

Liver Cancers in Mayak Workers

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Liver 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 liver cancer incidence rates indicate excess risk, especially among those with detectable plutonium body burdens and among female workers in the plutonium plant. Comparisons within the Mayak worker cohort which evaluate the role of plutonium body burden with adjustment for cumulative external dose indicate excess risk among workers with burdens estimated to exceed 7.4 kBq (relative risk = 17; 95% CI = 8.0–36) and among workers in the plutonium plant who did not have routine plutonium monitoring data based on urine measurements (relative risk = 2.8; 95% CI = 1.3–6.2). In addition, analyses treating the estimated plutonium body burden as a continuous variable indicate increasing risk with increasing burden ($P < 0.001$). Relative risks tended to be higher for females than for males, probably because of the lower baseline risk and the higher levels of plutonium measured in females. Because of limitations in current plutonium dosimetry, no attempt was made to quantify liver cancer risks from plutonium in terms of organ dose, and risk from external dose could not be reliably evaluated. © 2000 by Radiation Research

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INTRODUCTION

This paper reports on liver cancer mortality in workers at the Mayak nuclear facility in the Chelyabinsk region of the Russian Federation. Many of these workers were exposed to inhaled plutonium at levels much higher than those considered permissible today, and were also exposed to doses of external γ radiation that were substantially higher than current occupational dose limits. Results of analyses

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

DESCRIPTION OF THE DATA

Readers are referred to the companion paper on bone cancer risks for details of the study population and dosimetry (4). Like the bone cancer paper, the present paper includes workers who were initially employed in one of the main plants (nuclear reactors, radiochemical and plutonium production) in the years 1948–1958. Workers in all three plants were exposed to external γ radiation, with the highest doses received by the radiochemical plant workers. In addition, workers in the radiochemical plant were exposed to α -particle radiation from $^{239}\text{Pu}(\text{NO}_3)_4$, and workers in the plutonium production plant were exposed to the less soluble $^{239}\text{PuO}_2$. Occupational exposures to other radionuclides were insignificant.

Accumulated dose to the liver from plutonium exposure was calculated in an analogous manner to dose to the bone surface (4). For this reason, liver doses are a constant multiple (0.16) of the bone surface doses. Liver weight was assumed to be proportional to body weight, and the liver weight in standard man was assumed to be 1800 g. Absorbed doses to the liver from incorporated plutonium among those with positive body burdens range from 0.7 cGy to 23 Gy.

External dose was allowed to change as workers were followed over time, and, unless stated otherwise, analyses were based on the cumulative dose received 10 or more years before the time at risk.

STATISTICAL METHODS

The statistical methods are very similar to those used for analyzing bone cancer risks (4), and this paper should be referred to for details. They differed in that analyses were based on the cumulative dose received 10 or more years before the time at risk, instead of the 2-year period used in evaluating bone cancer risks. For the liver cancers, this would be 10 years before the time of death. Also, because there were more liver cancers than bone cancers, it was possible to give greater attention to the comparability of risks between male and female workers and to the shape of the exposure–response curve.

Comparisons with external rates were based on liver cancer incidence rates for the Russian Federation, which were available for the period 1990–1994 (5–8). Since liver cancer is rapidly fatal, these incidence rates should not differ greatly from mortality rates. Liver cancer mortality rates for the Russian Federation were not available, and, since liver cancer rates are known to vary widely internationally (9), it did not seem appropriate to use rates from another country. Because our comparisons are based on incidence rates, analyses include all liver cancers noted on the

TABLE 1
Number of Workers, Mean Body Burden, and Mean Doses to the Liver, Bone Surface, and Lung by Plant and Sex among Those with Detectable Plutonium Body Burdens

Plant and sex	Number of workers ^a	Mean body burden (kBq)	Mean dose to liver (Gy)	Mean dose to bone surface (Gy)	Mean dose to lung (Gy)
Radiochemical	1,359	2.00	0.31	1.95	0.11
Males	970	2.27	0.33	2.11	0.12
Females	389	1.34	0.24	1.54	0.07
Plutonium	848	8.44	1.06	6.71	0.85
Males	561	6.39	0.72	4.52	0.61
Females	287	12.45	1.74	11.00	1.32
Total	2,207	4.48	0.60	3.78	0.39
Males	1,531	3.78	0.47	2.99	0.30
Females	676	6.05	0.88	5.56	0.60

^a Number of workers with detectable plutonium burdens.

death certificate, regardless of whether they were considered to be the cause of death. This was also the case for the internal comparisons.

