

Bone Cancers in Mayak Workers

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Bone cancer mortality risks were evaluated in 11,000 workers who started working at the “Mayak” Production Association in 1948–1958 and who were exposed to both internally deposited plutonium and external γ radiation. Comparisons with Russian and U.S. general population rates indicate excess mortality, especially among females, plutonium plant workers, and workers with external doses exceeding 1 Sv. Comparisons within the Mayak worker cohort, which evaluate the role of plutonium body burden with adjustment for cumulative external dose, indicate excess mortality among workers with burdens estimated to exceed 7.4 kBq (relative risk = 7.9; 95% CI = 1.6–32) and among workers in the plutonium plant who did not have routine plutonium monitoring data based on urine measurements (relative risk = 4.1; 95% CI = 1.2–14). In addition, analyses treating the estimated plutonium body burden as a continuous variable indicate increasing risk with increasing burden ($P < 0.001$). Because of limitations in current plutonium dosimetry, no attempt was made to quantify bone cancer risks from plutonium in terms of organ dose, and risk from external dose could not be reliably evaluated. © 2000 by Radiation Research Society

INTRODUCTION

During the early period of operation of the Mayak nuclear facility, which is located in the Chelyabinsk region of the Russian Federation, many workers were exposed to inhaled plutonium at levels much higher than those considered permissible today. These workers were also exposed to doses of external γ radiation that were substantially higher than current occupational dose limits. Although workers exposed to plutonium in U.S. facilities have been studied, the level of the exposures and the small number of workers who have received such exposure greatly limit what can be

learned about plutonium-related health effects. The Mayak worker cohort thus offers a unique resource for studying the health effects of exposure to plutonium as well as the effects of protracted external dose.

It is known that the lung, bone and liver receive the largest doses from inhaled plutonium from data from both humans and experimental animals. Results of analyses of plutonium-related lung cancer have recently been reported (1–3). This paper addresses bone cancer risks, and a companion paper (4) addresses liver cancer risks.

DESCRIPTION OF THE DATA

The Mayak nuclear facility, which began operations in 1948, includes nuclear reactors, a radiochemical plant, and a plutonium production facility, but only the latter two facilities involve plutonium exposure. Analyses in this paper are based on the cohort of workers who were initially employed in one of the main plants in the years 1948–1958. Workers employed in more than one plant were classified according to the “most dangerous” plant they worked in with the plutonium production facility being considered the most dangerous and the nuclear reactors considered the least dangerous. Methods for determining vital status and cause of death have been described previously (1, 5). Annual external dose estimates are based on film badge monitoring data, maintained by the Radiation Safety Service of the Mayak plant.

Assessment of plutonium content and average doses to the bone from incorporated plutonium is based on interpretation of results of measurements of the radionuclide in the urine using a biokinetic model adopted at FIB-1 for monitoring of Mayak workers. The biokinetic model is a combination of the lung clearance model (6, 7) and the model of excretion of systemic plutonium (8). According to this combined model, the level of excretion of the radionuclide in the urine and its distribution by organs and tissues depend on history of exposure. Exposure history includes dynamics and duration of inhalation of plutonium aerosol taking into account a transportability factor. Transportability is an integral characteristic of the aerosol that determines behavior of the substance in the respiratory tract and influences distribution of this substance between the lung and extrapulmonary pool. Transportability of aerosols at various compartments is measured by the method of dialysis (9).

The level of plutonium excretion in the urine as a basic value for assessment of plutonium content and doses from plutonium is measured according to the results of radiochemical analysis of the urine in individuals hospitalized after their vacations, i.e. 30 or more days after cessation of plutonium intake. This allows us to avoid distortion of the results of measurements resulting from transient plutonium intake. Each worker was hospitalized on the average three or four times during his employment at Mayak. Three to five daily urine samples were taken for mea-

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surement at each hospitalization. The minimal detectable activity (MDA) was calculated using the method of Boecker *et al.* (10); in urine samples this was 4 mBq, which corresponds to a body burden of 0.26 kBq.

All primary individual biophysical examination data, including exposure history, are computerized. Of 8,048 radiochemical and plutonium plant workers with vital status data and hired in the period 1948–1958, 2,772 individuals had monitoring data prior to 1996. Plutonium body burden in monitored workers was in the range from background values to 173 kBq. If the plutonium body burden measured by plutonium urine excretion rate was below 0.26 kBq, it was considered as 0 kBq. About 20% of monitored individuals in the cohort under study were assigned zero values of plutonium body burden following this rule. If postmortem radiometry was conducted, the plutonium body burden was determined as a sum of activities detected in organs and tissues. Postmortem radiometry of autopsy materials has been conducted at the internal dosimetry laboratory since 1970. These studies show that about 50% of the plutonium content in the extrapulmonary pool is deposited in the skeleton.

