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# Lung Cancer and Internal Lung Doses among Plutonium Workers at the Rocky Flats Plant: A Case-Control Study

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The authors conducted a nested case-control study of the association between lung cancer mortality and cumulative internal lung doses among a cohort of workers employed at the Rocky Flats Plant in Colorado from 1951 to 1989. Cases ($n = 180$) were individually matched with controls ($n = 720$) on age, sex, and birth year. Annual doses to the lung from plutonium, americium, and uranium isotopes were calculated for each worker with an internal dosimetry model. Lung cancer risk was elevated among workers with cumulative internal lung doses of more than 400 mSv in several different analytical models. The dose-response relation was not consistent at high doses. Restricting analysis to those employed for 15–25 years produced a statistically significant linear trend with dose (chi-square = 67.2, $p < 0.001$), suggesting a strong healthy worker survivor effect. The association between age at first internal lung dose and lung cancer mortality was statistically significant (odds ratio = 1.05, 95% confidence interval: 1.01, 1.10). No associations were found between lung cancer mortality and cumulative external penetrating radiation dose or cumulative exposures to asbestos, beryllium, hexavalent chromium, or nickel.

lung neoplasms; occupational exposure; plutonium; radiation

Abbreviation: CINDY, Code for Internal Dosimetry.

In the mid-1990s, the first evidence for increased cancer risks from plutonium exposures was reported for workers at the Mayak facility in Russia (1–3). More recently, studies of lung cancer in Mayak workers have been improved with estimates of lung doses for individual workers, thereby reducing exposure misclassification and permitting estimates of risk per unit dose (4–7). Studies of Mayak workers have also identified increased risks from plutonium exposures for hematopoietic and lymphatic cancers (2, 8), cancers of the liver (9), and bone and connective tissue cancers (10).

In contrast to the findings from Russia, studies of plutonium workers in other countries have produced only suggestive evidence for cancer risks. Previous studies of Rocky Flats Plant workers in Colorado have identified elevated standardized mortality ratios for benign and unspecified neoplasms of the brain (11, 12) and elevated rate ratios for lymphopoietic neoplasms for workers with evidence of internal exposure to plutonium (12); however, an elevated risk for lung cancer was not identified for Rocky Flats Plant workers by Wilkinson et al. (12).

In a study of Los Alamos National Laboratory workers, Wiggs et al. (13) noted a relative risk of 1.78 (95 percent confidence interval: 0.79, 3.99) for lung cancer mortality among plutonium-exposed workers with systemic depositions of 74 Bq or greater. Omar et al. (14) studied Sellafield plutonium workers and concluded that there was no evidence for increased risk for mortality from any type of cancer.

It appears that the best explanation for the conflicting findings for studies of plutonium workers at different facilities is that the Mayak studies had adequate statistical power due to the comparatively high internal radiation doses received by Mayak workers (15), while other study populations had fewer plutonium-exposed workers with lower radiation doses. It is also possible that studies of US plutonium

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workers have not detected risks because estimates of systemic deposition misclassified internal doses.

To further explore the reasons for these different findings and in an effort to better assess lung cancer risk at lower levels of plutonium exposure, we designed a nested case-control study of lung cancer mortality with data from a cohort of plutonium workers at Rocky Flats, Colorado. With this design, we modeled internal doses to the lung for individual subjects and adjusted for a variety of confounding variables.

## MATERIALS AND METHODS

### Site description

The Rocky Flats Plant, located 15 miles (24.14 km) northwest of Denver, Colorado, produced nuclear weapons components from 1952 to 1989 (16). The fabrication of plutonium pits—the primary production activity at Rocky Flats—involved chemical processing of plutonium metal into plutonium dioxide, converting this compound to plutonium metal in reduction furnaces, and rolling and machining the metal into weapons components (17). Uranium and beryllium were also used in the production of weapons components.

Workers at Rocky Flats were exposed to several plutonium isotopes—plutonium 238, plutonium 239, plutonium 240, and plutonium 241 (collectively termed "plutonium"). They were also exposed to americium 241 (produced through neutron capture by plutonium 239 and plutonium 240) and uranium 234 and uranium 238 (collectively termed "uranium"). Uranium was used in the construction of some weapons components in the 1960s, and americium 241 was processed for weapons and other uses. Internal exposures to radionuclides occurred primarily by acute inhalation of radioactive particles accidentally released into the workplace atmosphere.

