was to understand if the pack-years value for the smokers (e.g. the subjects who had an above zero value for pack-years) had any relation to the other variables used to understand excess risk. If a relationship was present, a linear model would be built to predict the number of pack years for each of the subjects with missing data. There were 497 subjects with above zero smoking data recorded. The correlations of pack-years with other continuous risk factors can be seen in table 4.5.1.

Figure 4.5.1 Results of Correlations between pack-years and other risk factors

Variable	Correlation Coefficient	p-value
Age at First Exposure	0.018	0.724
Year of Death	0.100	0.025
Duration of Employment	-0.050	0.145
Year of First Hire	0.027	0.461
Age	0.129	0.004

Correlations between pack-years and the exposure covariates, external penetrating radiation, average lifetime dose, cumulative lifetime dose, number of years with a positive dose and the maximum annual dose, were calculated and it was found that pack-years was not significantly correlated with any of the exposure variables. However, pack-years was significantly correlated with age (ρ =0.129, p=0.004) and the year of death of the case (ρ =0.100, p=0.023). What is interesting to notice about the correlations is how loosely correlated pack-years is with the other covariates. The plots of pack-years with the other variables do not show a linear relationship. An example of this non-linear trend is seen in figure 4.5.2, the plot of pack-years versus age.

Figure 4.5.1 Pack-Years versus Age



Smoking was not significantly correlated with any of the covariates used to measure increased risk and a model could not be found that would be of use to simulate the missing smoking data.

Three t-tests were performed to understand if smoking was related to the number of fires an employee was exposed to, what job was performed (either blue collar or white collar), and gender. The results of the t-tests can be seen in table 4.5.2.

Table 4.5.2 Results of t-tests of pack-years with dichotomous risk factors

Variable	p-value
Number of Fires Exposed To	0.184
Job Performed	0.355
Gender	0.010

From table 4.5.2, it can be seen that pack-years is associated with gender. There is a significant difference between the men and women in relation to smoking. With this conclusion and the conclusions from the correlation coefficients, a linear model was attempted using gender, year of death and age as predictors, but no model (linear or otherwise) could be found that fit the data and significantly predicted pack-years.

Because the purpose of trying to simulate the data was to understand if smoking is a confounding variable and the data could not be simulated, seven one way analysis of variances (ANOVA) were conducted to try and understand if smoking is related to exposure. This analysis was also done only for subjects who were smokers. The exposure variables were external penetrating radiation, cumulative lifetime internal dose, the maximum annual internal dose, number of years with a positive internal dose, the average lifetime dose, and the age-specific cumulative internal dose covariates. Smoking was divided into four groups, based on the quartiles, and can be seen in table A2. The mean exposure in each group was calculated and the ANOVA process showed that there was no significant relationship between smoking and exposure. The results can be seen in figure 4.5.3 and there is no difference in exposures between the smokers and non-smokers.

Table 4.5.3 Results of ANOVA between pack-years and exposure covariates

Variable	p-value
External Penetrating Radiation	0.118
Maximum Annual Internal Lung Dose	0.290
Cumulative Lifetime Internal Lung Dose	0.212
Cumulative Dose Before Age 50	0.199
Cumulative Dose After Age 50	0.371
Number of Years with an Above Zero Internal Lung Dose	0.110
Average Lifetime Cumulative Dose	0.723

A univariate model for the 1:4 matched study was created using smoking as the predictor for mortality from lung cancer. The results, for both the continuous and categorical smoking data can be seen in table 4.5.4. From the table, it can be seen that smoking, in its continuous form, does increase the risk of mortality from lung cancer. When modeled categorically, the first, third and highest categories all increase risk by 2.1, 8.2, and 5.5 times, respectively. The second category, smoking between 19 and 25.5 pack-years, does not increase the risk. This could be used to conclude that the smoking data is not accurate since there is not a strong increased risk with increased smoking.

Table 4.5.4
Univariate Analysis: Smoking

Variable	Cases	Controls	Odds Ratio	95% CI
	N	n		
Smoking (Continuous)	180	720	1.018	1.013, 1.024
Smoking (Categorical)				
0	18	213	1.00	
1-19	26	142	2.141	1.130, 4.055
19+ - 25.5	11	146	0.815	0.370, 1.798
25.5+ -43	72	98	8.236	4.654, 14.573
43+	53	117	5.530	3.066, 9.975

An argument can be made to conclude that the smoking data is not truly accurate and the reservations concerning the introduction of bias into the data are true. A strong conclusion about smoking being a confounder between exposure to plutonium and death from lung cancer cannot be established. The results are questionable in the univariate analysis because there is missing data and the data and a full1:4 matched analysis could not be performed. The data that is available might not truly represent the smoking habits of the subjects. Additionally, there was not an increasing trend in risk with increased smoking and that could help prove that the smoking data is not precise and bias is present.

