The Effects of Internal Radiation Exposure on Cancer Mortality in Nuclear Workers at Rocketdyne/Atomics International

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We examined the effects of chronic exposure to radionuclides, primarily uranium and mixed-fission products, on cancer mortality in a retrospective cohort study of workers enrolled in the radiation-monitoring program of a nuclear research and development facility. Between 1950 and 1994, 2,297 workers were monitored for internal radiation exposures, and 441 workers died, 134 (30.4%) of them from cancer as the underlying cause. We calculated internal lung-dose estimates based on urinalysis and whole-body and lung counts reported for individual workers. We examined cancer mortality of workers exposed at different cumulative lung-dose levels using complete risk-set analysis for cohort data, adjusting for age, pay type, time since first radiation monitored, and external radiation. In addition, we examined the potential for confounding due to chemical exposures and smoking, explored whether external radiation exposure modifies the effects of internal exposure, and estimated effects after excluding exposures likely to have been unrelated to disease onset. Dose–response relations were observed for death from hemato- and lymphopoietic cancers and from upper aerodigestive tract cancers, adjusting for age, time since first monitored, pay type, and external (gamma) radiation dose. No association was found for other cancers, including cancers of the lung. Despite the small number of exposed deaths from specific cancer types and possible bias due to measurement error and confounding, the positive findings and strong dose–response gradients observed suggest carcinogenic effects of internal radiation to the upper aerodigestive tract and the blood and lymph system in this occupational cohort. However, causal inferences require replication of our results in other populations or confirmation with an extended follow-up of this cohort. *Key words*: cancer mortality, hematopoietic cancers, internal (alpha) radiation, lymphopoietic cancers, occupational cohort study, upperaerodigestive tract cancers. *Environ Health Perspect* 108:743–751 (2000). [Online 28 June 2000]
http://ehpnet1.niehs.nih.gov/docs/2000/108p743-751ritz/abstract.html

Compared to a wealth of information about effects of low-dose external radiation exposures (gamma and X rays), considerably fewer data are available for quantifying human health risks associated with chronic internal exposure to radionuclides. In animal experiments, high internal doses from alpha- and beta/gamma-emitting radionuclides have resulted in immunosuppressive and carcinogenic effects in organs where these radionuclides concentrate (*1*). The carcinogenic potential of such radionuclides has been confirmed in a few human populations exposed to high doses, including uranium miners and millers, radium dial painters, and patients treated with Thorotrast and ^{224}Ra (*2*,*3*). The sites of cancer have coincided with distribution patterns for the radionuclides within the body, with increases in the incidence of lung, liver, and head–sinus carcinomas, as well as leukemias and bone sarcomas.

Studies published to date examining health effects in workers in the nuclear industry who were exposed internally to radionuclides have yielded inconsistent findings at dose levels less than 1 Sv (100 rem) (Table 1). The lack of consistency may be partly a function of differences in the types of alpha radiation-emitting particles to which workers have been exposed at different nuclear facilities; for example, some workers were primarily exposed to ^{239}Pu and ^{238}Pu, others to uranium dusts, a mixture of tritium, plutonium, and other radionuclides, and others to ^{222}Rn or ^{210}Po (Table 1). After ingestion or inhalation, radioactive particles, depending on their size, solubility, and chemical structure, differ in their distribution through the body, their organ residence time, and the transfer, dissolution, and absorption of the radioactivity associated with the particles (*3*), and hence might be expected to vary in their effects across organ systems. Moreover, there has been considerable variation from study to study in the methods used to estimate internal dose levels. Some studies simply used monitoring status and/or duration as a crude proxy measure of internal exposure, whereas others relied on environmental monitoring of airborne dust concentrations to approximate personal exposures. Several studies used more extensive dose-modeling approaches based on variable combinations of urinalysis, fecal analysis, and *in vivo* organ or whole-body count data, sometimes in association with environmental measures, to calculate whole-body burden (a measure that applies an equal dose to all organs) or organ-specific doses such as to the lung, kidney, or spleen (Table 1). Because of large differences in exposure assessment and the lack of power in smaller cohorts with the most in-depth exposure characterization, comparisons of internal dose levels and of results across studies are problematic and the generalizability of findings may be limited. However, although this heterogeneity across studies may prohibit us from calculating a common effect estimate or validly comparing results across studies, each study contributes information about the potential carcinogenicity of specific radionuclides prevalent in the work environment of a nuclear facility.

In our study we calculated lung doses using several kinds of individual-level monitoring data provided by the facility to examine the cancer mortality risk associated primarily with exposures to uranium and mixed-fission products. Most of the employees included in the analyses were also monitored for external (gamma) radiation.

Materials and Methods

Study Design and Subject Selection

We carried out a retrospective cohort mortality study of workers employed since 1950 at Rocketdyne/Atomics International (RAI), of whom 4,607 were enrolled in the company's health physics radiation monitoring program between 1 January 1950 and 31 December 1993. The analyses were restricted to those

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We gratefully acknowledge the contributions of G. Wilkinson, F. Yu, Y. Wang, J. Moncau, and T. Riggs. We especially thank R. Harrison, L. Bilick, and members of the study's advisory panel.

This study was supported by a grant from the Department of Energy (subcontract 324A-8701-SO163), which was administered by the Public Health Institute in association with the California Department of Health Services. B. Ritz was supported in part by a fellowship of the German Academic Exchange Program.

Received 24 January 2000; accepted 11 April 2000.

Table 1. Nuclear industry cohort and case–control studies that monitored and reported findings for internal radiation exposure.