Accumulated dose to the cells of the bone surfaces was calculated as a time integral of the numbers of decays in the cells of bone surface and bone marrow tissue, using the biokinetic model of plutonium accumulation in the skeleton, mentioned above (6). The mass of the bone surface cells was assumed to be proportional to the body mass, given that this mass for the standard man is 120 g (6). Our calculations show that absorbed doses to bone surface cells from incorporated plutonium among those with positive body burdens range from 4.2 cGy to 144 Gy. Average absorbed bone doses are estimated to be a factor of 21.4 smaller than doses to the bone surface.

The above database includes only subjects with urine measurements based on routine monitoring. Such routine monitoring was not initiated until about 1970 and was conducted only for workers with potential for plutonium exposure. Workers in jobs with the greatest likelihood of plutonium exposure were likely to have been monitored earlier than workers for whom such exposure was less likely, and workers who continued to be employed at Mayak after 1970 were probably more likely to be monitored than those who terminated early. In some cases, workers who did not have data on plutonium body burden based on routine urine monitoring had data on plutonium exposure from other sources. These data were not used in the cohort-based statistical analyses but are noted in the descriptive information on the bone cancers that have occurred.

Currently efforts are under way to expand the number of workers for whom estimates of body burdens and organ doses are available, to use modern methods to estimate these burdens and doses, and to provide information on the pattern of accumulation of dose over time. These efforts will include use of urine excretion data, data on autopsy radiometry, and data on persons whose plutonium burdens were measured before the 1970s. In addition, uncertainties in the resulting estimates of body burden and dose will be evaluated. Because results of this effort are not yet available, the present analyses must be regarded as preliminary.

STATISTICAL METHODS

Statistical analyses used Poisson regression methods, where it is assumed that the number of bone cancer deaths in each category is a Poisson variable with mean given by the product of the person-years and a bone cancer mortality rate for the category. Analyses were implemented using the AMFIT module of the software package EPICURE (11). For these analyses, person-years were allocated by categories defined by age and calendar year (5-year categories except that the first category was 1948–1949 and the last category was 1995–1996), sex, plant (reactor, radiochemical, plutonium production), cumulative external dose (categorized as 0, >0 but <0.05, 0.05–, 0.1–, 0.2–, 0.3–, 0.5–, 0.75–, 1.0–, 1.5–, 2.0–, 3.0–, 4.0+ Sv), and estimated plutonium body burden (see below). External dose was allowed to change as workers were followed over time, and, unless stated otherwise, analyses were based on the cumulative dose received 2 or more years before the time at risk. Brief consideration is given to dose received between 2 and 15 years prior to

the time at risk and to dose received 15 or more years prior to the time at risk. For workers who were lost to follow-up, person-years were included up until the time that the loss occurred. Unmonitored workers and person-years prior to the time monitoring began were assigned zero doses.

Statistical analyses addressing the effects of plutonium exposure are limited to analyses of the estimated body burden, expressed in kilobecquerels, and are categorized as follows: unknown, 0, >0 but <0.74, 0.74–, 1.48–, 2.96–, 4.44–, 7.4–, 14.8–, 29.6–, 59.2+ kBq. For reactor workers, all person-years were assigned to the 0 kBq category. For workers in the radiochemical and plutonium plants, person-years prior to 1970 (when routine monitoring based on urine measurements began) were assigned to the unknown category, and person-years subsequent to this date were assigned to the body burden categories indicated. For workers in these two plants who were never monitored for plutonium, all person-years were assigned to the unknown category. In an alternative stratification, workers with plutonium monitoring data were considered to be monitored starting at a date of monitoring given in our files; however, this date was not always the first date that monitoring occurred. This stratification gave results that were very similar to those reported.

Note that 1.48 kBq is the level that has served in the past as a radiation protection guideline for lifetime exposure, and thus the cut points correspond to various multiples of this quantity. Analyses of body burden ideally should take account of the time that the burden was received, but these data were not available at the time of these analyses. However, it is likely that most burdens, particularly larger burdens, were received in the early period of operation prior to 1960. All but one of the bone cancers with plutonium monitoring data occurred in 1970 or later.

Ideally, person-years for workers employed in more than one plant should be allocated by plant, and data are being developed to allow this in the future. However, because current computerized files had information only on the most dangerous plant of employment, this was not possible at this time. Thus person-years are likely to be underestimated for the reactor plant and overestimated for the plutonium production plant. Similarly, workers should be considered monitored for plutonium beginning with the first year that monitoring occurred; because this date was not consistently available, person-years are likely to be underestimated for unmonitored workers and overestimated for monitored workers.

Standardized mortality ratios (SMRs) were calculated based on the assumption that the bone cancer mortality rate for a cell is given by $\lambda_j \exp(\theta_k)$, where j indexes categories defined by attained age, calendar year, and sex; k indexes categories of dose or other variables; and λ_j is an external rate for category j . The maximum likelihood estimate of the SMR, $\exp(\theta_k)$, is the familiar ratio of observed and expected cases in category k , where the expected cases are obtained as the sum over j of the $\lambda_j PY_{jk}$, where PY_{jk} is the number of person-years in cell jk .