4.6 Subjects with Bioassay Data

4.6.1 Bioassay Data and Exposure

Assuming that if urine deposit data was collected on a subject because of known exposure to plutonium, examination of those subjects should be considered to determine if they have an elevated risk of mortality from lung cancer. Summary statistics for the subjects with urine data is seen in table A22. There were 92 cases and 443 controls who had a urine test taken. It is important to study the subjects who have had urine tests and if they actually have a higher chance of being exposed. To do this, five t-tests were performed with the subjects who had urine data. Each subject had recorded a 1 if they had urine bioassay data collected and a 0 if they had not. Using this, the t-tests found that the subjects with urine data were significantly more likely to have been exposed using the number of years with a positive internal lung dose as the exposure metric ($t = 10.01$, $p = 0.001$). Therefore, if a person had a urine test, they were more likely to have a greater number of years of exposure. The other exposure metrics were not found to be significantly associated with the subjects who had urine data collected. The results of the t-tests can be seen in table 4.6.1. It can be seen that having bioassay data is related to the number of years with a positive internal lung dose.

Figure 4.6.1 Results of t-tests

Variable	p-values
External Penetrating Radiation	0.19
Maximum Annual Internal Lung Dose	0.09
Cumulative Lifetime Internal Lung Dose	0.11
Number of Years with an Above Zero Internal Lung Dose	0.001
Average Lifetime Internal Lung Dose	0.26

To further understand if there is a relationship between the outcome and having a urine test, a χ^2 test for a 2x2 table produced a $\chi^2 = 7.696 (p = 0.006)$. The 2x2 table can be seen in table 4.6.2. The χ^2 value indicates that there is a relationship between being a case or control and the presence of bioassay data. To verify this, a 2x2 table of case/control status and whether or not a urine test was taken to check to see if urine tests were different for cases and controls. It was shown that there was a significant difference among cases and controls and having a urine test. This can be seen in table 4.6.2.

Table 4.6.2 2x2 table of Outcome and Indicator for bioassay data

	No Urine Test	Urine Test Present
Control	263	443
Case	87	92

4.6.2 Matched Conditional Logistic Regression

Matched logistic regression was performed using an indicator variable for having a urine test/not having a urine test to predict risk. In the univariate model using the indicator variable, it is seen that having a urine test is associated with a decreased risk of mortality from lung cancer. The results can be seen in table A23. In the multivariate models using each exposure metric and the indicator variable for urine test, only having a urine test decreased the subjects' risk for lung cancer and being exposed did not increase risk. These results can be seen in tables A24-A26. An additional analysis was performed using the urine test as an indicator variable and controlling for exposure in a model to predict lung cancer in the matched study. In all the models, regardless of which exposure metric was used, having a urine test significantly decreased the risk of lung cancer. The explanation is that more controls had urine tests taken while employed at Rocky Flats.

4.6.3 Unmatched Logistic Regression

Using just the subjects who had urine data collected is a way to look at increased risk. Using the number of years with an above zero dose as the exposure metric (used because there is a significant difference among these subjects than non-urine tested subjects (table 4.6.1)) did not significantly predict the outcome in its continuous or categorical form (tables A27 and A28) when modeled univariately for this subset of subjects. Finding the best model to understand increased risk of these subjects, it was found that the model using the number of years with an above zero dose, modeled continuously, the period of first hire and age at first exposure was the best model. This was found using stepwise logistic regression. The results can be seen in table A28. The number of years with an above zero dose did not increase the risk of mortality from lung cancer in subjects with bioassay data, but age at first exposure increased the risk by a factor of 1.1. In tables A27-A28, the number of years with an above zero lung dose was not significantly associated with the outcome for these subjects and might indicate that the positive correlation is due to the fact that they worked there longer and were more likely to have a urine test taken.

4.7 Period of First Hire

In a majority of the models, the third period of hire from 1960 to 1967 significantly increased the risk of death from lung cancer. In order to understand why the group of subjects hired between 1960 and 1967 are at more risk, it was decided to investigate the variables that would be important in determining the risk. A χ^2 test for independence was performed among the categorical levels of the different covariates. This was done to find a relationship between the high-risk group (1960-1967) and the different categories of the variables that might contribute to an increased risk. Each table is given and the computed Chi-square and corresponding p-value is noted. All levels of significance are at the 0.05 level. The χ^2 values indicate a trend with duration of employment and external penetrating dose. These can be seen in tables A29-A35.

It is also important to understand if the averages in the above categories were different for the people in the high risk group and all others. The results obtained are given below.

Table 4.7.1 Results of t-tests between period of hire 1960-1967 and other risk factors

Variable	t-test
Number of Years with an Above Zero Internal Lung Dose	p=0.430
Duration of Employment	p=0.002
Smoking, measured in pack-years	p=0.541
External Penetrating Radiation	p=0.013
Age at First Exposure	p=0.325
Cumulative Internal Lung Dose	p=0.091
Maximum Internal Lung Dose	p=0.245

In a majority of the models, the third period of hire (1960-1967) significantly increased a subject's risk of lung cancer. This was also seen to be the case in previous studies of this cohort (4). Analysis was performed to try and see if there were specific reasons for the people hired during this period might have excess risk. The tables, A30 and A32, show that those subjects had a significantly different duration of employment and a significantly different external penetrating dose than the subjects hired in the other time periods. It can be concluded that the high-risk group had a shorter duration of employment and a larger external penetrating dose than the subjects hired at other times. A shorter duration of employment might imply that they are not being affected by the "healthy worker" effect and have an increased risk. In past studies (17, 18), external penetrating radiation increased mortality from lung cancer and since these subjects have a higher external penetrating radiation dose this might explain why they are at an elevated risk of lung cancer.