Study site (reference)	Type of work	No. of workers exposed or monitored	Radionuclides monitored for	Exposure measure used	No. of cancers in monitored workers[a]	Major findings
Rocky Flats (*4,5*)	Nuclear weapons fabrication and assembly	5,413	^{239}Pu	Whole body burden (urine bioassays)	95 cancers (1952–1979, 14.5 years)	Increased risk reported for all hemato- and lymphopoietic cancer mortality for workers with plutonium body burden ≥ 2 nCi
Y-12 at Oak Ridge (*6*)	^{235}U processing for nuclear weapons	3,490	Uranium	Lung dose (lung counting and urine bioassays)	40 lung cancers (1947–1979, 20.6 years)	Increased risk reported for lung cancer mortality for workers exposed to both internal and external radiation
Multiple sites (Y-12 at Oak Ridge, TEC, Fernald, and Mallinckrodt) (*7*)	^{235}U processing for nuclear weapons, uranium refining and processing	Unknown	Uranium, radon, radium	Lung dose (area monitoring and urine bioassays)	Y-12: 142 lung cancers (1947–1983), TEC: 567 lung cancers (1943–1983) Fernald: 51 lung cancers (1951–1983), Mallinckrodt: 27 lung cancers (1942–1983) (1:1 matching of controls to cases)	No increased lung cancer mortality with increase in exposure
Y-12 at Oak Ridge (*8*)	^{235}U processing for nuclear weapons	10,597	Uranium	Employment at Y-12	503 cancers (1947–1990)	Increased risks (SMRs) reported for lymphatic, brain, pancreatic, prostate, and kidney cancer mortality
Fernald (*9*)	Uranium refining and processing	4,014	Uranium	Lung dose (area monitoring and urine bioassays)	112 lung cancers (1951–1990, 31 years)	Increased risk reported for lung cancer mortality among workers exposed to > 200 mSv
Los Alamos National Laboratory (*10*)	Nuclear weapons fabrication and assembly	3,775	^{238}Pu, ^{239}Pu, tritium	Whole-body burden (urine bioassays)	125 cancers (1943–1990, 29 years)	Increased risk reported for lung cancer mortality for workers exposed to plutonium; Hodgkin disease, brain, and esophageal cancer mortality among workers exposed to both tritium and external radiation
Mound (*11*)	Metallurgy of ^{210}Po and plutonium processing	2,181	^{210}Po, ^{238}Pu	Kidney dose (urine bioassays)	126 cancers (1944–1984, 25.8 years)	No effect for internal exposure
Linde (*12*)	Uranium processing	995	Uranium, ^{222}Rn	Lung dose (area monitoring, surface contamination and bioassays)	74 cancers (1943–1979)	Increased risk reported for laryngeal cancer and respiratory disease mortality
Thorium processing plant (*13*)	Thorium processing	3,039	^{232}Th, thoron	Exposure status (yes/no) based on job titles, work areas, and area monitoring	99 cancers (1940–1976)	Increased risk reported for lung and pancreatic cancer mortality and exposure status
UK AEA (*14,15*)	Nuclear research and some power generation	1,418 3,154 5,846	Tritium, Plutonium, Others, unspecified	Annual monitoring status	244 cancers (1946–1986, 22 years)	Increased risk reported for prostate cancers for tritium-monitored workers, uterine cancers for female workers
UK AWE (*16*)	Atomic weapons research and development	3,742 3,044 1,562 638 281	Plutonium Uranium Tritium Polonium Actinium	Annual monitoring status	81 cancers (1951–1982, 18.6 years)	Increased risk reported for prostate and renal cancers among workers monitored for multiple radionuclides, lung cancer for plutonium-monitored workers
Multiple sites: UK AEA, UK AWE, and Sellafield, UK (*17*)	Atomic weapons research and development	17,565	Plutonium; uranium; tritium; polonium; actinium, others unspecified	Annual monitoring status and duration of monitoring	798 cancers (1946–1988, 25 years)	Increased risk reported for testicular and prostate cancers for tritium-monitored workers; lung, uterus, and prostate cancers for workers monitored for "other radionuclides," lung cancers for workers monitored for plutonium (≥ 5 years), all hemato- and lymphopoietic cancers for workers monitored for plutonium
Sellafield, UK (*18*)	Reprocessing and storing of used nuclear fuel	14,319	Plutonium	Annual monitoring status (and urine bioassays)	561 cancers (mortality: 1947–1992; incidence: 1971–1986)	Increased risk reported for breast cancers and ill-defined cancers for plutonium-monitored workers; hemato -and lymphopoietic cancers with increasing cumulative external and plutonium doses
Mayak, Russia (*19–22*)	Atomic weapons research and development	500	Plutonium	Lung dose and whole-body burden (urine bioassays)	162 lung cancers (1:2, 1:3 matching of controls)	Threefold increase in risk for lung cancer for workers exposed to > 5.5 kBq body burden; no effect for workers exposed to less

Abbreviations: AEA, Atomic Energy Authority; AWE, Atomic Weapons Establishment; nCi, nanocurie; kBq, kilobecquerel; TEC, Tennessee Eastman Corporation; SMR, standardized mortality ratio; UK, United Kingdom.
[a]Follow-up period and average length of follow-up in parentheses.

2,297 workers involved in nuclear fuel assembly and disassembly operations who were monitored for internal radionuclide exposure. We chose to exclude radiation workers who were not monitored for internal exposures for two reasons: to minimize exposure misclassification, since some unmonitored workers probably were exposed to radionuclides, especially before 1963; and to minimize possible selection bias resulting from differences in unmeasured risk factors between monitored and unmonitored workers, a phenomenon demonstrated in the Rocky Flats cohort by Wilkinson and Morgenstern (*23*).

It was necessary to exclude 39 otherwise eligible workers for whom the records lacked enough information to determine vital status. We did not restrict the cohort on the basis of employment duration, race, or gender. All but 44 of the workers included in the internal radiation assessments had also been monitored for external radiation exposure. Follow-up for each subject began at the start of internal monitoring or on 1 January 1950, whichever date was later. Follow-up ended on the date of death of a cohort member or on 31 December 1994, whichever date came earlier.

Ascertainment of Deaths

Vital status determinations identified 441 subjects who died between 1959 and 1994. We received death certificates of vested cohort members from the company. If two independent company data sources identified an employee as active, and thus alive, at the end of follow-up, we counted him or her as living. About 10% of the cohort members were identified as living.