### Study population

The Colorado Multiple Institutional Review Board (which provides federally sanctioned review of protocols for research involving human subjects at the University of Colorado Health Sciences Center and affiliated institutions) approved the protocol for data collection and analysis, as well as the manner in which informed consent was obtained from interviewees who provided smoking histories for subjects. Cases and controls were selected from a preliminary database of 22,883 workers who were employed at the Rocky Flats Plant between January 1, 1952, and July 10, 1996. The database was compiled from electronic records from the plant personnel office and from an electronic database for a cohort of 9,539 Rocky Flats' workers hired before 1980 and followed by the Los Alamos National Laboratory (analyses for a subset of this group were previously reported by Wilkinson et al. (12)). We determined vital status through December 31, 1996, for all subjects in this database by submitting personally identifying information to the Social Security Administration and Pension Benefits, Inc., a commercial provider of vital status information. Subsequent to the selection of cases and controls, a final cohort roster was developed for 16,258 production-era workers, who were employed for 6 months or more between 1952 and 1989. For subjects in this database, less than 2 percent were missing either a valid Social Security number, a date of birth or death, or death certificate data.

Cases were selected from the preliminary database according to the following criteria: 1) employment for at least 6 months at Rocky Flats between January 1, 1952, and December 31, 1989; 2) death before December 31, 1996; 3) death certificate diagnosis of primary lung cancer (*International Classification of Diseases*, Ninth Revision, code 162) listed as the underlying or contributing cause of death or cancer registry diagnosis of primary lung cancer. Of the 180 cases, 156 (86.7 percent) had death certificate diagnoses of lung cancer as the underlying cause; 10 (5.6 percent) had lung cancer listed as a contributing cause; and 14 (7.8 percent) had a cancer registry diagnosis of primary lung cancer that was not listed on the death certificate.

We used incidence density sampling to select controls from the set of subjects at risk at the time of death of each case. Four controls were randomly selected from each risk set for comparison with each lung cancer case. Risk sets were defined by sex and date of birth (within 2.5 years) of cases and employment at Rocky Flats for at least 6 months between January 1, 1952, and December 31, 1989. Controls were also required to have been alive at the age at death of the matched case and to have started work at Rocky Flats at an age younger than the age at death of the matched case. A total of 720 controls were matched to cases; 66 controls were selected more than once.

For the 59 subjects (6.6 percent) who died before 1979, death certificates or electronic files of classification codes were obtained from records maintained for previous studies and follow-up programs and from the Vital Statistics Division of the Colorado Department of Public Health and Environment. For over 99 percent of the 846 study subjects who died after 1978, electronic files with codes for multiple causes of death were obtained from the National Death Index. The remainder were coded from death certificates. Multiple causes for deaths were coded according to the *International Classification of Diseases*, Ninth Revision (18). Records from the Colorado Central Cancer Registry (with diagnoses based primarily on reports from hospital and commercial pathology laboratories) were used to identify 14 eligible cases with diagnoses of primary lung cancer that were not mentioned on death certificates and to exclude 13 subjects with death certificate diagnoses of primary lung cancers that conflicted with data from the cancer registry.

### Estimating exposures and doses

Data from a job exposure matrix (15) were used to estimate annual exposures to asbestos, beryllium, hexavalent chromium, and nickel, expressed as the product of time worked and the estimated time-weighted average daily breathing-zone concentrations that were usually experienced by workers.

For production-era workers, exposures to plutonium isotopes (primarily plutonium 239 and plutonium 241) were

routinely quantified with estimates of systemic deposition (19). For subjects in the nested case-control study, we estimated effective intakes and annual equivalent doses with the Code for Internal Dosimetry (CINDY), version 1.3C (20). The CINDY code is based on the dosimetry model developed by the International Commission for Radiological Protection in publication 30 (21). The sources of input data for the model were urine bioassay data for plutonium and uranium and lung count data for isotopes of both elements and their decay products (22). The intake of americium 241 associated with plutonium particles was estimated as a fraction of the estimated intake of plutonium 239 and plutonium 241, based on the isotopic ratios in the nuclear materials processed at Rocky Flats. No subjects in this study received exposures to pure americium 241 (that is, americium 241 that had been previously separated from plutonium isotopes).

Data for external radiation doses came from electronic databases of recorded doses from film and thermoluminescent personal dosimeters that measured total body doses from external gamma photon and neutron exposures. The dosimeters recorded doses for individual workers for periods ranging from quarter years to years.