CHAPTER 5

SUMMARY

5.1 Alternate Exposure Metrics

Previous studies of radiation workers in other countries have shown an increased risk of lung cancer when using cumulative lifetime dose as the exposure metric and previous studies of Rocky Flats workers using cumulative lifetime internal dose have shown no increased risk. In answering research question (1), the alternate exposure metrics calculated and used to measure internal lung dose for the employees of Rocky Flats showed no increased risk of mortality from lung cancer. Many factors may have contributed to the absence of finding an increased risk of lung cancer using the alternate exposure metrics. First, the latent period of developing radiation-induced lung cancer may be as long as 30-40 years (32, 33, 34) and this study did not have a sufficient follow-up time to allow for this. Second, problems with historical exposure records and dose calculations may have lead to underestimation of the internal lung doses (4) and an increased risk of mortality could not be detected in any of the additional exposure metrics quantifying dose. Lastly, because doses for U.S. workers are lower than other radiation workers, more subjects are needed to detect an effect if one does exist. It would be interesting to use the alternate exposure metrics used here to quantify exposure in the previous studies and validate their use as adequate exposure metrics to measure the intensity of internal lung dose. Determining if intensity of dose is related to increased risk of cancer is interesting because the metrics might be easier to calculate than cumulative lifetime dose and will give insight as to whether or not receiving more radiation in a short period of time is somehow different than receiving doses over a lifetime.

5.2 Age-Specific Doses

Researchers (16) have stated that adjusting for age with exposure is necessary to determine if age changes the way radiation affects the human body. It is suggested that categorizing the doses within age groups can assist in determining the differences in exposures for certain age groups. This was done for the employees of Rocky Flats to determine if age is an effect-modifier. Age was found not to be an effect-modifier of exposure to plutonium and mortality from lung cancer in the 1:4 matched study. The age-specific categories showed no significant difference in risk. However, there was an increasing trend seen in the age-categories. This can be interpreted to mean that adjusting for age with exposure is not necessary and age is not an effect-modifier in this study and matching on age is sufficient to control age as a main effect. The analysis also showed that exposure is not significantly related to the outcome, but age is an important factor to consider. This is a similar conclusion when the doses were not categorized by age in previous studies on the Rocky Flats cohort (4, 17) and can be attributed to the doses being smaller than other radiation worker cohorts. It would be interesting to categorize the doses by age for radiation workers where exposure did increase risk of mortality from lung cancer to determine if age is a confounder between exposure to plutonium and death from lung cancer.

5.3 Smoking

To address research question (3) and to asses smoking as a confounder in cancer studies for radiation workers, the analysis showed that better estimates of smoking data need to be obtained before smoking, and its relationship to radiation exposure, can be fully understood. Using the smoking data that was available in this study did not give the best estimates of odds ratios for plutonium exposure since not all of the subjects would have been included in the analysis. Better estimates could have been provided had all of the subjects had accurate smoking data included. Using the subjects that did have smoking data showed that smoking was not a confounder, but it is recommended that for future studies including smoking histories for all subjects in a study would produce clearer results. In the matched-analysis, using the age-specific exposure categories, the odds ratios are better estimates than the other exposure metrics since age, a main-effect, is controlled for and all subjects with smoking data are used. Uncertainties associated with the smoking data exist and alternate methods of collecting smoking data might help decrease the bias in future studies. This is an open question and is left to further research.

APPENDIX

Table A1

Descriptive statistics of Exposure Metrics in Entire Study n=900

Variable	Cases n=180		Controls n=720	
	N	Mean / Median	N	Mean / Median
Cumulative lifetime dose	180	35.55 cSv / 17.62 cSv	720	63.15 cSv / 16.16 cSv
0 cSv	93		386	
0<-10cSv	33		127	
10<-40cSv	21		101	
>40cSv	33		110	
Age Specific Internal Lung Dose	180		720	
Lung dose in 20's and 30's		2.36 cSv / 0cSv		14.69 cSv / 0cSv
0 cSv	166		640	
0<-8.7 cSv	8		41	
>8.7 cSv	6		39	
Lung dose in 40's		10.55 cSv/ 0cSv		17.01 cSv/ 0cSv
0 cSv	129		498	
0<-28.5 cSv	31		152	
>28.5 cSv	20		70	
Lung dose in 50's and older		16.80 cSv/ 0cSv		42.73 cSv/ 0cSv
0 cSv	95		360	
0<-20 cSv	46		193	
>20 cSv	39		167	
Average Annual Dose	180	3.48 cSv / 2.51 cSv	720	6.65 cSv / 2.06 cSv
0 cSv/yr	93		386	
0<-0.6511 cSv/yr	19		84	
0.6511<-2.257 cSv/yr	22		84	
2.257<-4.415 cSv/yr	20		85	
4.415<-6.5 cSv/yr	11		27	
6.5 + cSv/yr	15		54	
Maximum Annual Dose	180	8.68 cSv / 5.10 cSv	720	12.39 cSv / 47.01 cSv
0 cSv	93		386	
>0 -0.85 cSv	16		67	
>0.85-4.70 cSv	23		89	
>4.7-12 cSv	23		90	
12 + cSv	25		88	
Number of Years with an Above Zero Dose	180	8.84 yrs / 8 yrs	720	10.34 yrs / 9 yrs
None	93		386	
1-5	34		102	
6-10	18		83	
11-14	20		59	
15+	15		90	