Employees not identified as alive or dead by company records were checked against three different record systems: the Social Security Administration (SSA) beneficiary-records files (period covered, 1935–1994), the vital statistics files for the State of California (period covered, 1960–1994), and the U.S. National Death Index (NDI) (period covered, 1979–1994). Matches were verified from a review of information on death certificates. We were able to obtain all but 12 death certificates for deceased subjects. Among these 12 deaths, 7 (58%) workers were unexposed, 4 (33%) belonged to the 1–< 5 mSv group, and 1 (8%) to the 5–30 mSv group. Because this exposure distribution is similar to the one observed for all workers (Table 2), we concluded that we did not differentially lose exposed or unexposed workers, and thus did not expect this lack of information to bias our results.

The underlying and contributing causes of death recorded on the certificates were coded using the *International Classification of Diseases, Ninth Revision* (ICD-9) (*24*,*25*) by a licensed nosologist. The accuracy of the coding was verified by members of the study team. For some analyses the ICD-9 codes were translated into *Eighth Revision of the International Classification of Diseases* (ICD-8) codes (Table 3). All results presented in this paper are based on cancers as the underlying cause of death.

Radiation Measurements

Throughout the study period, RAI conducted periodic bioassays of urine or feces, as well as *in vivo* whole-body counts and lung counts, to estimate internal doses for workers assigned to areas potentially contaminated by radioactive materials. These doses resulted from inhalation and, to a lesser

Table 2. Characteristics of 2,297 cohort members monitored for internal radiation, by sex.

	Male	Female	Total (%)
Number of employees	2,218	79	2,297
Average follow-up time (years)	25.5	23.1	25.4
Average age at entry into cohort (years)	34.5	33.7	34.5
Number of person-years	56,610	1,827	58,837
Number of deaths	433	8	441
Total mortality rate (per 10^5/year)	764.9	437.9	749.5
Total cancer mortality rate (per 10^5/year)	234.9	54.7	227.7
Pay type			
Salaried managerial/professional	682	25	707
Salaried technical/administrative	189	33	214
Hourly/union	1,272	18	1,290
Unknown	75	3	78
Internal radiation dose (mSv)			
0	1,279	54	1,333 (58.0)
0–< 5	672	19	691 (30.1)
5–< 30	250	6	256 (11.2)
≥ 30	17	0	17 (0.7)

Table 3. Observed (OBS) and expected (EXP) numbers of deaths among male subjects and estimated SMR, by cause of death: comparison with the U.S. white male population.

Cause of death	No. OBS	No. EXP	SMR	95% CI
All causes of death (ICD-8 001–998)	433	598.32	0.72	0.66–0.80
All cancers (ICD-8 140–229)	133	152.72	0.87	0.73–1.03
Cancers				
Buccal cavity and pharynx (ICD-8 140–149)	3	4.05	0.74	0.15–2.16
Digestive organs and peritoneum (ICD-8 150–159)	36	36.67	0.98	0.69–1.36
Esophagus (ICD-8 150)	5	3.84	1.30	0.42–3.04
Stomach (ICD-8 151)	6	5.07	1.18	0.43–2.57
Large intestines (ICD-8 153)	15	13.54	1.11	0.62–1.83
Pancreas (ICD-8 157)	8	7.49	1.07	0.46–2.11
Respiratory system (ICD-8 160–163)	50	59.46	0.84	0.62–1.11
Larynx (ICD-8 161)	4	2.01	1.99	0.54–5.11
Lung, primary and secondary (ICD-8 162)	46	56.95	0.81	0.59–1.08
Skin (ICD-8 172,173)	5	3.48	1.44	0.46–3.36
Prostate (ICD-8 185)	7	9.59	0.73	0.29–1.50
Bladder (ICD-8 188)	3	3.39	0.89	0.18–2.59
Kidney (ICD-8 189)	5	3.97	1.26	0.41–2.94
Brain and other central nervous system (ICD-8 191,192)	6	4.60	1.31	0.48–2.84
Leukemia and aleukemia (ICD-8 204–207)	8	5.47	1.46	0.63–2.88
Lymphopoietic cancer (ICD-8 200–208)	12	14.45	0.83	0.43–1.45
Other causes				
All diseases of circulatory system (ICD-8 390–458)	183	270.24	0.68	0.58–0.78
Arteriosclerotic heart disease, including CHD (ICD-8 410–414)	118	192.61	0.61	0.51–0.73
All vascular lesions of CNS (ICD-8 430–438)	20	26.98	0.74	0.45–1.15
All respiratory diseases (ICD-8 460–519)	30	40.26	0.75	0.50–1.06
Emphysema (ICD-8 492)	7	6.27	1.12	0.45–2.30
All diseases of digestive system (ICD-8 520–577)	12	28.98	0.41	0.21–0.72
Cirrhosis of liver (ICD-8 571)	9	16.69	0.54	0.25–1.02
All diseases of genito-urinary system (ICD-8 580–629)	5	6.44	0.78	0.25–1.81
All external causes of death (ICD-8 800–998)	35	56.54	0.62	0.43–0.86
Suicide (ICD-8 950–959)	9	14.88	0.60	0.28–1.15
Total residual[a]	12	1.30	9.22	
Cancer residual[b]	5	11.75	0.43	

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval.
[a]Including undetermined causes of death and missing causes of death due to missing death certificates. [b]Cancers of unspecified site.

degree, ingestion and skin absorption of radionuclides. Most of the available internal dose records were for the period 1963–1983. Before 1963, few measures of internal exposures were taken, and by 1983, all major operations involving radionuclides had been discontinued. Company policy during the early years was to monitor only those individuals with a significant possibility of receiving annual lung-dose equivalents in excess of 150 mSv.