For the years 1952–1958 and 1964–1975, neutron and gamma doses were recorded only as a combined dose, making it impossible to separate the contributions from these two exposures. Neutron doses based on analyses of film dosimeters by light microscopy were found to be in error for the early years of plant operation. We corrected the neutron doses for this period by developing ratios of neutron to gamma doses for administrative building assignments and job titles based on the neutron doses that were judged to be accurate (15).

Histories of smoking frequency for cases and controls were obtained by telephone interviews with surrogate interviewees, regardless of the vital status of the subject, in an effort to provide reliable historical data and to reduce the potential bias from self-reporting (23–25). We first attempted to contact close relatives of subjects. If they could not be located, we abstracted data from medical records at Rocky Flats, if available. If data were unavailable from these two sources, we attempted to obtain information from former workers who knew the study subjects well enough to characterize their smoking habits. Over 80 percent of the smoking histories were obtained from a family member, 11.4 percent came from medical records, and almost 8 percent were obtained from coworkers. The goal of the smoking history questionnaire was first to determine smoking status (ever or never) and then to estimate the cumulative number of pack-years for study subjects using a timeline-based approach (26).

### Missing data for exposures and doses

External dosimetry data for some individual subjects were missing because they were not recorded or inadvertently deleted from electronic databases or because the subject was actually not exposed. We used the "nearby" method (15, 27) to impute missing annual doses for individual subjects, by substituting the mean of the recorded doses within 2 years before and 2 years after the year for which a dose was missing. For strings of 5 or more years of missing external penetrating doses, notional doses were computed using the job exposure matrix to identify mean annual doses for other workers with similar job titles and work locations. If job-exposure-matrix data were not available, the annual geometric mean for all workers was substituted. External penetrating doses for 1 or more years were imputed for 93 cases (51.7 percent) and for 424 controls (58.9 percent). Doses of zero were assigned for missing data as an alternative to the nearby method to explore the effect of possible misclassification by imputing values for missing doses. The results of analyses with this alternative were similar to those from analyses made with imputed doses.

Subjects with no records of organization, job, and building were considered to have been unexposed to asbestos, beryllium, hexavalent chromium, or nickel. For workers who had recorded data for general organization and job and administrative building assignment, but no estimate of exposure in the job exposure matrix, we made exposure estimates based on the distributions of exposures assigned to other combinations of organization, job, and building (15). Missing chemical exposures were imputed using the nearby method for subjects who had some estimates of chemical exposures. Exposures to the four chemical agents for 1 or more years were imputed for 117 cases (65.0 percent) and for 494 controls (68.6 percent). Annual exposures of zero were assigned for missing data as an alternative to the nearby method to explore the effect of possible misclassification by imputing values for missing exposures. The results of analyses with this alternative were similar to those from analyses made with imputed exposures.

### Statistical methods

Before constructing multiple variable models, we explored the effect of a number of variables on the risk for lung cancer by comparing distributions of cases and controls across strata for the variables, and with univariate conditional logistic regression models with all cases and controls.

We developed multiple logistic regression models with three different groups of cases and controls to assess possible confounding between smoking frequency and cumulative internal lung dose and whether missing smoking histories for 170 subjects introduced selection bias. The first model maintained matching between cases and controls, thus excluding any case-control pair for which one or both subjects lacked smoking histories, leaving 549 subjects for analysis. The second model used all 730 subjects for whom smoking data were collected by breaking the 1:4 matching and adjusting analyses for birth year in ordinary logistic regression models.

The third model maintained matching with conditional multiple logistic regression analysis by including a missing-indicator variable to adjust for differences between those with ($n = 730$) and those without ($n = 170$) smoking histories. This method used data in the incomplete pairs while preserving the matching in the complete pairs, thereby retaining information for all 900 cases and controls. This

approach is regarded as a compromise between matched and unmatched analyses (28).

Odds ratios computed for variables of interest with each approach were compared to assess whether the data sets defined by the availability of smoking histories were biased samples of the entire group of cases and controls. Logistic regression models were developed with Statistical Analysis System software (29). For matched sets of cases and controls, conditional multiple logistic regression with 1:4 matching was implemented, after forming a stratum for each matched set. Survival time for each control was calculated with the date of death for the matched case.

Because there were only seven female cases, analyses of exposure-lung cancer associations were not conducted separately for males and females. Analyses restricted to subjects who were employed for 15–25 years and to subjects who received internal lung doses (for the purpose of evaluating age at first dose) were performed with ordinary logistic regression models.

Covariates were included in the final logistic regression models if they changed, by 10 percent or more, the odds ratio that was computed for the main effect in bivariate models (30), or if they were statistically significant risk factors in multivariate models.