Finding an appropriate external control was problematic since age- and sex-specific bone cancer (ICD-9 170; ref. 11) mortality rates for the Russian Federation were available only for recent years (1990–1994) and were combined with the rates for soft tissue cancers (ICD-9 171). Three approaches were used in conducting external comparisons. Analyses including deaths with bone or soft tissue cancer indicated on the death certificate as the cause of death were conducted with expected deaths calculated using both Russian (age- and sex-specific for 1990–1994) and U.S. mortality rates (age-, sex- and calendar year-specific) for the combined category of bone and soft tissue cancer. In addition, analyses including only deaths with bone cancer indicated on the death certificate as the cause of death were conducted with expected deaths calculated using U.S. bone cancer mortality rates.

In part because of the difficulties with external rates, internal comparisons (without the use of external rates) by plant, external dose, and body burden are emphasized. For these analyses, all deaths in which bone cancer was considered to be either the cause of death or a contributing cause (two deaths) were included; in addition, four deaths with soft tissue cancer that occurred in tissue very close to the bone (three synovial sarcomas and one fibrosarcoma) as a cause or contributing cause (one death) were included. These analyses were based on a model of the form $\lambda_j RR_w$, where j again indicates categories defined by attained age and cal-

endar year (5-year intervals) and sex, RR_w is the relative risk, and the subscript w indicates the dependence on variables such as plant, body burden, and external dose. The parameter λ_j is the baseline bone cancer mortality rate for category j with the λ_j estimated from the data. Alternative analyses explored parametric modeling of the baseline risk, but this did not substantially affect conclusions.

Analyses emphasize evaluation of the effects of plutonium exposure, with adjustment for the possible effects of external dose. Because of current limitations in the plutonium exposure data, the effects of external exposure could not be reliably evaluated. The following three models are emphasized.

Model 1: $RR_k = \exp(\theta_k)$, where k indexes plant;

Model 2: $RR_{kx} = \exp(\theta_k)[1 + \beta_1 x]$, where k indexes categories of plutonium exposure and x is cumulative external dose in sieverts; and

Model 3: $RR_{kzw} = 1 + \beta_1 x + \beta_2 z + \gamma'w$, in which x is external dose in sieverts and z is plutonium body burden z in kilobecquerels. The vector w consists of indicator variables, possibly sex-specific, for workers employed in the radiochemical or plutonium plants and not monitored for plutonium exposure; the choice of these variables was determined by whether they substantially improved the fit of the model.

The linear relative risk model (used in Models 2 and 3) has been used extensively in analyzing epidemiological data on radiation risks including risks of cancer, and the coefficients β_1 and β_2 are referred to as excess relative risks (ERR) per unit of external dose (Sv) or body burden (kBq). Using this model, the excess number of cases resulting from exposure can be calculated as described by Preston *et al.* (12).

All confidence intervals and P values were based on the likelihood ratio statistic, and all reported P values are two-sided.

RESULTS

Description of Bone Cancers in the Mayak Cohort

Table 1 gives characteristics of the 27 cases of malignant neoplasms with ICD-9 codes 170–171 detected in workers hired at Mayak in the period between 1948 and 1958. Of the 27 cases, 19 cases were bone and cartilage neoplasms (16 osteosarcomas and 3 chondrosarcomas) coded as 170. The other 8 cases were soft tissue neoplasms (ICD-9 code 171), including 1 fibrosarcoma, 3 synovial sarcomas, and 4 myosarcomas. Although not shown in Table 1, only one bone cancer occurred in workers hired after 1958; this cancer occurred in a plutonium plant worker who was not monitored for either external or plutonium exposure.

In three cases, bone cancer was not the underlying cause of death based on death certificate information. In case P5, the underlying cause of death was plutonium pulmonary sclerosis, and in case P2, the underlying cause was lung cancer; in both cases, osteosarcomas were detected at histological examination at autopsy. For case C9, autopsy data eventually indicated that the cause of death was synovial sarcoma, but the initial information from the death certificate gave the cause of death as lung cancer. These three cases were excluded from analyses based on comparisons with national statistics. For case P7, lung cancer was found at postmortem histological examination, but the underlying cause of death was osteosarcoma.

As noted in the Statistical Methods section, analyses based on internal comparisons included both bone neoplasms (ICD-9 170) and selected soft tissue neoplasms (ICD-9 171). Soft tissue neoplasms differ considerably with

respect to the possibility of their induction by incorporated plutonium. Incorporated plutonium might play a role in the induction of fibrosarcomas and synovial sarcomas, since connective tissue and synovial structures are directly adjacent to bone surfaces, where plutonium is deposited. However, it is improbable that plutonium could play a role in the induction of myosarcomas, since the length of α -particle tracks is too short to reach muscular tissue, and muscular tissue itself does not accumulate plutonium. Accordingly, our internal comparisons included all cancers in Table 1 with the exception of the myosarcomas (R5, C8, P10 and P11).

Although 14 of the cases in Table 1 are indicated as having monitoring data for plutonium exposure, only 7 had data based on routine urine monitoring after 1970; these 7 are the only cases considered to have plutonium monitoring data in the statistical analyses that are presented. The remaining 7 cases had data from other sources (such as medical records) that were not available for the entire cohort.