We calculated an estimated internal cumulative dose to the lung for each employee. The primary radionuclides included in the dose estimates were *a*) uranium, with a range of degrees of enrichment for ^{235}U; *b*) mixed-fission products (unspecified as to radionuclide); *c*) ^{90}Sr; *d*) ^{137}Cs; and *e*) small amounts of plutonium. In addition, measurements of gross beta and gross alpha radiation in samples were available for some individuals. Methods for converting bioassay results to annual dose (in units of millisieverts) were based on the biokinetic models of International Commission on Radiological Protection publications (*26*,*27*) and on the mathematical techniques described in a report by Crawford-Brown and co-workers (*28*,*29*). This approach yielded the following conversion factors for the primary radionuclides of interest:

- For uranium urinalyses, each 15 dpm excreted per day translates to an average value of 5 mSv exposure to the lung per year. This conversion factor represents a mean lung removal half-time of 120 days and a urine excretion fraction of 0.8.
- For *in vivo* uranium lung counts, the conversion factor is obtained directly from the RAI estimate of the percent maximum permissible lung burden. In each case, the time-averaged percent maximum permissible lung burden (%MPLB) for an individual is multiplied by 1.5 mSv. The conversion factor for the dose to the bone marrow is approximately 0.2 mSv/%MPLB.
- For mixed-fission products, the conversion depends on the availability of information on the radionuclide involved. In cases where the radionuclide was specified in the records (e.g., ^{90}Sr or ^{137}Cs), committed effective dose equivalents had already been calculated by the facility health physics staff. These calculations were checked and, if confirmed, used as the dose for an individual. Where the radionuclide was not specified, a representative conversion factor based on an assumption of ^{90}Sr intakes and a class Y retention half-time in the lung was used. The resulting conversion factor is 5 mSv/year to the lung per 250 dpm excreted per day.
- For plutonium, the conversion factor used was 10 mSv/year exposure to the lung per disintegrations per minute per day. This factor is appropriate for a class Y plutonium compound.

For urinalysis measurements of uranium, plutonium, and mixed-fission products, we used radiometric or fluorometric techniques. The more reliable radiometric method was the primary basis of dose estimation for uranium intakes in this study. When records listed "mixed-fission products," it was possible only in a few cases to determine the radionuclide present in the sample. In addition, there were limited *in vivo* lung counting results for ^{235}U. For every worker, we examined records for each of the radionuclides separately and sorted them by calendar time within each year. A time-weighted average measurement for an individual was then obtained for each year by weighting each reading in that year by the fraction of the year until the next reading in the temporal sequence. For example, if X_1 were a reading obtained on 1 January of a year and if X_2 were a reading obtained on July 1 of that same year, then the average for the year would be $0.5X_1 + 0.5X_2$, since each reading would represent the exposure measure for approximately 50% of that year. The exception was at the end of the monitoring period (indicated by the end of monitoring records for an individual), in which case the radionuclide was assumed to be removed with a half-life depending on the particular radionuclide, and the resulting integral of activity versus time was calculated. We obtained a time-weighted average lung burden for each worker. More than 95% of the reported or calculated doses from internal exposures were from uranium and mixed-fission products.

At RAI, the health physics team identified workers potentially exposed to significant internal radiation doses from airborne contaminants for inclusion in a routine quarterly monitoring program. Some workers were monitored only in the event of accidents involving radioactive material spills. Thus, there might be no measurements available for an individual during a certain period, even though exposure may have occurred. Most records did not distinguish between routine and accident-driven monitoring, and we assumed that the record represented a routine measurement. Consequently, the assumption of time weighting used in this study overestimates doses for instances in which the measurement was due to an accident, but was not designated as such.

Fortunately, it was possible to separate routine and accident-related measurements for individuals with large annual doses (> 10 mSv in a year). For other measurements that were due to an accident, however, we overestimated the true average annual dose by counting the measurement as an average dose, instead of a one-time peak dose. On the other hand, a potential for underestimation of the true average annual dose existed due to the minimum detection limits (MDLs) of the assay methods in use (the MDL was 2 mSv for uranium and plutonium and 0.5 mSv for mixed-fission products).

We used RAI records of external radiation monitoring, including whole-body dose measurements for gamma rays and X rays, to calculate cumulative dose from external exposure (*30*). For those 44 workers never monitored for external radiation exposure, we assumed an external dose of 0 mSv.

Treatment of Potential Confounders

We used personnel and medical records to explore such potential confounders as occupational/socioeconomic status, race, workplace exposure to carcinogenic chemicals, and smoking history. Based on personnel records, workers were assigned to one of three pay-type categories (hourly, salaried technical/administrative, or managerial/professional); this variable was used as a proxy for occupational/socioeconomic status. Employees who changed titles or pay type were categorized according to the titles and pay types held longest at RAI. The 78 subjects lacking job titles and pay type were assigned to the hourly category. Because RAI did not systematically collect data on the race of its employees before 1972, we were unable to control for the influence of this factor in our analyses. According to the information on death certificates, however, 96% of all deceased workers were white.

Job titles, employment periods, and, when available, job locations were used to create proxy measures for chemical exposures during the study period. We determined that hydrazine, asbestos, beryllium, and many solvents had been used extensively at Rocketdyne/AI. We categorized workers as highly, moderately, potentially, or not likely to be exposed to asbestos and hydrazine.

Information about tobacco smoking was systematically recorded for two subgroups of subjects in routinely administered medical questionnaires from different periods. Questionnaires from 1961 to 1969 indicated only whether the worker was a smoker (yes/no); after 1980, the level of smoking and dates of starting and quitting were specified. Because information on smoking was not available for most of the study cohort, we examined the association between smoking status and cumulative radiation dose in those workers for whom information on smoking was available (658 subjects) to assess potential confounding in the larger cohort.