Internal comparisons were based on a model in which the liver cancer mortality rate was expressed as $\lambda_j R_w$, where j indicates categories defined by attained age, calendar 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 liver cancer mortality rate for category j with the λ_j estimated from the data.

The following three models expressing the liver cancer mortality rate are emphasized.

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

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

Model 3: $RR_{xzw} = 1 + \beta_1 x + \beta_2 z + \gamma'w$, in which x is external dose in sieverts and z is plutonium body burden 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 improved the fit of the model.

To address the effects of sex modification, both sex-specific and non-sex-specific estimates of the parameters θ_k , β_1 , β_2 and γ were obtained. Using Model 3, the numbers of excess cases resulting from exposure were calculated as described by Preston *et al.* (10).

RESULTS

Descriptive Results

Table 1 provides information on the body burdens and doses from plutonium for the 2,207 workers with detectable plutonium burdens. Body burdens and doses are much larger for plutonium plant workers than for radiochemical plant workers. Within the plutonium plant, burdens and doses for females are about twice those for males. Estimated doses to the liver are a factor of 0.16 times the dose to the bone, but larger than doses to the lung.

Tables 2, 3 and 4 provide information on the characteristics of the 60 liver cancers in workers hired at Mayak in the period between 1948 and 1958. (Tables 3 and 4 also provide analytical results, which are discussed below.) In four cases, the underlying cause of death based on death

certificate information was not liver cancer but cancer of the stomach (2 cases), pancreas (1 case), or lung (1 case).

Table 2 presents data on the workers with liver cancers that are not available for the full cohort, classified by sex and plutonium exposure status. Twenty-three (23) of the cancer cases had detectable plutonium body burdens based on routine urine monitoring data, and an additional 10 cases had data from other sources that were not available for the full cohort. Seventeen (17) of the 19 females with cancers had detectable burdens, in contrast to 16 of the 41 cancers in males. Forty-five (45) of the 60 cancers had autopsy data, and these tended to be the same cases who died in Ozyorsk. Those dying outside Ozyorsk and/or without autopsy data were more likely to lack plutonium monitoring data than other workers. None of the cases without autopsy data had information on histological type, and because death certificate diagnoses are not always fully reliable, it is not possible to be certain that these are primary liver cancers. The most striking feature of the classification of cancers by histological type is that all 10 of the hemangiosarcomas occurred in workers with detectable plutonium burdens, and 8 of these occurred in females. All but one of the workers with hemangiosarcomas had external doses exceeding 1 Sv. Thirty (30) of the 41 male workers with cancers consumed alcohol, whereas only 1 of the 19 female workers consumed alcohol. Alcohol consumption data were based on self-reports from workers as provided in medical records except for two cases where chronic alcoholism was diagnosed clinically.

Results of Statistical Analyses

Table 3 shows comparisons with Russian liver cancer incidence rates. The SMR for all females is twice that for males. No evidence of excess risk is found for those with external doses less than 1 Sv or for workers with no detectable plutonium exposure. There is clear evidence of excess risk for workers in the plutonium plant, workers with external doses exceeding 1 Sv, and workers with detectable

TABLE 2
Characteristics of Liver Cancers (ICD-9 code: 155) in Mayak Workers Hired 1948–1958 by Plutonium Exposure Status and Sex