Information on traumatic injuries and other pathological conditions was collected from medical records. There were bone fractures in two cases at the sites where cancers occurred subsequently. Spondylitis was reported on medical records in three cases.

Results of Statistical Analyses

Table 2 shows numbers of workers and bone cancers (those included for internal comparisons as discussed above) categorized by plutonium body burden and external dose and also shows the mean external dose for each category. The 1719 workers with unknown vital status were excluded from Table 2 since most (1582) were lost to follow-up before 1970. Workers with plutonium monitoring data and workers in the reactor plant were considered to have "known" plutonium body burdens, while the remaining workers were considered as "unknown". For the 0 kBq category, 83% of the workers and all of the bone cancers were from the reactor plant. For 49% of the workers and 13 of the 23 bone cancers, the plutonium body burden was unknown. For the 7.4+ kBq category, 75% of the workers and all of the bone cancers were from the plutonium plant. Although not shown in Table 2, the mean age of hire was 25 years. For workers in the radiochemical and plutonium plants with positive plutonium burdens, the mean body burden was 4.5 kBq and the mean dose to the bone surface cells from plutonium was 3.8 Gy (for the radiochemical plant alone, these values were 2.0 kBq and 1.9 Gy, respectively; for the plutonium plant alone, these values were 8.4 kBq and 6.7 Gy, respectively).

Table 3 shows comparisons with external rates. For comparisons including both bone and soft tissue cancers, the SMRs based on Russian rates were smaller than those based on U.S. rates. The U.S. rate-based SMRs were larger for bone cancers alone than when both bone and soft tissue cancers were included, and show evidence of excess risk

TABLE 1
Characteristics of Malignant Bone and Soft Tissue Cancers (ICD-9 codes: 170–171) in Mayak Workers Hired 1948–1958

ID	Sex	Ages at hire and at death (years)	Years of hire and death	External γ -ray dose (Gy)	Plutonium body burden in kBq (α -particle dose to bone in Gy)	Histological type of tumor	Location of tumor	ICD-9 code
Reactor plant								
R1	M	42–61	1952–1972	NM	NM	Chondrosarcoma	Sciatic bone	170.6
R2	M	29–40	1954–1966	0.38	NM	Chondrosarcoma	Left foot	170.8
R3	M	30–69	1952–1992	0.47	NM	Osteosarcoma	Lower jaw	170.1
R4	F	24–66	1950–1992	0.11	NM	Chondrosarcoma	Sacrum	170.6
R5	M	40–74	1952–1986	0.93	NM	Myosarcoma	Shank	171.3
Radiochemical plant								
C1	M	23–53	1951–1980	0.83	NM	Osteosarcoma	Vertebrae	170.2
C2	M	18–54	1958–1994	0.31	NM	Osteosarcoma	Pelvis	170.6
C3	M	22–51	1950–1980	3.03	NM	Osteosarcoma	Vertebrae	170.2
C4	M	23–65	1950–1992	2.63	Monitored ^a	Osteosarcoma	Femur	170.7
C5	M	22–64	1948–1990	6.52	NM	Osteosarcoma	Vertebrae	170.2
C6	F	25–59	1948–1983	3.94	1.65 (0.07)	Fibrosarcoma	Lower jaw	171.0
C7	F	21–54	1951–1984	1.56	NM	Osteosarcoma	Vertebrae	170.2
C8	F	22–51	1951–1980	2.84	Monitored ^a	Rhabdomyosarcoma	Chest	171.4
C9	M	18–53	1953–1988	2.61	1.19 (0.04)	Synovial sarcoma	Pelvis	171.6
Plutonium plant								
P1	M	20–54	1948–1982	2.77	47.8 (1.66)	Osteosarcoma	Vertebrae	170.2
P2	M	20–49	1952–1981	0.03	1.4 (0.02)	Osteosarcoma	Rib	170.3
P3	M	29–65	1949–1985	1.55	NM	Synovial sarcoma	Femur	171.3
P4	M	27–67	1948–1988	3.34	Monitored ^a	Sarcoma	Scapula	170.4
P5	F	32–44	1949–1961	3.77	Monitored ^a	Osteosarcoma	Rib, femur	170.3
P6	F	19–41	1948–1971	1.68	114 (3.65)	Osteosarcoma	Shank	170.8
P7	F	20–42	1948–1970	1.69	Monitored ^a	Osteosarcoma	Rib	170.3
P8	F	24–46	1948–1970	1.99	Monitored ^a	Osteosarcoma	Unknown	170.9
P9	F	25–53	1949–1978	1.61	93.7 (2.79)	Synovial sarcoma	Humerus	171.2
P10	M	39–58	1950–1969	5.53	19.5 (0.48)	Rhabdomyosarcoma	Glutea	171.6
P11	F	21–68	1949–1996	0.39	NM	Rhabdomyosarcoma	Pelvis	171.6
P12	F	28–67	1949–1989	0.26	Monitored ^a	Osteosarcoma	Femur	170.7
P13	F	38–77	1951–1990	NM	NM	Osteosarcoma	Lower jaw	170.1

Note. CRS, chronic radiation syndrome; PS, pneumosclerosis; NM, not monitored.