Table A2

Descriptive Statistics for the Rocky Flats Lung Cancer Case-Control Study 1:4 matching (10 yr lag)

	Cases n=180			Controls n=720		
	n	Mean		N	Mean	
Gender						
Male	173			692		
Female	7			28		
Vital Status						
Alive	0			501		
Dead	180			219		
Age at First Plutonium Lung Dose (years) Applies to subjects with nonzero lung doses only	98	48.4		412	46.9	
Employment Duration	180	11.6		718	13.9	
Period of First Hire	180	1961		718	1961	
1950-1953	38			186		
1954-1959	40			175		
1960-1967	64			175		
1968-1989	38			182		
External Penetrating Radiation (cSv)	180	0.15		718	0.12	
Smoking (pack-yrs)	123	39.72		604	22.79	
0	18			213		
1-12.75	21			108		
12.75+ - 25.5	20			97		
25.5+ -43	24			103		
43+	40			83		

Table A3
Univariate analysis and descriptive statistics: Average lifetime internal lung dose (10-year lag)

Model Variable	Cases (n=180)		Controls (n=720)		Risk Ratio	95%CI
	n	mean	n	mean		
Average dose (continuous)	180	3.48	720	6.55	0.978	0.931, 1.027
Average Annual Dose						
0 cSv/yr	93		386		1.0	
0<-0.6511 cSv/yr	19		84		0.875	0.502, 1.523
0.6511<-2.257 cSv/yr	22		84		0.994	0.575, 1.718
2.257<-4.415 cSv/yr	20		85		0.946	0.544, 1.645
4.415<-6.5 cSv/yr	11		27		1.708	0.799, 3.648
6.5 + cSv/yr	15		54		1.152	0.609, 2.178

Table A4
Multivariate analysis of average lifetime internal lung dose

Model Variables	Cases (n=180)	Controls (n=720)	Risk Ratio	95% CI
	n	n		
Average Annual Dose				
0 cSv/yr	93	386	1.0	
0<-0.6511 cSv/yr	19	84	1.071	0.602, 1.902
0.6511<-2.257 cSv/yr	22	84	1.645	0.886, 3.056
2.257<-4.415 cSv/yr	20	85	1.585	0.844, 2.974
4.415<-6.5 cSv/yr	11	27	2.832	1.248, 6.423
6.5 + cSv/yr	15	54	1.794	0.884, 3.640
Cummulative Penetrating dose (cSv)				
0	46	183	1.0	
0-0.5	120	495	0.920	0.618, 1.370
0.5+	14	40	0.959	0.463, 1.988
Period of first hire				
1951-1953	38	186	1.470	0.816, 2.646
1954-1959	40	175	1.442	0.822, 2.529
1960-1967	64	175	1.975	1.209, 3.227
1968-1989	38	182	1.0	
Duration of employment	180	720	0.957	0.934, 0.980

Table A5

Multivariate analysis of average lifetime internal lung dose with smoking data

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Average Lifetime Internal Lung Dose				
0 cSv/yr	93	386	1.00	
0<-0.6511 cSv/yr	19	84	1.025	0.570, 1.846
0.6511<-2.257 cSv/yr	22	84	1.541	0.819, 2.900
2.257<-4.415 cSv/yr	20	85	1.515	0.797, 2.881
4.415<-6.5 cSv/yr	11	27	2.719	1.175, 6.292
0 cSv/yr	15	54	1.614	0.996, 3.269
Period Of First Hire				
1951-1953	38	186	1.480	0.890, 2.676
1954-1959	40	175	1.456	0.822, 2.576
1960-1967	64	175	2.111	1.320, 3.901
1967-1989	38	182	1.00	
Durationof Employment	180	720	0.959	0.936, 0.983
Smoking				
0	18	213	1.00	
1-19	26	142	0.878	0.492, 1.565
19+ - 25.5	11	146	1.059	0.596, 1.884
25.5+ -43	72	98	0.747	0.405, 1.375
43+	53	117	2.167	1.392, 3.371

Table A6
Univariate analysis with descriptive statistics: Maximum lifetime internal lung dose (10-year lag)