	Total liver cancers	Died in Ozyorsk (yes, no)		Source of information (autopsy, VSB ^a , relatives)				Histological type ^b				Alcohol consumption (yes, no, unknown)		
Total	60	42	18	45	14	1	24	8	10	2	16	31	23	6
No detectable exposure ^c	13	9	4	10	2	1	6	3	0	1	3	8	3	2
Detectable exposure—I ^d	23	22	1	21	2	0	8	3	9	1	2	9	13	1
Detectable exposure—II ^e	10	5	5	8	2	0	7	0	1	0	2	4	5	1
Unknown ^f	14	6	8	6	8	0	3	2	0	0	9	10	2	2
Males	41	28	13	29	11	1	16	8	2	2	13	30	5	6
No detectable exposure ^c	11	7	4	8	2	1	4	3	0	1	3	8	1	2
Detectable exposure—I ^d	12	11	1	11	1	0	5	3	2	1	1	9	2	1
Detectable exposure—II ^e	4	4	0	4	0	0	4	0	0	0	0	3	0	1
Unknown ^f	14	6	8	6	8	0	3	2	0	0	9	10	2	2
Females	19	14	5	16	3	0	8	0	8	0	3	1	18	0
No detectable exposure ^c	2	2	0	2	0	0	2	0	0	0	0	0	2	0
Detectable exposure—I ^d	11	11	0	10	1	0	3	0	7	0	1	0	11	0
Detectable exposure—II ^e	6	1	5	4	2	0	3	0	1	0	2	1	5	0
Unknown ^f	0	0	0	0	0	0	0	0	0	0	0	0	0	0

^a Vital Statistics Bureau.

^b Hepatocellular/cholangiocellular/hemangiosarcoma/nondifferentiated cell type/unknown.

^c Reactor plant workers.

^d Detectable exposure based on routine urine measurements and for whom quantitative estimates are available.

^e Detectable exposure based on non-routine monitoring prior to 1970 and for whom quantitative estimates not yet available. These workers are not considered as monitored in statistical analyses presented in Tables 3–5.

^f Workers in the radiochemical and plutonium plants who were not monitored for plutonium exposure. For one hepatocellular cancer in this group, nonroutine monitoring indicated no detectable exposure.

plutonium burdens, with especially large SMRs for female workers in these categories. Modest evidence of excess risk is seen for workers in the radiochemical and reactor plants who were not monitored for plutonium exposure. Patterns by calendar year and age at risk are unremarkable, although there is some evidence of a decline in the SMR with increasing age in female workers.

Results of comparisons within the cohort, without the use of external rates, are shown in Tables 4 and 5 both for the entire cohort and separately by sex. Relative risks by plant, shown in Table 4 and not adjusted for external dose or plutonium exposure, indicate risks for females in the plutonium plant that are higher than those for females in the reactor and radiochemical plants. The relative risk for these females is also higher than that for males in the plutonium plant, although this difference is not statistically significant ($P = 0.08$) and occurs in part because there were only two liver cancers in female reactor plant workers. The relative risks (with 95% CI) for females compared to male reactor plant workers are 0.4 (0.07–1.6), 0.2 (0.04–0.9), and 2.2 (1.0–4.9) for reactor, radiochemical and plutonium plant workers, respectively.

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; this relative risk is larger for female than for male workers ($P = 0.024$). The body bur-

dens for the 16 liver cancer deaths among those with burdens exceeding 7.4 kBq ranged from 11 to 173 kBq with a mean of 76 kBq; the means for male and female deaths were 45 and 101, respectively; 12 of these 16 deaths occurred in plutonium plant workers.

Elevated risk was found for female plutonium plant workers who were not monitored for plutonium exposure, but there was no evidence of elevated risk for female workers in the radiochemical plant, and little evidence of elevated risks for male workers in either plant who were not monitored for plutonium exposure. Estimating the relative risks separately for unmonitored workers in the two plants improved the fit for the data for females ($P = 0.0013$) over a model in which a single variable for unknown plutonium body burden was included, but no improvement was found for the data for males ($P = 0.28$). 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 significantly improve the fit for males or females.