Statistical Methods

We used two different analytic approaches: external comparisons of our monitored

workers with the general U.S. white male population; and internal comparisons among monitored workers according to measured dose levels of radiation exposure (dose–response analyses). In external comparisons, the Monson program (*31*) was used to estimate standardized mortality ratios (SMRs; = observed/expected deaths) for the monitored study population. We estimated expected numbers of deaths from the mortality rates of the U.S. white male population, stratified by age (5-year categories) and calendar year (5-year intervals). Estimation of 95% confidence limits for the SMRs was based on a formula derived by Byar and recommended by Breslow and Day (*32*).

Because our study population yielded 10 or fewer deaths for many types of cancer, it was not possible to perform informative dose–response analyses; thus, it was necessary to combine deaths from selected cancers. The choice of which cancers and cancer groups to evaluate was made *a priori* on the basis of the distribution within the body of the radionuclides of major concern. These radionuclides emit densely ionizing alpha radiation that usually reaches and damages only the tissues in its immediate vicinity—within micrometers of the particle (*1*). Exceptions are the air-filled spaces in the lung, which allow alpha particles to reach greater distances, such that almost any tissue constituent of the lung may receive a considerable dose of radiation, and radionuclides that dissolve from particles into systemic circulation from which they deposit in other tissues. Cells located at bifurcations, where removal is significantly slower than in the tubular airways, will experience significantly higher doses than those lining the tubular airways. In addition, for alpha emitters such as those considered here, microdosimetric considerations show that most cells will have a dose of zero, with a small fraction of cells having doses on the order of tens of rads due to the passage of one or a few alpha particles through the nucleus. Because risk coefficients generally are developed using mean tissue doses, however, we chose to use mean dose in the present study rather than the more detailed microscopic dose distribution.

Relatively insoluble radioactive particles that reach the alveoli are gradually translocated to tracheobronchial and other thoracic lymph nodes, which may accumulate concentrations of inhaled material several hundred times greater than in the regions of the lung (*1*). Larger particles (≥ 10 μm) rarely reach the lower respiratory tract or, if they do, are cleared rapidly and completely. Such particles can deliver intense doses of concentrated alpha radiation to regions of the naso- and oropharyngeal systems and the upper gastrointestinal tract.

Thus, any effects of internally deposited radionuclides are most likely to be evident in those tissues receiving the highest dose. In general, these will be the tissues of the portal organs (lungs for inhalation and gastrointestinal tract for ingestion) for the highly insoluble compounds, or the bone for the more soluble compounds (for translocation of uranium and strontium). Because solubility is unknown for this population, it was not possible to estimate doses to tissues other than the lung tissue, and even for the lung we obtained only a relative measure of dose, as the absolute value of the dose depends on solubility. Accordingly, we conducted dose–response analyses for *a*) lung cancer (ICD-9 162); *b*) upper aerodigestive tract cancers encompassing the naso-oropharyngeal regions, esophagus, and stomach (ICD-9 140–151); *c*) hemato- and lymphopoietic cancers (ICD-9 200–208, excluding chronic lymphatic leukemias); *d*) urinary-tract cancers (ICD-9 188–189); and *e*) prostate cancer (ICD-9 185). Other organs to which some radionuclides are translocated and stored are the liver (Thorotrast), bones (plutonium), and the thyroid (iodine). We did not, however, observe any bone, thyroid, or primary liver cancers among workers monitored for internal radiation.

To estimate effects in the dose–response analyses, we used the risk-set approach for the analysis of cohort study data, which was recommended by Breslow and Day (*32*), using the full cohort information. In this approach, conditional logistic regression is used to compare individuals who have died of cancer (outcome events) with all individuals still at risk of dying from cancer (survivors). We constructed risk sets of deaths and survivors matched on calendar time for use in the analysis by matching to each cancer death all cohort members who were still alive at the time of the index subject's death. This approach allowed us to treat cumulative dose and all other time-varying variables, such as time since first monitoring, as time dependent, (i.e., values for these factors were determined for all risk-set members at the time of each index death).

We modeled cumulative internal radiation dose both as a set of binary variables and as a continuous variable (in 10-mSv increments). Based on the dose distribution in our cohort, we categorized dose equivalents into 4 levels: 0 mSv, > 0–5 mSv, > 5–< 30 mSv, and ≥ 30 mSv. To allow for a period of induction/latency between radiation exposure and cancer death and to reduce possible selection bias (*33*), we lagged cumulative doses by 0, 2, and 10 years. Lagging entailed limiting the level of cumulative dose for each individual in a risk set to the dose level achieved 0, 2, and 10 years before the index death occurred. As recommended, we adjusted in all models for time since first monitored to avoid the possible selection bias inherent in the analyses of cumulative exposures (*34*).

We used results of the conditional logistic regression analyses to estimate rate ratios (RR) and 95% confidence intervals (CI) for internal radiation and other covariates in the model. To test for a monotonic trend in the association between cumulative dose and cancer mortality, the mean of the four dose categories were used as exposure scores. We explored a variety of potential confounders, but retained in the final models only those covariates that changed the estimated RR for radiation exposure by > 10% for any outcome (*35*). Accordingly, pay status, time since first monitored, and age at risk (continuous) but not exposure to chemicals were included in all models presented in this paper. Because Checkoway et al. (*6*) reported a positive association between internal and external radiation dose in Oak Ridge workers, all analyses of internal radiation effects were also adjusted for the effect of external radiation dose (treated as continuous in 10-mSv increments).

Results

The Rocketdyne/AI cohort monitored for internal radiation exposure was characterized by a long follow-up period (average 25.4 years), a high percentage of salaried employees (40.1%), and few women (Table 2). Only 0.7% of these workers received estimated internal radiation doses to the lung > 30 mSv, and slightly more than half of the workers had recorded doses of 0 mSv.

During the study period, 19.2% of the cohort members died (441 total deaths). We observed 133 deaths from cancer as the underlying cause among males and one such cancer death among females, yielding a total cancer mortality rate of 235 per 10^5/ year (Table 1).