^a Monitored, but the biophysical examination was performed before routine monitoring method was developed (before 1970). These data are now being verified. These cases were not considered as monitored in statistical analyses.

^b Cause of death: In all other cases bone or soft tissue cancer was the cause of death.

^c Vertebral column and left heel bone fracture.

^d Rib fracture during lung cancer surgery; sarcoma at the site of fracture.

in every category considered. Although the Russian rate-based SMRs were lower, they too show evidence of excess risk, particularly for females, plutonium plant workers, those with external doses of 1+ Sv, and radiochemical and plutonium plant workers who were not monitored for plutonium. The SMRs for females were more than twice those for males, and this comes about in part because both the Russian and U.S. rates for females were lower than those for males. Although not shown, this difference was particularly striking for plutonium plant workers, where the SMRs based on Russian rates with their 95% CI were 1.3 (0.4–3.0) and 7.4 (3.2–14) for males and females, respectively. The SMRs were smaller before 1980 than later. This effect was more striking when the calendar-specific U.S.

rates for bone cancer alone were used, since U.S. bone cancer mortality rates have declined with time.

Results of comparisons within the cohort, without the use of external rates, are shown in Tables 4 and 5. Relative risks by plant, shown in Table 4 and not adjusted for external dose or plutonium exposure, suggest higher risks for those in the plutonium plant. Table 5 shows relative risks by categories of plutonium body burden. These analyses, which were adjusted for external dose by including it as a linear variable (Model 2), indicate elevated risks among those with estimated body burdens exceeding 7.4 kBq. Elevated risk was also found for plutonium plant workers who were not monitored for plutonium exposure, but there was little evidence of elevated risk for such workers in the ra-

TABLE 1
Extended

Source of information on cancers	Died in town	Other relevant conditions
Autopsy + histology	Yes	None
Autopsy + histology	Yes	Fracture ^c
Death certificate	No	None
Death certificate + histology	Yes	None
Death certificate	No	None
Death certificate	No	Spondilitis
Death certificate + histology	Yes	Spondilitis
Relatives	No	CRS
Death certificate	No	Spondilitis, CRS
Death certificate	No	CRS
Autopsy + histology	Yes	CRS
Relatives	No	None
Relatives	No	None
Autopsy + histology	Yes	Lung cancer ^b , CRS
Autopsy + histology	Yes	CRS, PS
Autopsy + histology	Yes	Lung cancer ^b , fracture ^d
Autopsy + histology	Yes	None
Death certificate	No	CRS
Autopsy + histology	Yes	PS ^b
Autopsy + histology	Yes	CRS, PS
Autopsy + histology	Yes	Lung cancer, CRS, PS
Death certificate	No	CRS, PS
Autopsy + histology	Yes	CRS
Autopsy + histology	Yes	CRS
Death certificate	No	None
Death certificate	No	None
Death certificate	No	None

radiochemical plant. Estimating the relative risks separately for unmonitored workers in the two plants improved the fit somewhat ($P = 0.095$) over a model in which a single variable for unknown plutonium body burden was included. Adding a term that separated those with plutonium body burdens of 0 (primarily reactor workers) from those with positive burdens less than 1.48 kBq did not improve the fit ($P > 0.5$). The results in Table 5 are based on a model in which the effects of plutonium are assumed to multiply the effects of external dose. Because most of the cohort had external doses of at least 0.1 Sv, comparisons by categories of plutonium exposure are driven by comparisons among those who were also exposed externally. Thus the elevated relative risks for those with burdens exceeding 7.4 kBq or for unmonitored workers in the plutonium plant could at least partly reflect interactions of plutonium exposure and external dose.

Analyses in which both external dose and the estimated body burden were treated as quantitative linear variables (Model 3) were also conducted. In an attempt to partially

adjust for plutonium exposure among those who were not monitored for this exposure, the use of sex-specific indicator variables for both the radiochemical and plutonium plant in the unmonitored stratum was explored. Including such a variable for unmonitored females in the plutonium plant improved the fit ($P = 0.027$) with a linear coefficient of 6.1, but additional indicator variables were not needed. However, the inclusion of this variable did not greatly affect the results reported below.

The coefficient for body burden differed significantly from zero ($P < 0.001$), and including the body burden as a quantitative variable provided a significantly better fit than simply including an indicator variable for plutonium plant workers with plutonium monitoring data ($P = 0.001$). Adjusting for external dose by including separate variables for exposure received 2–15 and 15 or more years prior to the time at risk did not modify the plutonium body burden results greatly, and also did not improve the fit of the model ($P > 0.5$). Including separate estimates for males and females for both plutonium burden and external dose did not substantially improve the fit ($P > 0.5$), although risk coefficients for females were larger than those for males.