Model Variables	Cases (n=180)		Controls (n=720)		OR (risk ratio)	95% CI
	n %	mean	n %	mean		
Maximum Annual Dose (continuous)	180	8.86	720	12.39	0.991	0.972, 1.010
Maximum Annual Dose (categorical)						
0 cSv	93		386		1.0	
>0 -0.85 cSv	16		67		0.887	0.479, 1.640
>0.85-4.70 cSv	23		89		0.992	0.598, 1.646
>4.7-12 cSv	23		90		0.942	0.552, 1.609
12 + cSv	25		88		1.145	0.684, 1.917

Table A7
Multivariate analysis of maximum annual internal lung dose

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Maximum Lifetime Internal Lung Dose (categorical)				
0 cSv	93	386	1.0	
>0 -0.85 cSv	16	67	1.088	0.578, 2.050
>0.85-4.70 cSv	23	89	1.439	0.823, 2.515
>4.7-12 cSv	23	90	1.757	0.926, 3.333
12 + cSv	25	88	1.773	0.997, 3.218
Cummulative Penetrating dose (cSv)				
0	46	183	1.0	
0-0.5	120	495	0.925	0.622, 1.376
0.5+	14	40	0.983	0.474, 2.040
Period of first hire				
1951-1953	38	186	1.413	0.786, 2.540
1954-1959	40	175	1.380	0.787, 2.419
1960-1967	64	175	1.907	1.170, 3.109
1968-1989	38	182	1.0	
Duration of employment	180	720	0.958	0.935, 0.982

Table A8
Multivariate analysis of maximum annual internal lung dose

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	N		
Maximum Lifetime Internal Lung Dose (categorical)				
0 cSv	93	386	1.0	
>0 -0.85 cSv	16	67	1.092	0.580, 2.055
>0.85-4.70 cSv	23	89	1.437	0.824, 2.504
>4.7-12 cSv	23	90	1.752	0.927, 3.312
12 + cSv	25	88	1.782	0.993, 3.200
Period of First Hire				
1951-1953	38	186	1.391	0.779, 2.483
1954-1959	40	175	1.369	0.784, 2.392
1960-1967	64	175	1.892	1.171, 3.056
1967-1989	38	182	1.0	
Duration of Employment	180	720	0.958	0.935, 0.981

Table A9
Multivariate analysis of maximum annual internal lung dose

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Maximum Lifetime Internal Lung Dose (categorical)				
0 cSv	93	386	1.0	
>0 -0.85 cSv	16	67	0.734	0.276, 1.952
>0.85-4.70 cSv	23	89	0.923	0.413, 2.061
>4.7-12 cSv	23	90	1.079	0.485, 2.398
12 + cSv	25	88	1.181	0.491, 2.412
Period of first hire				
1951-1953	38	186	2.140	0.614, 7.461
1954-1959	40	175	2.012	0.649, 6.236
1960-1967	64	175	3.094	1.221, 7.838
1968-1989	38	182	1.0	
Duration of employment	180	720	0.952	0.909, 0.997
Age at First Exposure	98	412	1.054	0.995, 1.118

Table A10
Multivariate analysis of maximum annual internal lung dose

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	N		
Maximum Lifetime Internal Lung Dose (categorical)				
0 cSv	93	386	1.0	
>0 -0.85 cSv	16	67	1.058	0.567, 1.975
>0.85-4.70 cSv	23	89	1.389	0.808, 2.388
>4.7-12 cSv	23	90	1.661	0.898, 3.071
12 + cSv	25	88	1.824	1.023, 3.253
Duration of Employment	180	720	0.958	0.937, 0.980

Table A11
Multivariate analysis of maximum annual internal lung dose with smoking data

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Maximum Lifetime Internal Lung Dose (categorical)				
0 cSv	93	386	1.00	
>0 -0.85 cSv	16	67	0.998	0.524, 1.901
>0.85-4.70 cSv	23	89	1.405	0.793, 2.490
>4.7-12 cSv	23	90	1.739	0.907, 3.334
12 + cSv	25	88	1.635	0.898, 2.979
Period Of First Hire				
1951-1953	38	186	1.428	0.791, 2.577
1954-1959	40	175	1.407	0.795, 2.491
1960-1967	64	175	2.052	1.250, 3.369
1967-1989	38	182	1.00	
Durationof Employment	180	720	0.959	0.935, 0.983
Smoking				
0	18	213	1.00	
1-19	26	142	0.876	0.492, 1.560
19+ - 25.5	11	146	1.052	0.591, 1.872
25.5+ -43	72	98	0.745	0.404, 1.373
43+	53	117	2.202	1.416, 3.424

Table A12
Univariate Analysis with descriptive statistics: Number of Years with a positive dose (10-year lag)

Model Variables	Cases (n=180)		Controls (n=720)		OR	95% CI
	n	mean	n	mean		
Number of Years with an Above Zero Dose (continuous)	180	8.84	344	10.34	0.951	0.909, 0.995
Number of Years with an Above Zero Dose (categorical)						
none	93		386		1.00	
1-5	34		102		1.287	0.818, 2.023
6-10	18		83		0.886	0.504, 1.557
11-14	20		59		1.349	0.769, 2.366
15+	15		90		0.617	0.329, 1.155

Table A13
Multivariate analysis of number of years with an above zero internal lung dose