Comparing the mortality experience of male RAI workers monitored for internal radiation with the white male U.S. population resulted in SMRs of 0.72 (95% CI, 0.66–0.80) for all causes, 0.87 (95% CI, 0.73–1.03) for all cancers, and 0.68 (95% CI, 0.58–0.78) for all circulatory system diseases (Table 3). These results indicate that members of the RAI cohort are healthier than the general population [i.e., a strong healthy worker (selection) effect exists], an effect we would expect to observe in a cohort with a large proportion of higher socioeconomic status employees and extensive health insurance coverage (see also "Discussion"). For specific cancer sites, we did not observe SMRs for which the 95% CIs excluded the null value of 1.

In dose–response analyses, monotonic associations were observed between cumulative internal dose and mortality from

hemato- and lymphopoietic cancers and from cancers of the upper aerodigestive tract (Tables 4 and 5). The rate ratios for hemato- and lymphopoietic cancers, comparing a cumulative dose ≥ 30 mSv with 0 mSv, was 44.6 (95% CI, 5.64–353), and the corresponding rate ratio for upper-aerodigestive tract cancers was 57.2 (95% CI, 8.17–401). Total cancer mortality was also elevated somewhat for cumulative doses ≥ 30 mSv (RR = 2.56; 95% CI, 0.93–7.09). We found no effects of internal radiation on mortality from lung cancer, urinary tract cancers, or prostate cancer (Tables 4 and 5). Lagging doses by 2 and 10 years did not change the results of the analyses (Table 5), nor did adding to the cancers specified as underlying causes of death all cancers listed as contributing causes (results not shown).

For the 2,253 workers monitored for both external and internal radiation, we estimated the combined effects on total cancer mortality of both types of radiation, cross-classified into nine dose categories. Although there were no cancer deaths in the highest combined dose category (≥ 200 mSv external and ≥ 30 mSv internal radiation), the cancer mortality RRs were elevated appreciably (RR > 5) for monitored workers in the next highest combined dose categories (Table 6). However, the 95% confidence intervals are quite wide for these estimates, indicating low precision of these estimates based on small numbers.

We did not find an association between smoking and cumulative internal radiation dose during the 1960s (Table 7). On the other hand, exposed workers who were still employed in the 1980s were more likely than unexposed workers to have quit smoking, and the fraction of unexposed workers who continued smoking remained disproportionately high relative to both their exposed co-workers and California males in general (*36*).

Discussion

We observed a strong healthy worker (selection) effect in our cohort: compared to the U.S. population, monitored RAI nuclear workers experienced lower rates of death from all causes, from all cancers, and particularly from all circulatory system diseases. This phenomenon is characteristic of occupational cohorts in general, but is especially strong in the nuclear industries for which mean all-cause SMRs have been reported to be even lower (0.79) than the corresponding mean SMRs (0.83) reported for a large number of other industries (*37*). The all-cause SMR in our cohort is low (0.72) mainly because RAI employees exhibit a large deficit in cardiovascular disease mortality (SMR = 0.62) which may be due to differences in lifestyle factors (diet, smoking, physical activity) when comparing these Californian workers to the rest of the United States or may be related to the extensive health insurance coverage these nuclear workers enjoyed throughout their employment. Greater health insurance coverage of workers may also be responsible for reducing fatality rates of many common cancers such as those of the colon, prostate, and bladder; for these organs, fatality depends on early detection and medical treatment of the cancer (*38*).

Exposure levels in the cohort studied were relatively low; the mean lung dose from internal radionuclide exposure for 2,297 monitored workers was estimated to be 2.1 mSv, a dose much lower, for example, than the average lung dose of 82.1 mSv reported for 3,491

Table 4. Adjusted rate ratio (RR) estimates (and 95% confidence intervals) for the effect of cumulative internal radiation dose and other factors on cancer mortality, by cancer type, assuming zero lag for exposure: results of conditional logistic regression analyses.

Predictors	All cancers	Hemato- and lymphopoietic cancers (ICD-9 200–208)[a]	Lung cancers (ICD-9 162)	Upper aerodigestive tract cancers (ICD-9 140–151)	Bladder and kidney cancers (ICD-9 188,189)	Prostate cancers (ICD-9 185)
Age at risk[b]	1.10 (1.08–1.12)	1.10 (1.03–1.18)	1.10 (1.07–1.13)	1.09 (1.04–1.15)	1.18 (1.09–1.27)	1.20 (1.10–1.31)
Time since first monitored[b,c]	0.99 (0.97–1.01)	0.99 (0.89–1.09)	0.97 (0.93–1.02)	0.94 (0.85–1.03)	0.95 (0.84–1.07)	0.98 (0.92–1.04)
Pay type						
Salaried managerial/ professional vs. other	0.75 (0.51–1.10)	1.05 (0.26–4.27)	0.49 (0.21–0.97)	0.64 (0.17–2.35)	0.79 (0.16–4.06)	1.23 (0.22–6.95)
External radiation dose (10 mSv)[c,d]	1.02 (0.98–1.06)	1.06 (1.00–1.13)	1.06 (1.01–1.11)	0.92 (0.76–1.12)	1.05 (0.91–1.21)	0.19 (0.03–1.32)
Internal radiation dose (mSv)[c]						
0	1.00 (n = 79)[e]	1.00 (n = 2)	1.00 (n = 30)	1.00 (n = 3)	1.00 (n = 5)	1.00 (n = 5)
> 0–< 5	0.86 (0.58–1.27) (n = 36)	2.31 (0.37–14.2) (n = 3)	0.58 (0.28–1.21) (n = 9)	4.75 (1.12–20.2) (n = 6)	1.07 (0.23–5.02) (n = 3)	1.59 (0.28–9.06) (n = 2)
≥ 5–< 30	0.87 (0.45–1.67) (n = 15)	6.10 (0.89–41.7) (n = 3)	0.45 (0.12–1.67) (n = 5)	10.56 (1.91–58.4) (n = 3)	0.00 (n = 0)	0.0 0 (n = 0)
≥ 30	2.56 (0.93–7.09) (n = 4)	44.6 (5.64–353) (n = 2)	0.00 (n = 0)	57.2 (8.17–401) (n = 2)	0.00 (n = 0)	0.00 (n = 0)
p for trend[f]	0.087	0.0001	0.20	0.0001	0.43	0.65

[a]Excluding chronic lymphatic leukemias. [b]Measured in one year increments. [c]Treated as time-dependent. [d]Assumes dose due to radionuclides equal to zero for employees not monitored for external radiation. Measured in 10-mSv increments. [e]Number of cancer deaths shown in parentheses. [f]The test for trend was performed by entering an interval variable with the category means as the score values into the logistic regression model.