When all workers were assumed to have the same ERR/Sv, an association was suggested for external dose ($P = 0.11$). Because of concerns regarding confounding of the effects of external dose by plutonium exposure among the unmonitored, analyses were conducted in which the effects of external dose were estimated separately for three categories: those with “known” burdens, radiochemical plant workers with unknown plutonium body burdens, and plutonium plant workers with unknown plutonium body burdens. This model fit the data substantially better than a model in which the external effects were assumed to be homogeneous ($P = 0.004$) and indicated that the evidence for an association with external exposure was strongest among plutonium plant workers without plutonium monitoring data, while workers with known plutonium burdens showed no evidence of an association (the ERR/Sv was negative). Furthermore, these differences persisted ($P = 0.02$) in analyses that adjusted only for working in the plutonium plant without adjusting for plutonium body burden; in this case the ERR/Sv in the “known” burden group was positive but did not differ significantly from zero ($P > 0.5$). Using only data on workers with known plutonium body burdens, and assuming that the ERR/Sv for external dose in this group was zero, it was estimated that 4.4 of the 10 bone cancers (44%) that occurred in this group were due to plutonium exposure.

DISCUSSION

Aside from a single bone cancer in a group of 26 Los Alamos Manhattan Project workers (13), this paper is the first to present evidence based on data for humans for bone cancers resulting from exposure to plutonium. No deaths from bone cancers occurred in other Los Alamos workers

TABLE 2
Number of Workers, Number of Bone Cancers, and Mean External Dose by Categories of Plutonium Monitoring and External Dose

Plutonium body burden	All workers		Males		Females	
	Number of workers (bone cancers ^a)	Mean dose ^b (Sv)	Number of workers (bone cancers ^a)	Mean dose ^b (Sv)	Number of workers (bone cancers ^a)	Mean dose ^b (Sv)
By plutonium body burden (kBq):						
Known						
0	3,314 (4, 0)	0.81	2,418 (3, 0)	0.93	896 (1, 0)	0.51
>0–1.48	1,297 (0, 2)	1.55	856 (0, 2)	1.48	441 (0, 0)	1.68
1.48–7.40	659 (1, 0)	1.74	495 (0, 0)	1.95	164 (1, 0)	1.10
7.40+	251 (3, 0)	2.24	180 (1, 0)	2.36	71 (2, 0)	1.93
Subtotal	5,521 (8, 2)	1.16	3,949 (4, 2)	1.24	1,572 (4, 0)	0.96
Unknown ^c						
Radiochemical	3,134 (6, 0)	1.35	2,262 (5, 0)	1.40	872 (1, 0)	1.22
Plutonium	2,142 (6, 1)	0.40	1,465 (2, 0)	0.40	677 (4, 1)	0.40
Subtotal	5,276 (12, 1)	0.96	3,727 (7, 0)	1.01	1,549 (5, 1)	0.86
Unmonitored						
>0, <0.1	1,416 (2, 0)	0.00	836 (1, 0)	0.00	580 (1, 0)	0.00
0.1–1	1,182 (0, 1)	0.04	814 (0, 1)	0.04	368 (0, 0)	0.04
1–3	4,290 (6, 0)	0.47	3,093 (4, 0)	0.47	1,197 (2, 0)	0.45
3+	2,955 (8, 1)	1.79	2,203 (3, 1)	1.80	752 (5, 0)	1.77
3+	954 (4, 1)	4.35	730 (3, 0)	4.38	224 (1, 1)	4.29
Total	10,797 (20, 3)	1.07	7,676 (11, 2)	1.13	3,121 (9, 1)	0.91

^a The first number is the number of bone cancers indicated as the cause of death on the death certificate. Three of these tumors were coded as soft tissue tumors (ICD 171) as discussed in the text and indicated in Table 1. The second number is the number of bone cancers indicated as a contributing cause of death on the death certificate. One of these tumors was coded as a soft tissue tumor (ICD 171) as discussed in the text and indicated in Table 1.

^b External γ -ray dose. Dose for the 2 years preceding the end of follow-up was excluded.

^c This group included workers in the radiochemical and plutonium plants for whom no monitoring data were available prior to 1996; 493 of these workers had monitoring data for 1996 or later.

who were exposed to plutonium (14), in plutonium workers at Rocky Flats (15), or in plutonium workers at the Sellafield plant of British Nuclear Fuels (16). For the Mayak cohort, 23 cancers occurred in the bone or soft tissue directly adjacent to bone surfaces.

In addition to describing the bone cancers that have occurred in Mayak workers, we have conducted statistical analyses that compare bone cancer mortality rates with external rates, and also compare bone cancer risks within the Mayak cohort by plant, plutonium monitoring status, and external dose. Comparisons with external rates are problematic. Neither the Russian nor the U.S. rates are fully appropriate for the Mayak worker population, which differs from the general population in many respects. Results based on Russian rates are diluted because of the need to include soft tissue cancers, which are not as likely to be linked to plutonium exposure. In addition, these rates do not reflect changes over time. Although the U.S. rates reflect such changes and are available for bone cancers alone, their applicability to a Russian population is questionable, although bone cancer rates do not exhibit large geographic variation (17). The decline in U.S. bone cancer rates over time is thought to reflect improved diagnosis and treatment (17). It is not known whether a similar decline has occurred in Russia, or whether such a decline would be reflected in the Mayak cohort, where careful review has been conducted of

all bone cancer deaths. Still another difficulty is that available external rates do not allow separate consideration of soft tissue cancers occurring near the surface. Nevertheless, the fact that SMRs are largest for workers in the plutonium plant and for workers with larger external doses strongly suggests that exposures have contributed to the elevated SMRs. A contributor to the difference in male and female SMRs is that baseline risks are smaller for females than for males; thus similar absolute risks resulting from exposure for the two sexes would lead to larger relative risks for females than for males.