Analyses in which both external dose and the estimated body burden were treated as quantitative linear variables (Model 3) were also conducted, both for the entire cohort and for the two sexes separately. In these analyses, indicator variables for plutonium plant workers without plutonium monitoring data were included as linear terms. Although this did not significantly improve the fits of the models ($P = 0.06, 0.23$ and 0.36 for the entire cohort, males and fe-

TABLE 3
Observed Deaths and Standardized Mortality Ratios (SMR) Based on Russian Liver Cancer Incidence Rates by Sex, Calendar Year Period, Plant, External Dose, and Plutonium Exposure Status

	All workers		Males		Females	
	Number of liver cancer	SMR (95% CI)	Number of liver cancers	SMR (95% CI)	Number of liver cancers	SMR (95% CI)
Total	60	1.8 (1.4–2.3)	41	1.5 (1.1–2.0)	19	3.0 (1.9–4.6)
By age at death:						
<55	15	1.7 (1.0–2.7)	7	1.0 (0.4–1.9)	8	5.2 (2.4–9.8)
55–64	31	2.3 (1.5–3.1)	24	2.1 (1.4–3.1)	7	2.7 (1.2–5.3)
65+	14	1.3 (0.7–2.0)	10	1.1 (0.6–2.0)	4	1.8 (0.6–4.2)
By calendar year period:						
1948–1969	6	1.9 (0.7–3.8)	5	1.8 (0.7–3.9)	1	2.1 (0.1–9.5)
1970–1979	10	1.6 (0.8–2.8)	5	1.0 (0.3–2.0)	5	4.7 (1.7–10)
1980–1989	26	2.1 (1.4–3.0)	17	1.7 (1.0–2.6)	9	3.9 (1.9–7.1)
1990–1996	18	1.5 (0.9–2.3)	14	1.5 (0.8–2.4)	4	1.6 (0.5–3.8)
By plant:						
Reactor	13	1.4 (0.7–2.2)	11	1.3 (0.7–2.3)	2	1.4 (0.2–4.5)
Radiochemical	19	1.4 (0.8–2.1)	17	1.5 (0.9–2.3)	2	0.7 (0.1–2.3)
Plutonium	28	2.8 (1.9–3.9)	13	1.6 (0.9–2.7)	15	6.9 (4.0–11)
By external dose:						
0–0.1 Sv	9	1.0 (0.5–2.8)	8	1.2 (0.5–2.2)	1	0.5 (0.03–2.0)
0.1–1 Sv	12	1.0 (0.5–1.7)	9	0.9 (0.4–1.6)	3	1.3 (0.3–3.4)
1–3 Sv	26	2.8 (1.9–4.1)	15	1.9 (1.1–3.1)	11	7.9 (4.1–13)
3+ Sv	13	3.8 (2.1–6.2)	9	3.0 (1.4–5.4)	4	9.2 (2.9–21)
By plutonium exposure status:						
No detectable exposure ^a	13	1.1 (0.6–1.8)	11	1.1 (0.6–1.9)	2	1.0 (0.2–3.2)
Detectable exposure	23	3.4 (2.2–5.0)	12	2.2 (1.2–3.7)	11	8.3 (4.3–14)
Not monitored ^b	24	1.6 (1.0–2.3)	18	1.5 (0.9–2.3)	6	2.0 (0.8–4.1)

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

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

males, respectively), including them seemed desirable since it is reasonably certain that many of these workers were exposed to plutonium and since some coefficients were large (the coefficients were 1.4, 0.8 and 5.1 for the entire cohort, males and females, respectively). Indicator variables for unmonitored workers in the radiochemical plant were not included since there was little indication of improvement in fit.

Both the overall and the sex-specific coefficients 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 ($P < 0.001$). Both the ERR/kBq for plutonium exposure and the ERR/Sv for external exposure

were larger for females than for males, but differed significantly only for plutonium exposure (P values for differences by sex were 0.03 for plutonium and >0.5 for external exposure).