Table 5. Adjusted rate ratio (RR) estimate (and 95% confidence interval) and two-tailed p-value for the effect of cumulative internal radiation dose in 10-mSV increments, by cancer type and lag for exposure: results of conditional logistic regression analyses.

Internal radiation dose (per 10 mSv)	All cancers (n = 134)		Hematopoietic and lymphopoietic cancers[a] (ICD-9 200–208) n = 10		Lung cancers (ICD-9 162) n = 44		Upper aerodigestive tract cancers (ICD-9 140–151) n = 14		Bladder and kidney cancers (ICD-9 188, 189) n = 8		Prostate cancers (ICD-9 185) n = 7	
	RR	p	RR	p	RR	p	RR	p	RR	p	RR	p
0-year lag	1.03 (0.88–1.20)	0.70	1.23 (0.97–1.55)	0.08	0.75 (0.32–1.76)	0.50	1.25 (1.05–1.48)	0.01	0.13 (0.00–18.5)	0.42	0.08 (0.00–375)	0.56
2-year lag	1.03 (0.89–1.21)	0.66	1.23 (0.97–1.55)	0.08	0.76 (0.33–1.76)	0.52	1.25 (1.05–1.49)	0.01	0.13 (0.00–18.8)	0.43	0.08 (0.00–374)	0.56
10-year lag	1.04 (0.88–1.22)	0.68	1.24 (0.98–1.55)	0.07	0.74 (0.29–1.92)	0.54	1.23 (1.01–1.50)	0.04	0.19 (0.00–20.8)	0.49	0.09 (0.00–371)	0.57

[a]Excluding chronic lymphatic leukemias.

workers monitored for uranium exposure at the Oak Ridge Y-12 facility (*6*). Moreover, because the quality of our internal radiation data did not allow us to calculate specific organ doses other than to the lung, all internal exposure risk estimates were calculated on the basis of expected doses to the lung. Thus, we relied on lung doses to approximate dose levels to a range of organs involved in radionuclide passage through the body (see Methods), some of which may have been subjected to very different levels of exposure, depending on the radioactive decay process and the retention function of the radionuclide for different organs. Although the computed lung doses can serve as crude indicators of the magnitude of doses delivered to other organs, our dose estimates should be interpreted in relative rather than in absolute terms. In general, dose comparisons with other studies may not be appropriate even for those also relying on lung doses because we lacked information on solubility, on which accurate estimates of lung dose depend.

Despite these limitations, we detected increases in mortality from hemato- and lymphopoietic cancers with increasing internal radiation dose among RAI employees, a finding also reported by two previous studies of nuclear workers exposed to plutonium (*4*,*5*,*18*). Wilkinson et al. (*4*) reported that Rocky Flats employees with positive plutonium body burdens experienced elevated mortality from blood and lymphatic system cancers. These results were more pronounced and showed a dose–response gradient when the follow-up of the Rocky Flats cohort was extended (*5*). Omar et al. (*18*) observed an increase in the incidence of these cancers with increasing cumulative plutonium plus external radiation doses among Sellafield workers. Elevated rates of hemato- and lymphopoietic cancers have also been observed in groups of medical patients treated with high doses of Thorotrast (*3*). Archer et al. (*39*) reported an SMR of 4 for these cancers among uranium miners and millers (based on four cases), and Waxweiler et al. (*40*) found a small increase for lymphatic cancers among uranium millers (also based on small numbers).

The dose–response relationship that we observed between internal radiation exposure and death from cancers of the upper aerodigestive tract has not previously been described in occupational cohorts exposed to low doses. At high levels of exposure, radium dial painters have suffered an excess of head–sinus cancers (*3*). Furthermore, the effect estimates based on the continuous dose (Table 5) did not change when we considered only the 11 esophageal and gastric cancers out of the group of 14 upper aerodigestive tract cancers. Wilkinson (*41*) reported a strong ecologic association between uranium deposits and gastric cancer mortality among counties in New Mexico. These results should be interpreted with caution, however, because of possible ecologic bias (*42*) and confounding due to the effects of other environmental carcinogens such as arsenic and cadmium.

Other studies of nuclear workers have not reported increases in cancers of the upper aerodigestive tract at (lung) doses apparently higher than those in our cohort, yet it is not clear whether other researchers ever examined effects on these organs in a dose–response analysis. Our external comparisons did not alert us to an excess mortality for cancers of these organs compared to the general U.S. population, possibly because RAI workers drank less alcohol (the observed number of liver cirrhosis deaths was about half that expected; Table 3), while dose–response analyses showed strong effects with increasing radionuclide exposure. Thus, researchers using external comparisons to guide their choice of organ sites for dose–response analyses may have been misled. Our positive findings may be due, in part, to the long follow-up period in our study and the properties of the radioactive particles to which workers at RAI were exposed. Moreover, the true dose delivered to the upper aerodigestive tract may be higher than indicated by our exposure measures, which were calculated as doses to the lung and derived mainly from urinalysis and lung-count data. Although most internal exposures are likely to involve inhalation, some radionuclide particles, depending on size, will not reach the lower respiratory tract or will be cleared by the ciliary system and swallowed. Because such particles have little or no residence time in the lungs, they are unlikely to be detected in a lung count. Because they are excreted through feces, they would also be missed by urinalysis; however, fecal analyses were rarely performed in our cohort. Nevertheless, these particles can deliver intense doses of concentrated alpha radiation to regions of the naso- and oropharyngeal and upper gastrointestinal system (*1*). Thus, our dose categories based on lung-dose estimates should be interpreted in a qualitative rather than quantitative fashion for the gastro-intestinal tract and other organs. It is reasonable, however, to assume that workers with higher lung doses were at greater risk for exposure to non-respirable radioactive particles, although the ratio of respirable to non-respirable particles may have varied.