Internal and external radiation doses, chemical exposures, and smoking frequency for individual subjects were unlagged and lagged by 5, 10, and 15 years in multivariate models. With the exception of radiation doses, ranges for each variable were specified according to quartiles for distributions of the data for all subjects. Numerical ranges for categories of radiation doses were selected to include sufficient subjects in the dose categories and to be comparable to ranges reported in previous studies. Alternate analyses performed with a variety of cutpoints produced similar results.

In preliminary exploratory analyses with employment duration stratified by a variety of lengths of time, we found that employment duration affected the dose-response relation between categories of cumulative internal lung dose and lung cancer risk. In preliminary models, employment duration was only weakly correlated with cumulative internal lung dose. We included employment duration as a continuous variable in multivariate models, because it met the aforementioned selection criteria, and because it allowed us to assess the healthy-worker survivor effect. Multivariate models with employment duration as a design variable showed results similar to those for models with employment duration as a continuous variable. We also developed a multivariate model for the period of employment duration (10–25 years) that had the strongest effect on the dose-response relation in stratified univariate models.

Because plutonium is retained in the lung for many years after an inhalation exposure and because the distribution of plutonium over time in the lung tissue is not well understood, dosimetry models may not have accurately estimated cumulative doses to the lung, particularly for subjects with many years of follow-up after first exposure. We assessed the effect of dose duration by creating a variable for the number of years that a subject was assigned an above-zero lung dose and included it in multivariate models.

## RESULTS

### Univariate analyses

Control subjects were distributed evenly over the four periods of hire, but cases were more likely to have been hired between 1960 and 1967 than in other periods (table 1). On average, controls were employed for about 2 years longer than cases, and the mean age at first internal lung dose was from 1 to 3 years greater for cases than for controls (table 1).

For cases, 98 percent of the collective internal lung dose (the sum of cumulative internal lung doses for all cases) was from the combination of plutonium isotopes and americium 241. Twenty cases received internal lung doses from uranium 234, and seven cases received doses from uranium 238. Ninety-six percent of the collective internal lung dose for controls was from a combination of plutonium isotopes and americuim 241. Fifty controls received internal lung doses from uranium 234 and three from uranium 238.

In a univariate model with doses lagged by 10 years, the odds ratios were elevated for some of the dose categories, but none was statistically significant (table 2). The odds ratio for cumulative internal lung dose, modeled as a continuous variable, was not elevated. Subjects first hired between 1960 and 1967 were at significantly elevated risk for lung cancer mortality, and the odds ratios for external penetrating radiation doses were only slightly elevated (table 2). Lagging internal and external doses by 5- and 15-year intervals produced results similar to those for a 10-year lag period (data not shown). Pack-years of smoking, analyzed as continuous and design variables, were significantly associated with lung cancer (data not shown). The odds ratios for each of the four cumulative exposures to chemical carcinogens, analyzed as continuous and design variables, were not significantly elevated when unlagged and lagged by 5-, 10-, and 15-year intervals (data now shown).

Employment duration was significantly and negatively associated with lung cancer when modeled univariately as a continuous variable (table 2). The risks for employment duration were not uniform, however. Subjects employed for 10 years or less or for more than 25 years were at lower risk than those employed from 11 to 25 years (data not shown).

### Multivariate models

In the final conditional multiple logistic regression model, the odds ratios for all but one above-zero cumulative internal lung dose categories were elevated (table 3). For doses lagged by 5 years, odds ratios increased in a monotonic fashion from the lowest dose group (0 mSv) to the penultimate dose group (644–940 mSv) but diminished in magnitude at the highest dose category. For doses lagged by 10 and 15 years, odds ratios increased in a monotonic fashion from the group with no dose to the group with doses between 400 and 644 mSv, but they diminished in magnitude for the highest two dose groups.