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Number of Years with An above Zero Internal Lung Dose (Categorical)				
none	93	386	1.0	
1-5	34	102	1.619	1.003, 2.613
6-10	18	83	1.282	0.685, 2.399
11-14	20	59	2.044	1.068, 3.911
14+	15	90	0.951	0.468, 1.933
Cummulative Penetrating dose (cSv)				
0	46	183	1.0	
0-0.5	120	495	0.924	0.620, 1.376
0.5+	14	40	1.123	0.538, 2.343
Period of first hire				
1951-1953	38	186	1.463	0.815, 2.625
1954-1959	40	175	1.413	0.807, 2.475
1960-1967	64	175	1.960	1.198, 3.209
1968-1989	38	182	1.0	
Duration of employment	180	720	0.964	0.942, 0.988

Table A14

Multivariate analysis of number of years with an above zero internal lung dose

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Number of Years with an Above Zero Internal Lung Dose				
None	93	386	1.0	
1-5	34	102	1.615	1.001, 2.606
5-9	18	83	1.314	0.708, 2.439
10-14	20	59	2.076	1.093, 3.944
14+	15	90	0.979	0.468, 1.972
Period of First Hire				
1951-1953	38	186	1.463	0.808, 2.564
1954-1959	40	175	1.408	0.807, 2.458
1960-1967	64	175	1.964	1.212, 3.184
1967-1989	38	182	1.0	
Duration of Employment	180	720	0.964	0.941, 0.987

Table A15
Multivariate analysis of number of years with an above zero internal lung dose with smoking data

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n %	n %		
Number of Years with an Above Zero Internal Lung Dose				
None	93	386	1.00	
1-5	34	102	1.502	0.919, 2.454
5-9	18	83	1.245	0.663, 2.340
10-14	20	59	1.951	1.013, 3.756
14+	15	90	0.937	0.460, 1.911
Period Of First Hire				
1951-1953	38	186	1.474	0.818, 2.654
1954-1959	40	175	1.429	0.811, 2.518
1960-1967	64	175	2.096	1.275, 3.447
1967-1989	38	182	1.00	
Duration of Employment	180	720	0.965	0.942, 0.989
Smoking				
0	18	213	1.00	
1-19	26	142	0.952	0.532, 1.703
19+ - 25.5	11	146	1.067	0.601, 1.896
25.5+ -43	72	98	0.729	0.396, 1.345
43+	53	117	2.170	1.400, 3.365

Table A16
Adding cumulative lifetime dose to multivariate model with number of years with a positive dose.

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Number of Years with An above Zero Internal Lung Dose (Categorical)				
None	93	386	1.0	
1-5	34	102	1.036	0.326, 3.287
6-10	18	83	0.875	0.267, 2.871
11-14	20	59	1.277	0.372, 4.385
14+	15	90	0.638	0.168, 2.419
Cummulative Internal Lifetime Dose	180	720	0.998	0.994, 1.002
Cummulative Penetrating dose (cSv)				
0	46	183	1.0	
0-0.5	120	495	0.991	0.534, 1.840
0.5+	14	40	1.158	0.385, 3.481
Period of first hire				
1951-1953	38	186	1.078	0.352, 3.296
1954-1959	40	175	1.279	0.510, 3.212
1960-1967	64	175	1.983	0.845, 4.657
1968-1989	38	182	1.0	
Duration of employment	180	720	0.966	0.927, 1.006

Table A17
Adding cumulative lifetime dose to multivariate model with number of years with a positive dose.

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Number of Years with an Above Zero Internal Lung Dose				
None	93	386	1.00	
1-5	34	102	1.033	0.326, 3.279
5-9	18	83	0.896	0.277, 2.892
10-14	20	59	1.313	0.388, 4.442
14+	15	90	0.659	0.177, 2.456
Cummulative Internal Lifetime Dose	180	720	0.998	0.994, 1.002
Period Of First Hire				
1951-1953	38	186	1.082	0.355, 3.294
1954-1959	40	175	1.280	0.514, 3.190
1960-1967	64	175	2.036	0.897, 4.621
1967-1989	38	182	1.00	
Duration of Employment	180	720	0.965	0.927, 1.005

Table A18
Adding cumulative lifetime dose to multivariate model with number of years with a positive dose. Including smoking data.

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Number of Years with an Above Zero Internal Lung Dose				
None	93	386	1.00	
1-5	34	102	0.905	0.280, 2.927
5-9	18	83	0.719	0.215, 2.405
10-14	20	59	1.091	0.311, 3.828
14+	15	90	0.593	0.155, 2.271
Cummulative Internal Lifetime Dose	180	720	0.998	0.994, 1.003
Period Of First Hire				
1951-1953	38	186	1.204	0.372, 3.897
1954-1959	40	175	1.314	0.494, 3.494
1960-1967	64	175	2.083	0.864, 5.019
1967-1989	38	182	1.00	
Duration of Employment	180	720	0.961	0.923, 1.002
Smoking				
0	18	213	1.00	
1-19	26	142	1.247	0.512, 3.038
19+ - 25.5	11	146	0.759	0.314, 1.837
25.5+ -43	72	98	0.773	0.296, 2.222
43+	53	117	2.159	1.069, 4.357