When all workers were assumed to have the same ERR/Sv, an association was suggested for external dose ($P = 0.05$), but this association was not statistically significant in the sex-specific analyses ($P = 0.21$ and > 0.5 , for males and females, respectively). 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. These were workers with “known” burdens, radiochemical plant workers with unknown plutonium body burdens, and plutonium plant work-

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

Plant	All workers		Males		Females	
	Person-years (liver cancers)	Relative risk ^a (95% CI)	Person-years (liver cancers)	Relative risk ^a (95% CI)	Person-years (liver cancers)	Relative risk ^a (95% CI)
Reactor	110,043 (13)	1.0	80,108 (11)	1.0	29,935 (2)	1.0
Radiochemical	193,421 (19)	1.0 (0.5–2.1)	131,925 (17)	1.2 (0.6–2.7)	61,496 (2)	0.5 (0.06–4.1)
Plutonium	124,036 (28)	2.1 (1.1–4.1)	81,144 (13)	1.3 (0.6–3.0)	42,891 (15)	5.2 (1.5–33)

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

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

Plutonium body burden (kBq)	All workers		Males		Females	
	Person-years (liver cancers)	Relative risk ^a (95% CI)	Person-years (liver cancers)	Relative risk ^a (95% CI)	Person-years (liver cancers)	Relative risk ^a (95% CI)
0–1.48	162,540 (16)	1.0	112,996 (14)	1.0	49,544 (2)	1.0
1.48–7.40	15,614 (4)	1.5 (0.4–4.2)	11,278 (2)	0.9 (0.1–3.2)	4,336 (2)	7.1 (0.9–59)
7.40+	4,410 (16)	17 (8.0–36)	3,159 (7)	9.2 (3.3–23)	1,252 (9)	66 (16–453)
Unknown						
Radiochemical	147,878 (10)	1.0 (0.4–2.2)	101,801 (9)	1.1 (0.5–2.6)	46,078 (1)	0.6 (0.03–6.1)
Plutonium	97,058 (14)	2.8 (1.3–6.2)	63,944 (9)	2.0 (0.8–4.8)	33,114 (5)	13 (2.4–94)

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

ers with unknown plutonium body burdens. This model fit the data substantially better than a model in which the effects of external dose were assumed to be homogeneous ($P < 0.001$), and indicated that the evidence for an association with external dose 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 ($P = 0.004$) in analyses that adjusted only for working in the plutonium plant without adjusting for plutonium body burden; however, in this case, the ERR/Sv in the “known” burden group was positive, and differed significantly from zero ($P = 0.012$). Sex-specific analyses indicated that the ERR/Sv for external dose was especially large for unmonitored female plutonium plant workers.

To estimate the number of liver cancers that were due to plutonium exposure, we used only data for workers with known plutonium body burdens, and assumed that the ERR/Sv for external dose was zero [since the estimated coefficient was negative and did not differ significantly from zero ($P = 0.24$)]. Using sex-specific estimates of the ERR/kBq, it was estimated that 19.5 of 36 liver cancers in this group (54%) were due to plutonium exposure. The sex-specific estimates were 8.7 of 23 cancers (38%) in males and 10.8 of 13 (83%) cancers in females.

The shape of the exposure–response function was investigated by considering whether the addition of either the squared external dose or the squared body burden improved the fit. The addition of the squared external dose did not improve the fit ($P > 0.5$), but the addition of the squared body burden significantly improved the fit of the model ($P < 0.001$). With the inclusion of the squared term, the linear coefficient for body burden was negative, and including the linear term did not significantly improve the fit over a model in which only the quadratic term was included ($P = 0.24$). Similar results were obtained when males and females were analyzed separately. The analyses described in the four paragraphs immediately above were repeated using the squared body burden instead of the linear term. The only result that this affected substantively was the difference between the sexes for the effects of body burden. As noted above, the sex-specific ERRs/kBq differed signifi-

cantly with $P = 0.03$; however, the ERRs/(kBq)² did not differ significantly ($P = 0.21$), although the coefficient for females was still larger than that for males.

DISCUSSION

This paper is the first to provide evidence of increased risks of liver cancer in a human population exposed to plutonium. Other studies have involved much lower levels of plutonium exposure. No deaths from liver cancer occurred in plutonium workers at Los Alamos (11), Rocky Flats (12), or the Sellafield plant of British Nuclear Fuels (13). A single death from liver cancer (with an estimated body burden of 0.1 kBq) was reported in Hanford workers, but liver cancer was not statistically evaluated as a separate category in this study (14). To our knowledge, these are the only plutonium-exposed human populations that have been studied.