Internal comparisons by level of exposure should be less subject to bias than those based on comparisons with external rates. Based on such comparisons, a strong case can be made that bone cancer risks are related to plutonium exposure in the Mayak cohort. Both categorical and continuous analyses demonstrate an increase in risk with increasing estimated body burden, and, in addition, elevated risks are found among workers in the plutonium plant who were not monitored for plutonium exposure. The categorical analyses (Table 4) indicate that the excess is found primarily among those with very high body burdens. The three bone cancer cases with body burdens exceeding 7.4 kBq had estimated burdens of 47.8, 93.7 and 114.0 kBq and estimated doses to the bone surface of 35, 60 and 78 Gy, respectively. Workers with more modest burdens (1.48–7.4

TABLE 3
Observed Deaths and Standardized Mortality Ratios (SMR) by Sex, Calendar Year Period, Plant, External Dose, and Whether or Not Monitored for Plutonium

	Number of deaths from bone and soft tissue cancers ^a (ICD 170–171)	Based on age-sex-specific Russian mortality rates for 1990–1994	Based on age-sex-calendar year specific U.S. mortality rates	
		(ICD 170–171) SMR (95% CI)	(ICD 170–171) SMR (95% CI)	(ICD 170) SMR (95% CI)
Total	24 (17)	1.8 (1.2–2.6)	3.1 (2.0–4.6)	6.6 (3.9–10)
By sex:				
Males	13 (10)	1.2 (0.7–2.0)	2.4 (1.3–3.9)	5.0 (2.5–8.8)
Females	11 (7)	3.9 (2.0–6.7)	5.1 (2.6–8.7)	11.9 (5.1–23)
By calendar year period:				
1948–1979	7 (5)	1.3 (0.6–2.5)	2.2 (1.0–4.3)	3.1 (1.1–6.8)
1980–1989	10 (6)	2.2 (1.1–3.9)	4.3 (2.1–7.5)	11.5 (3.6–23)
1990–1996	7 (6)	1.9 (0.8–3.6)	3.3 (1.4–6.3)	12.9 (5.1–26)
By plant:				
Reactor	5 (4)	1.3 (0.5–2.9)	2.4 (0.9–5.3)	5.8 (1.8–13)
Radiochemical	8 (6)	1.4 (0.6–2.6)	2.4 (1.1–4.6)	5.5 (2.2–11)
Plutonium	11 (7)	2.7 (1.4–4.7)	4.8 (2.5–8.1)	8.8 (3.8–17)
By external dose:				
0–1 Sv	10 (8)	1.2 (0.6–2.1)	2.0 (1.0–3.5)	4.6 (2.1–8.6)
1+ Sv	14 (9)	2.8 (1.6–4.5)	5.2 (3.0–8.5)	10.6 (5.1–19)
By plutonium exposure status:				
No detectable exposure ^b	5 (4)	1.1 (0.4–2.3)	2.0 (0.7–4.3)	5.0 (1.5–12)
Detectable exposure	4 (2)	1.6 (0.5–3.8)	3.0 (0.9–7.1)	5.8 (1.0–18)
Not monitored ^c	15 (11)	2.3 (1.3–3.7)	3.9 (2.3–6.3)	7.7 (4.0–13)

^a Only cancers in which bone or soft tissue cancer (170–171) was indicated as the cause of death on the death certificate were included. The numbers in parentheses are cases where the indicated cause of death on the certificate was bone cancer (170).

^b Includes reactor workers and monitored workers in the radiochemical and plutonium plants with no detectable exposure.

^c Workers in the radiochemical and plutonium plants who were not monitored for plutonium exposure.

kBq) had no higher risks than those with smaller burdens or reactor plant workers with no plutonium exposure (although the possibility of elevated risks for these workers could not be excluded). In addition, there is evidence of excess risk among unmonitored plutonium plant workers, some of whom may also have had large burdens; in fact, preliminary data indicate that two of the bone cancers in this group had body burdens substantially higher than 7.4 kBq. It is also noted that 8 of the 10 cancers in the two subgroups with elevated risks occurred in workers who had external doses exceeding 1 Gy; thus some of the excess could have occurred because of interaction of plutonium exposure and external dose. Because of dosimetry limita-

tions, it is not possible to quantify the effect of bone dose from plutonium exposure at this time.