Adjusting for the number of years a subject received an internal lung dose (modeled as a continuous variable) produced higher estimates of odds ratios for all categories for doses lagged by 10 years, and all were statistically significant (table 4). Moreover, there was a significant inverse

**TABLE 1. Characteristics of workers in the Rocky Flats lung cancer case-control study, Colorado, 1951–1989**

| Variable | Cases | | Controls | |
|---|---|---|---|---|
| | No. | % | No. | % |
| No. of subjects | 180 | | 720 | |
| Sex | | | | |
| Male | 173 | 96.0 | 692 | 96.0 |
| Female | 7 | 4.0 | 28 | 4.0 |
| Vital status | | | | |
| Alive | 0 | 0 | 501 | 69.6 |
| Dead | 180 | 100 | 219 | 30.4 |
| Period of first hire | 180 | | 718* | |
| 1968–1989 | 38 | 21.1 | 182 | 25.3 |
| 1960–1967 | 64 | 35.6 | 175 | 24.3 |
| 1954–1959 | 40 | 22.2 | 175 | 24.3 |
| 1951–1953 | 38 | 21.1 | 186 | 25.8 |
| | Median | IQR† | Median | IQR |
| Employment duration (years) | 12 | 4–18 | 13 | 5–22 |
| Age at first internal lung dose (years) | 49 | 43–55 | 47 | 41–54 |

* Hire dates are missing for two control subjects.
† IQR, interquartile range.

**TABLE 2. Univariate odds ratios for selected variables in the Rocky Flats lung cancer case-control study, Colorado, 1951–1989**

| Model variable | No. of cases | No. of controls | OR* | 95% CI* |
|---|---|---|---|---|
| Cumulative internal lung dose (mSv)† | | | | |
| 0 | 93 | 386 | 1.0 | |
| >0–100 | 33 | 127 | 1.10 | 0.70, 1.74 |
| >100–400 | 21 | 97 | 0.89 | 0.51, 1.55 |
| >400–644 | 13 | 34 | 1.62 | 0.80, 3.27 |
| >644–940 | 12 | 34 | 1.53 | 0.74, 3.16 |
| >940 | 8 | 40 | 0.83 | 0.30, 1.72 |
| Cumulative penetrating radiation dose (mSv)† | | | | |
| 0 | 25 | 103 | 1.0 | |
| >0–50 | 126 | 504 | 1.05 | 0.61, 1.80 |
| >50 | 29 | 111 | 1.11 | 0.57, 2.17 |
| Period of first hire | | | | |
| 1968–1989 | 38 | 182 | 1.0 | |
| 1960–1967 | 64 | 175 | 1.74 | 1.09, 2.79 |
| 1954–1959 | 40 | 175 | 1.09 | 0.64, 1.87 |
| 1951–1953 | 38 | 186 | 0.98 | 0.57, 1.69 |
| Employment duration (years) | 180 | 718 | 0.97 | 0.96, 0.99 |
| Age at first internal lung dose (years) | 98 | 412 | 1.04 | 0.99, 1.09 |

* OR, odds ratio; CI, confidence interval (logistic regression model, adjusted for birth year).
† Lag period of 10 years.

TABLE 3. Conditional multiple logistic regression analyses for the Rocky Flats lung cancer case-control study, Colorado, 1951–1989

| Model variables | Doses lagged by 5 years | | Doses lagged by 10 years | | Doses lagged by 15 years | |
|---|---|---|---|---|---|---|
| | OR* | 95% CI* | OR | 95% CI | OR | 95% CI |
| Cumulative internal lung dose (mSv) | | | | | | |
| 0 | 1.0 | | 1.0 | | 1.0 | |
| >0–100 | 1.26 | 0.77, 2.06 | 1.42 | 0.87, 2.33 | 1.02 | 0.59, 1.76 |
| >100–400 | 1.81 | 0.98, 3.35 | 1.60 | 0.83, 3.10 | 1.17 | 0.59, 2.29 |
| >400–644 | 1.95 | 0.83, 4.57 | 2.71 | 1.20, 6.09 | 3.32 | 1.50, 7.34 |
| >644–940 | 2.27 | 0.95, 5.41 | 2.30 | 0.96, 5.53 | 1.34 | 0.49, 3.64 |
| >940 | 1.54 | 0.65, 3.62 | 1.48 | 0.56, 3.89 | 0.79 | 0.24, 2.66 |
| Cumulative penetrating radiation dose (mSv) | | | | | | |
| 0 | 1.0 | | 1.0 | | 1.0 | |
| >0–50 | 1.26 | 0.58, 2.71 | 0.99 | 0.52, 1.87 | 0.92 | 0.50, 1.69 |
| >50 | 1.25 | 0.46, 3.36 | 0.98 | 0.40, 2.41 | 1.00 | 0.41, 2.42 |
| Period of first hire | | | | | | |
| 1968–1989 | 1.0 | | 1.0 | | 1.0 | |
| 1960–1967 | 1.87 | 1.13, 3.09 | 1.82 | 1.08, 3.05 | 1.79 | 1.02, 3.13 |
| 1954–1959 | 1.32 | 0.73, 2.39 | 1.30 | 0.71, 2.37 | 1.34 | 0.69, 2.60 |
| 1951–1953 | 1.37 | 0.74, 2.53 | 1.36 | 0.72, 2.54 | 1.31 | 0.66, 2.61 |
| Employment duration (years) | 0.96 | 0.93, 0.98 | 0.96 | 0.94, 0.98 | 0.96 | 0.94, 0.99 |

* OR, odds ratio; CI, confidence interval (ORs are adjusted for each variable listed in table).

relation between the number of years with a positive lung dose and the risk for lung cancer.