Table A19
Univariate analysis with descriptive statistics: Age-Specific internal lung dose (10-year lag)

Model Variables	Cases (n=180)		Controls (n=720)		OR (risk ratio)	95% CI
	n %	mean	n %	mean		
Age Specific Internal Lung Dose	180		720			
Lung dose in 20's and 30's		2.36 cSv		14.69 cSv		
0 cSv	166		640		1.0	
0<-8.7 cSv	8		41		0.755	0.330, 1.727
>8.7 cSv	6		39		0.569	0.220, 1.473
Lung dose in 40's		10.55 cSv		17.01 cSv		
0 cSv	129		498		1.0	
0<-28.5 cSv	31		152		0.870	0.536, 1.415
>28.5 cSv	20		70		1.341	0.705, 2.552
Lung dose in 50's and older		16.80 cSv		42.73 cSv		
0 cSv	95		360		1.0	
0<-20 cSv	46		193		0.949	0.615, 1.464
>20 cSv	39		167		0.848	0.516, 1.393

Table A20
Multivariate analysis age-specific cumulative internal lung dose

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n	n		
Age Specific Internal Lung Dose	180	720		
Lung dose in 20's and 30's				
0 cSv	166	640	1.0	
0<-8.7 cSv	8	41	0.743	0.314, 1.759
>8.7 cSv	6	39	0.553	0.202, 1.515
Lung dose in 40's				
0 cSv	129	498	1.0	
0<-28.5 cSv	31	152	1.008	0.607, 1.676
>28.5 cSv	20	70	1.397	0.707, 2.760
Lung dose in 50's and older				
0 cSv	95	360	1.0	
0<-20 cSv	46	193	1.346	0.811, 2.231
>20 cSv	39	167	1.271	0.723, 2.234
Cummulative Penetrating dose (cSv)				
0	46	183	1.0	
0-0.5	120	495	0.962	0.646, 1.433
0.5+	14	40	1.093	0.525, 2.276
Period of first hire				
1951-1953	38	186	1.571	0.828, 2.982
1954-1959	40	175	1.556	0.856, 2.828
1960-1967	64	175	2.021	1.214, 3.362
1968-1989	38	182	1.0	
Duration of employment	180	720	0.963	0.940, 0.988

Table A21
Multivariate analysis of age-specific cumulative internal lung dose with smoking data

Model Variables	Cases (n=180)	Controls (n=720)	OR (risk ratio)	95% CI
	n %	n %		
Age_Specific Internal Lung Dose (categorical)				
Lung dose in 20's and 30's				
0 cSv	166	640	1.0	
0<-8.7 cSv	8	41	0.682	0.284, 1.634
>8.7 cSv	6	39	0.533	0.190, 1.494
Lung dose in 40's				
0 cSv	129	498	1.0	
0<-28.5 cSv	31	152	1.030	0.620, 1.711
>28.5 cSv	20	70	1.364	0.682, 2.728
Lung dose in 50's and older				
0 cSv	95	360	1.0	
0<-20 cSv	46	193	1.271	0.759, 2.128
>20 cSv	39	167	1.225	0.688, 2.181
Period of first hire				
1951-1953	38	186	1.572	0.824, 3.000
1954-1959	40	175	1.578	0.861, 2.892
1960-1967	64	175	2.182	1.302, 3.657
1968-1989	38	182	1.00	
Duration of Employment	180	720	0.965	0.941, 0.990
Smoking				
0	18	213	1.00	
1-19	26	142	0.885	0.495, 1.580
19+ - 25.5	11	146	1.048	0.591, 1.856
25.5+ -43	72	98	0.764	0.415, 1.406
43+	53	117	2.231	1.439, 3.459

Table A22

Table: Descriptive Statistics for the Rocky Flats Lung Cancer Case-Control Study Subjects with Urine Deposit Data (10 yr lag)

	Cases n=92			Controls n=443		
	No.	Mean		No.	Mean	
Gender						
Male	89			434		
Female	3			9		
Vital Status						
Alive	0			501		
Dead	92			219		
Age at First Plutonium Lung Dose (years) Applies to subjects with nonzero lung doses only	65	48.4		275	45.6	
Employment Duration	92	17		443	18.27	
Period of First Hire	92	1963		443	1962	
1950-1953	12			111		
1954-1959	22			102		
1960-1967	32			96		
1968-1989	26			134		
External Penetrating Radiation (cSv)	92	0.19		443	0.13	
Smoking (pack-yrs)	92	40.69		443	23.48	
0	8			126		
1-19	16			88		
19+ - 25.5	5			74		
25.5+ -43	28			70		
43+	35			81		

Table A23
Univariate Analysis: Indicator variable for bioassay data 1:4 matched

Variable	Cases (n=180)	Controls (n=720)	Odds Ratio	95% CI
Indicator Variable for Urine Data 0=no test/1=test	179	706	0.605	0.427, 0.859