Although it may be reasonable to assume that most of the larger plutonium exposures occurred in the 1940s and 1950s, we do not yet have reliable estimates of the pattern of bone dose accumulation over time. Thus we cannot meaningfully examine the dependence of risks on time

TABLE 5
Numbers Person-Years and Bone Cancers, and Relative Risks (with 95% CI) by Categories of Plutonium Body Burden

	Number of person-years (bone cancers)	Relative risk ^a (95% CI)
By plutonium body burden (kBq):		
0–1.48	162,540 (6)	1.0
1.48–7.40	15,614 (1)	0.9 (0.05–5.5)
7.40+	4,410 (3)	7.9 (1.6–32)
Unknown		
Radiochemical	149,878 (6)	1.4 (0.4–4.7)
Plutonium	97,058 (7)	4.1 (1.2–14)

^a Stratified by age, calendar year, and sex and adjusted for external dose as a linear variable (Model 2).

TABLE 4
Numbers of Person-Years and Bone Cancers and Relative Risks (with 95% CI) by Plant

Plant	Number of person-years (bone cancers)	Relative risk ^a (95% CI)
Reactor	110,043 (4)	1.0
Radiochemical	193,421 (8)	1.2 (0.4–4.6)
Plutonium	124,036 (11)	2.4 (0.8–8.8)

^a Stratified by age, calendar year, and sex.

since exposure. However, most of the cancers occurred at least 20 years after the initial date of hire (Table 1).

Other than the Mayak cohort, evidence of bone cancer risks from plutonium for humans is limited to the single bone cancer that occurred in 1 of 26 Manhattan project workers at Los Alamos in the U.S. These workers had body burdens ranging from 0.05 to 3.2 kBq, with a median of 0.5 kBq. The estimated body burden for the worker who developed a bone cancer was 0.6 kBq, while the estimated dose to the bone surface was 0.44 Gy.

Evidence of bone cancer risks from other α -particle emitters in humans has been reviewed by UNSCEAR (18). Persons injected with the short-lived ^{224}Ra for therapy have experienced 56 bone cancers (in 54 persons) compared with 0.2 expected, and risks peaked at 6–8 years after exposure with little evidence of risk found after 30 years. The average absorbed dose to the bone for these subjects was 4 Gy; dose to the bone surface would have been larger by a factor of about 7.5 to 9 (19). The exposures differ from those at Mayak in that the dose would have been received fairly soon after the injections at a high dose rate. Risk of bone cancers from the longer-lived ^{226}Ra and ^{228}Ra has also been demonstrated. These exposures may have been more comparable to those at Mayak in that dose was accumulated more gradually over time. The best-known study is that of radium dial painters with average doses ranging from 0.8 to 12 Gy, and where bone cancers have continued to occur more than 60 years after exposure (18).

Results of experimental studies in rats and beagle dogs summarized by the ICRP (20) show that bone cancers can arise after inhalation of soluble plutonium compounds, i.e. in cases where the radionuclide moves from the lung and accumulates in the skeleton. Osteosarcomas arose in 1–18% of rats (depending on dose) that inhaled plutonium citrate, plutonium nitrate, and plutonium pentacarbonate. Moreover, in experiments conducted in Russia, even inhaled polymeric plutonium (with low solubility) induced osteosarcomas in 12% of dogs at absorbed doses to the bone of the order of 2 Gy (21). In more recent studies of beagle dogs in the U.S., evidence of excess bone cancer risk was found in dogs that inhaled $^{239}\text{Pu}(\text{NO}_3)_4$ (22) and $^{238}\text{PuO}_2$ (23), both of which are more soluble forms of plutonium. In the latter study, estimated average skeletal doses ranged from 0.0002 to 5.8 Gy and risks increased as a nonlinear function of dose. However, no evidence of dose-related bone cancer risk has been observed in dogs or rodents that inhaled insoluble $^{239}\text{PuO}_2$ (20, 24, 25). In addition, dogs injected with ^{239}Pu as young adults have exhibited increased bone cancer risks, and the risk (at comparable dose levels) was about doubled when the exposure was protracted, replicating likely industrial inhalation exposures with prolonged transfer of the radionuclide from the lung to the skeleton (26, 27).

External radiation exposure has not been clearly linked with bone cancer risk in other studies, perhaps in part because of the rarity of the disease. For both the A-bomb

survivor incidence and mortality data, the estimated ERR/Sv were positive but did not differ significantly from zero (28, 29). It is reasonable to think that external exposure could contribute to bone cancer risks in Mayak workers, and analyses in which the ERR/Sv was assumed to be homogeneous for the entire cohort suggest this. However, no evidence of an association was found among workers monitored for plutonium (where it was possible to adjust for the plutonium burden), and the strongest evidence was found in plutonium plant workers who were not monitored for plutonium (where adjustments for plutonium burden could not be made). Given current limitations in plutonium dosimetry, a reliable evaluation of the effects of external dose and its possible interaction with dose from plutonium exposure is not possible at this time.

In the future, better plutonium dosimetry, including estimates of bone doses, is expected to become available. It is hoped that dose estimates can be made not only for those who currently have plutonium-monitoring data, but also for workers who do not now have such data. Although it will never be possible to obtain precise estimates of bone dose for all workers in the Mayak cohort, it is hoped that in the future improved plutonium dosimetry will allow better quantification of bone cancer risks from both plutonium and external exposure than is currently possible.

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