Because dose-response relations varied with employment duration, we analyzed the final multivariate model with subjects employed for 15–25 years and adjusted for birth year. In this model, the odds ratios increased with cumulative internal lung dose over all six above-zero dose categories, and the test for linear trend was statistically significant (table 5). Similar analysis restricted to subjects hired for less than 15 years and to subjects hired for more than 25 years produced odds ratios that were actually less than one for most categories, and none was statistically significant.

The odds ratios for estimates of plutonium systemic deposition (available for 439 or 49 percent of the 900 study subjects) were not significantly elevated when this variable was dichotomized (zero vs. above zero) in a conditional multiple logistic regression model adjusted for employment duration, year of hire, and cumulative penetrating radiation dose (data not shown). When plutonium systemic deposition estimates were grouped by quartiles and modeled as design variables in the previously described model, the odds ratio for the highest systemic deposition group was 1.23, but this was not statistically significant; a test for linear trend over the four categories for systemic deposition was not statistically significant (data not shown).

The odds ratios for above-zero categories of cumulative penetrating radiation dose were not significantly elevated in the final multivariate models (tables 3 and 4). There was no evidence of interaction between cumulative internal lung dose and cumulative penetrating radiation dose (data not shown).

In multivariate models, the odds ratios for periods of first hire before 1968 were elevated and statistically significant for the period 1960–1967 (tables 3 and 4). The odds ratios for duration of employment, modeled as a continuous variable, were significantly less than one (tables 3 and 4).

None of the cumulative exposures for the four chemical carcinogens was significantly associated with lung cancer mortality in the final multivariate models (data not shown).

For the subjects who actually received internal lung doses, the odds ratio for age at first internal lung dose was significantly elevated (table 6) when lagged by 10 years; the risk increased by 5 percent for each year of age. The results were similar in models with unlagged doses and doses lagged by 5 and 15 years (data not shown). There was no interaction between cumulative internal lung dose and either age at first internal lung dose or attained age (age at the end of the study period or age at death) when these variables were modeled as both continuous and categorical variables (data not shown).

To assess confounding by smoking frequency of the relation between cumulative internal lung dose and lung cancer,

TABLE 4. Conditional multiple logistic regression analysis for the Rocky Flats lung cancer case-control study, with and without adjustment for years of above-zero doses, Colorado, 1951–1989

| Model variables | No. of cases | No. of controls | Unadjusted | | Adjusted* | |
|---|---|---|---|---|---|---|
| | | | OR† | 95% CI† | OR | 95% CI |
| Cumulative internal lung dose (mSv)‡ | | | | | | |
| 0 | 93 | 386 | 1.0 | | 1.0 | |
| >0–100 | 33 | 127 | 1.42 | 0.87, 2.33 | 1.77 | 1.04, 3.02 |
| >100–400 | 21 | 97 | 1.60 | 0.83, 3.10 | 3.31 | 1.31, 8.38 |
| >400–644 | 33 | 108 | 2.71 | 1.20, 6.09 | 6.09 | 2.03, 18.31 |
| >644–940 | 12 | 34 | 2.30 | 0.96, 5.53 | 5.54 | 1.69, 18.19 |
| >940 | 8 | 40 | 1.48 | 0.56, 3.89 | 3.59 | 1.02, 12.68 |
| Cumulative penetrating radiation dose (mSv)‡ | | | | | | |
| 0 | 25 | 103 | 1.0 | | 1.0 | |
| >0–50 | 126 | 504 | 0.99 | 0.52, 1.87 | 0.91 | 0.47, 1.73 |
| >50 | 29 | 111 | 0.98 | 0.40, 2.41 | 0.98 | 0.40, 2.44 |
| Period of first hire | | | | | | |
| 1968–1989 | 38 | 182 | 1.0 | | 1.0 | |
| 1960–1967 | 64 | 175 | 1.82 | 1.08, 3.05 | 1.80 | 1.08, 3.05 |
| 1954–1959 | 40 | 175 | 1.30 | 0.71, 2.37 | 1.29 | 0.71, 2.37 |
| 1951–1953 | 38 | 186 | 1.36 | 0.72, 2.54 | 1.28 | 0.72, 2.54 |
| Employment duration (years) | 180 | 718 | 0.96 | 0.94, 0.98 | 0.96 | 0.94, 0.99 |
| Years with above-zero doses | 180 | 718 | | | 0.97 | 0.94, 0.99 |