The observed excess rate of total cancer mortality in workers in the highest dose category (≥ 30 mSv) (Table 4) is due entirely to

Table 6. Adjusted rate ratio (RR) estimates (and 95% CIs) for the combined effects of cumulative internal and external radiation dose on total cancer mortality among all 2,253 subjects monitored for both internal and external radiation, by dose level assuming a zero year lag for both exposures: results from a conditional logistic regression analyses.[a]

	Internal dose					
	< 5 mSv		≥ 5–< 30 mSv		≥ 30 mSv	
External dose	No. of cancer deaths	RR	No. of cancer deaths	RR	No. of cancer deaths	RR
< 20 mSv	92	1.00[b]	5	0.86 (0.35–2.12)	2	2.05 (0.50–8.38)
20–< 200 mSv	21	1.18 (0.73–1.90)	4	0.84 (0.31–2.30)	2	5.99 (1.47–24.45)
≥ 200 mSv	1	1.36 (0.19–9.79)	3	5.33 (1.66–17.10)	0	–

[a]Adjusted for age at risk, pay type (salaried managerial/professional versus other), and time since first internally monitored. [b]Reference category.

Table 7. Smoking prevalence for internally monitored cohort members who were included in a medical survey containing questions about smoking at two different periods, by cumulative internal radiation dose level.

	1961–1969			1980–1992			
Dose level (mSv)	No. of smokers (%)	No. of nonsmokers (%)	Total (%)	No. of smokers (%)	No. of ex-smokers (%)	No. of nonsmokers (%)	Total (%)
0	170 (64.2)	95 (35.8)	265 (100)	40 (42.1)	31 (32.6)	24 (25.3)	95 (100)
≥ 0	152 (64.4)	84 (35.6)	236 (100)	18 (29.0)	28 (45.2)	16 (25.8)	62 (100)
Total	322 (64.3)	179 (35.7)	501 (100)	58 (36.9)	59 (37.6)	40 (25.5)	157 (100)

deaths from cancers of the hemato- and lymphopoietic system and upper aerodigestive tract. We did not observe an effect of internal radiation on cancers of the urinary tract or prostate among RAI workers. British studies found increased incidence rates of prostate and renal cancers in nuclear workers who were either exposed primarily to tritium or to a variety of different radionuclides (*14–16*). Our negative results for urinary tract and prostate cancers might be attributable to the absence of tritium exposures in our cohort, the lower power of our study, lower radionuclide doses delivered to the urinary system (perhaps with a greater degree of partitioning to the gastrointestinal tract), or the use of mortality rather than incidence data. Furthermore, the absence of bone, liver, or thyroid cancers may be due to the fact that RAI workers were primarily exposed to uranium compounds and not other radionuclides favorably deposited in the latter two organs and/or the small number of such cancers expected in our cohort.

We also did not detect a positive association between internal radiation dose and lung cancer mortality in our cohort. British studies demonstrated a trend of increasing mortality from lung cancers with increasing external radiation doses only among those workers who were also monitored for internal exposure to radionuclides, and an overall increase in respiratory tract cancers among plutonium workers could not be explained by external radiation doses (*14–16*). Similarly, at Oak Ridge Y-12, Checkoway et al. (*6*) found the strongest gradient for the effect of cumulative gamma radiation dose (external) on lung cancer mortality in a subgroup of workers exposed to > 50 mSv of internal alpha radiation, primarily from uranium. Dupree et al. (*7*) were unable to confirm these results when extending the Oak Ridge follow-up by 3 years. However, the later analysis differed from the original in one important aspect: nonmonitored workers were included in the unexposed group. Wiggs et al. (*10*) reported a slightly elevated lung cancer mortality among plutonium-exposed workers at the Los Alamos National Laboratories. Fernald uranium processing workers exposed to alpha radiation at levels > 200 mSv also experienced an increased risk of dying from lung cancers (*9*). Several Russian studies of plutonium workers employed at the Mayak nuclear enterprise recently also reported an increased risk of lung cancers among workers exposed to high levels of plutonium (*19–22*).

The lack of a positive association between lung cancer mortality and radionuclide dose in our cohort may be due to RAI workers having actually received relatively low doses to the lung tissue, very few workers having been exposed to plutonium, or incomplete control for confounding by other risk factors. The most likely potential confounders are smoking and exposure to chemical carcinogens such as asbestos, hydrazine, and beryllium. We did not have the information necessary to adjust for beryllium exposures, and our measures of asbestos and hydrazine exposure, based almost entirely on job titles, are likely to suffer from misclassification. Although we could not adjust for smoking in the analyses, we were able to evaluate smoking data in a subgroup of internally monitored workers. We found that among those still employed in the 1980s, the proportion of current smokers was substantially higher for unexposed than for exposed workers. This disparity suggests that negative confounding due to smoking might be occurring in our cohort, potentially obscuring the effect of radiation exposure on lung cancer mortality.

In summary, despite the small sample size and relatively low lung doses recorded for workers at RAI, this study has demonstrated a dose–response association between cumulative internal radiation dose and mortality from hemato- and lymphopoietic cancers. In addition, we have seen evidence for a dose-response association with upper aerodigestive tract cancers that may have resulted from the ingestion of nonrespirable particles that were cleared from the upper and lower respiratory tract. Our latter finding is based on a pooling of specific cancer types that have not been examined as a group in previous radiation studies. Although we found strong dose–response gradients for these two types of cancers, our estimates are imprecise due to the small number of cases in each group and should be confirmed by further follow-up of the present cohort.

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