Table A24
Multivariate analysis: Average lifetime dose and indicator for urine test 1:4 matched

Variable	Cases (n=180)	Controls (n=720)	Odds Ratio	95% CI
Indicator Variable for Urine Data 0=no test/1=test	179	706	0.539	0.367, 0.790
Average Annual Dose	180	720		
0 cSv/yr	93	386	1.00	
0<-0.6511 cSv/yr	19	84	0.996	0.567, 1.751
0.6511<-2.257 cSv/yr	22	84	1.213	0.682, 2.155
2.257<-4.415 cSv/yr	20	85	1.216	0.678, 2.181
4.415<-6.5 cSv/yr	11	27	2.097	0.962, 4.569
6.5 + cSv/yr	15	54	1.543	0.788, 3.022

Table A25
Multivariate analysis: Maximum lifetime dose and indicator for urine test 1:4 matched

Variable	Cases (n=180)	Controls (n=720)	Odds Ratio	95% CI
Indicator Variable for Urine Data 0=no test/1=test	179	706	0.551	0.376, 0.809
Maximum Annual Dose	180	720		
0 cSv	93	386	1.00	
>0 -0.85 cSv	16	67	1.002	0.538, 1.866
>0.85-4.70 cSv	23	89	1.195	0.701, 2.036
>4.7-12 cSv	23	90	1.209	0.685, 2.132
12 + cSv	25	88	1.448	0.838, 2.502

Table A26
Multivariate analysis: Number of years with a positive dose and indicator for urine test 1:4 matched

Variable	Cases (n=180)	Controls (n=720)	Odds Ratio	95% CI
Indicator Variable for Urine Data 0=no test/1=test	179	706	0.565	0.385, 0.829
Number of Years with an Above Zero Dose	180	720		
None	93	386	1.00	
1-5	34	102	1.454	0.912, 2.317
6-10	18	83	1.114	0.617, 2.010
11-14	20	59	1.777	0.969, 3.260
15+	15	90	0.772	0.404, 1.475

Table A27
Univariate analysis: Number of years with a positive dose (10-year lag) unmatched

Variable	Cases (n=92)	Controls (n=443)	Odds Ratio	95% CI
	n	n		
Number of years with an above zero internal lung dose (continuous)	92	443	0.988	0.951, 1.026
Number of years with an above zero internal lung dose (categorical)				
None	27	172	1.00	
1-5	18	76	1.509	0.78, 2.90
6-10	17	71	1.525	0.78, 2.97
11-14	17	50	2.166	1.09, 4.29
15+	13	74	1.119	0.547, 2.29

Table A28
Multivariate analysis: Number of years with a positive dose (10-year lag) unmatched

Variable	Cases (n=92)	Controls (n=443)	Odds Ratio	95% CI
	n	n		
Number of years with an above zero internal lung dose (continuous)	92	443	1.022	0.974, 1.072
Period of First Hire				
1950-1953	12	111	0.480	0.185, 1.245
1954-1959	22	102	0.852	0.365, 1.988
1960-1967	32	196	1.700	0.826, 3.497
1968-1989	26	134	1.0	
Age at First Exposure	65	275	1.053	1.011, 1.097

Table A29
Trend analysis for third period of hire and number of years with an above zero internal lung dose χ^2=0.535 (p=0.84)

	0 years	1-5 years	5-9 years	10-14 years	14+ years
1960-1967	129	37	26	22	25
All other hire years	346	104	75	57	79

Table A30
Trend analysis for third period of hire and duration of employment χ^2=16.35 (p=0.0001)

	<1 year	1-5 years	5-13 years	13-21 years	21+ years
1960-1967	3	88	53	48	47
All other hire years	2	164	172	153	170

Table A31
Trend analysis for third period of hire and smoking χ^2=2.06 (p=0.64)

	0 pack-years	1-19 pack-years	19-25.5 pack-years	25.5-43 pack-years	43+ pack-years
1960-1967	59	33	25	28	41
All other hire years	172	74	82	85	129

Table A32
Trend analysis for third period of hire and external penetrating radiation χ^2=26.97 (p=0.0001)

	0 cSv	0-0.5 cSv	0.5+ cSv
1960-1967	48	161	30
All other hire years	181	454	24

Table A33
Trend analysis for third period of hire and age at first exposure χ^2=3.24 (p=0.43)

	22-40 years old	40-46 years old	46-52 years old	52+ years old
1960-1967	24	36	25	26
All other hire years	88	80	66	85

Table A34
Trend analysis for third period of hire and cumulative internal lung dose χ^2=8.28 (p=0.054)

	0 cSv	0-10 cSv	10-40 cSv	40-64.4 cSv	64.4+ cSv
1960-1967	10	46	22	18	17
All other hire years	29	117	98	32	32

Table A35
Trend analysis for third period of hire and maximum annual internal lung dose χ^2=5.14 (p=0.12)

	0 cSv	>0 -0.85 cSv	>0.85-4.70 cSv	>4.7-12 cSv	12-45 cSv	45+ cSv
1960-1967	10	15	36	5	24	31
All other hire years	29	67	79	22	69	82

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