* Adjusted for years with above-zero doses.
† OR, odds ratio; CI, confidence interval (ORs are adjusted for each variable listed in table).
‡ Lag period of 10 years.

TABLE 5. Multiple logistic regression analysis for the Rocky Flats lung cancer case-control study, for workers employed for 15–25 years, Colorado, 1951–1989

| Model variables | No. of cases | No. of controls | OR* | 95% CI* |
|---|---|---|---|---|
| Cumulative internal lung dose (mSv)† | | | | |
| 0 | 13 | 84 | 1.0 | |
| >0–100 | 10 | 51 | 1.14 | 0.46, 2.86 |
| >100–400 | 14 | 46 | 2.11 | 0.86, 5.20 |
| >400–644 | 7 | 17 | 2.74 | 0.92, 8.19 |
| >644–940 | 9 | 16 | 3.20 | 1.15, 8.94 |
| >940 | 7 | 11 | 5.04‡ | 1.55, 16.40 |
| Period of first hire | | | | |
| 1968–1989 | 10 | 41 | 1.0 | |
| 1960–1967 | 22 | 50 | 2.56 | 0.91, 7.21 |
| 1954–1959 | 19 | 64 | 1.55 | 0.50, 4.86 |
| 1951–1953 | 9 | 70 | 1.05 | 0.25, 4.38 |
| Employment duration (years) | 60 | 225 | 0.87 | 0.79, 0.97 |

* OR, odds ratio; CI, confidence interval (ORs are adjusted for each variable listed in table).
† Lag period of 10 years.
‡ Chi-square statistic for linear trend = 67.2 ($p < 0.001$).

TABLE 6. Multiple logistic regression analysis for the Rocky Flats lung cancer case-control study, adjusted for age at first internal lung dose, Colorado, 1951–1989

| Model variables | No. of cases | No. of controls | OR* | 95% CI* |
|---|---|---|---|---|
| Cumulative internal lung dose (mSv)† | | | | |
| 0 | 11 | 80 | 1.0 | |
| >0–100 | 33 | 127 | 1.41 | 0.55, 3.58 |
| >100–400 | 21 | 97 | 1.73 | 0.64, 4.65 |
| >400–644 | 13 | 34 | 2.94 | 0.95, 9.05 |
| >644–940 | 12 | 34 | 2.32 | 0.71, 5.60 |
| >940 | 8 | 40 | 1.76 | 0.50, 6.28 |
| Cumulative penetrating radiation dose (mSv)† | | | | |
| 0 | 5 | 50 | 1.0 | |
| >0–50 | 66 | 258 | 2.72 | 0.84, 8.98 |
| >50 | 27 | 104 | 2.98 | 0.79, 12.67 |
| Period of first hire | | | | |
| 1968–1989 | 24 | 116 | 1.0 | |
| 1960–1967 | 36 | 91 | 2.43 | 1.13, 5.21 |
| 1954–1959 | 25 | 112 | 1.74 | 0.68, 4.46 |
| 1951–1953 | 13 | 93 | 1.38 | 0.48, 3.99 |
| Employment duration (years) | 98 | 412 | 0.94 | 0.91, 0.97 |
| Age at first lung dose (years) | 98 | 412 | 1.05 | 1.01, 1.10 |

* OR, odds ratio; CI, confidence interval (ORs are adjusted for each variable listed in table).
† Lag period of 10 years.

we modeled each of the three multivariate model analyses performed with smoking data both with and without design variables for smoking frequency in pack-years (data not shown). Inclusion of the design variables in the model did not change by 10 percent or more the association between cumulative internal lung dose and lung cancer in any of the analyses.

## DISCUSSION

We found statistically significant risks for lung cancer mortality at cumulative internal lung doses above 400 mSv. Elevated risks for lung cancer in Mayak plutonium workers have been detected at unlagged doses above 1,800 mSv, but the risks (as estimated with standardized mortality ratios stratified by dose) were not statistically significant at unlagged doses below about 7,000 mSv (6).

When plutonium exposure was quantified as systemic deposition, there was a weak and nonsignificant risk for lung cancer. Ruttenber et al. (15) reported a range of three orders of magnitude in lung dose for estimates of plutonium systemic deposition below about 50 Bq and two orders of magnitude between 50 Bq and 100 Bq. It is likely, therefore, that misclassification of lung dose by plutonium systemic deposition is responsible for the weak association between plutonium systemic deposition and lung cancer.

In models with all subjects, the odds ratios did not increase with cumulative internal lung doses above 644 mSv. Adjusting for the number of years with above-zero doses doubled the odds ratios for doses above 100 mSv but did not alter the dose-response relations. The inverse relation between this interval and risk suggests that the CINDY code has overestimated lung doses disproportionately for subjects with high cumulative lung doses. If the actual dose delivered to the pulmonary epithelium changed over time but the estimated cumulative dose did not—by sequestration of plutonium in the lymphatics, for instance—then the actual lung cancer risk for high doses would be lower for persons whose cumulative lung dose accrued over long time periods as compared with short time periods. Such effects may be responsible for the absence of a dose-response relation for doses above 644 mSv in our models. Since the CINDY code is based on a dosimetry model (21) that has been improved recently (31), dose-response relations may be improved in analyses with dose estimates made with the newer model.

The statistically significant protective effect of employment duration suggests a strong healthy-worker survivor effect (32–35), likely due to routine medical screening and dose monitoring for workers employed for long periods in plutonium processing. It also appears that dose-response relations are strongly influenced by this effect, as stratifying analyses by categories of employment duration produced a statistically significant linear trend in odds ratios for subjects who worked for 15–25 years and odds ratios of less than one for workers employed for both shorter and longer periods. Others have examined the healthy-worker survivor effect

with variables such as time since hire, age at hire, age at risk, and employment status, and it is not clear which variable is preferable (33). For case-control studies of cancer mortality in subjects with internally deposited radionuclides with long retention times, employment duration is a reasonable choice, as it is less likely to be correlated with dose than is time since first hire, and it can be parameterized as a time-independent variable, as opposed to employment status and age at risk.

Age at first internal lung dose was a significant risk factor in models with the subset of subjects who received internal doses. Adjusting for age did not affect the size of the odds ratios for the categories of cumulative internal lung dose, but it did lower slightly their statistical significance, likely due to reduced statistical power caused by eliminating subjects with zero cumulative doses.

The effect on cancer risk of the age at which radiation doses were received has been noted in many studies of workers exposed to external penetrating radiation. Most studies (36–40) have modeled the ages at which the penetrating radiation doses were received, rather than the age at first dose. In these studies, the relation between radiation dose and risk for cancer was stronger for doses received at older ages, as compared with doses received at younger ages.

Adjusting for age at first internal lung dose increased substantially the risk for doses from external penetrating radiation. It is not clear whether this change is due to an effect of age at dose or to selection bias created by excluding subjects who had received no internal lung doses. By excluding such subjects, we may have selectively removed either cases with low or zero external penetrating doses or controls with high external penetrating doses, or both. The effect of age at received dose deserves further clarification in cohort-based analyses.

There is not an obvious explanation for the risks associated with periods of first hire. Because production activities at Rocky Flats changed over time, it is possible that the chemical and physical properties of airborne plutonium particles also varied with time. Such differences could have produced errors in dosimetry that were related to calendar time. It is also possible that these risks are related to bias in the selection of control subjects.

In separate analyses (41), smoking did not confound by 10 percent or greater (29) the relation between cumulative lung dose and lung cancer. Compared with subjects who had data for smoking frequency, subjects without such data received lower doses from both internal and external radiation exposures, were less likely to have worked during the earlier years of plant operation, and were more likely to have been deceased at the time interviews were conducted. Since data on smoking frequency were not obtained for 32 percent of cases and 16 percent of controls, eliminating subjects without these data altered the distribution of internal and external radiation doses among cases and controls. Because smoking did not confound the relation between cumulative internal lung dose and lung cancer mortality, excluding this variable from multivariate models allowed us to include data for all subjects and to avoid problems with selection bias.

Our analyses suggest that epidemiologic studies of plutonium workers need to account for a number of possible confounding variables in dose-response analyses. They must also be conducted with populations that are representative of those workers who were at risk for internal exposure in order to minimize selection bias. It is also critical that future studies of plutonium workers include estimates of organ doses based on the best available dosimetric models.

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