Comparisons of liver cancer mortality with Russian cancer incidence rates could be biased for the purposes of comparison with the Mayak cohort. The completeness of the ascertainment and the reliability of the diagnoses for these data are not clear. Furthermore, liver cancer rates vary considerably within the Russian Federation (15) and were available only for the period 1990–1994, so these rates may not be fully appropriate. However, the patterns of these comparisons by plant, external dose, and plutonium exposure status are indicative of excess risk among early Mayak workers. It seems unlikely that bias could explain some of the larger SMRs that are observed among those with detectable plutonium burdens. It should be noted that none of these comparisons were adjusted for variables other than age, calendar year, and sex; thus excesses among those with large external doses could reflect the effects of plutonium exposure, and vice versa. A striking feature of these comparisons is that SMRs are much larger for female workers than for males among those with large external doses and among those with detectable plutonium burdens. This may result in part because plutonium burdens are larger in female than in male workers. In addition, baseline risks are smaller for females than for males; thus similar absolute

risk 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 liver 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, an elevated risk was found among female workers in the plutonium plant who were not monitored for plutonium exposure. Categorical analyses (Table 4) indicate that the excess is found primarily among those with very high body burdens, although female workers also exhibited excess risk in the intermediate category (1.48–7.4 kBq).

Both alcohol consumption and infection with hepatitis are strong risk factors for liver cancer (9) and are potential confounders of the association with plutonium exposure. Data on hepatitis infection were unavailable, and alcohol consumption data were available only for the liver cancer deaths and were based on self-reports. However, the large effect we observed could be produced by these factors only if they were very strongly associated with plutonium exposure, and this seems highly unlikely.

Evidence was found that liver cancer risk was not a linear function of body burden, and that a pure quadratic function fitted the data reasonably well. Although the body burden is highly correlated with currently available estimates of liver doses (correlation coefficient = 0.95), further analyses based on better estimates of liver dose are needed to examine further the shape of the dose–response function. These analyses should take account of the pattern of accumulation of liver dose over time.

With regard to the excess in unmonitored female plutonium plant workers, all five cancers occurred in females who had detectable plutonium exposure based on nonroutine monitoring prior to 1970 and also had cumulative doses exceeding 1 Sv. It is also noted that 15 of the 16 liver cancers in workers with body burdens exceeding 7.4 kBq had external doses exceeding 1 Sv. Thus some of the excess in both these groups could have resulted from exposure to external dose and/or interaction of plutonium exposure and external dose.

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 liver dose accumulation over time. Thus we cannot meaningfully examine the dependence of risks on time since exposure. However, 54 of the 60 cancers occurred at least 20 years after the initial date of hire, including all of the cancers in those with detectable plutonium burdens.

As noted above, other studies of workers exposed to plutonium have not indicated increased risk of liver cancer. However, workers in these studies had much smaller body burdens than in the Mayak cohort. For example, the highest estimated body burden among the 26 Manhattan project

workers at Los Alamos in the U.S. was 3.2 kBq (16). Among Sellafield workers, the highest burden was about 7 kBq (13). By contrast, workers at the Mayak plutonium plant who were monitored for plutonium had a mean body burden of 8.4 kBq and a maximum burden of 173 kBq. Furthermore, several studies of patients injected with Thorotrast have clearly demonstrated that exposure to α -particle emitters can result in excess risk of liver cancer (9, 17, 18). In the large German study (18), the average cumulative dose to the liver was estimated to be about 5 Gy, larger than the average dose for monitored Mayak plutonium plant workers of about 1 Gy (Table 1), but probably more comparable to liver doses for Mayak workers in categories where excess liver cancer risk was most clearly demonstrated.

In experimental studies conducted in beagle dogs in the U.S., excess liver cancer risk has been demonstrated in dogs exposed intravenously to ^{239}Pu citrate (19) and in dogs exposed to inhaled $^{239}\text{Pu}(\text{NO}_3)_4$ (20) and $^{238}\text{PuO}_2$ (21), both of which are soluble forms of plutonium. In the latter study, liver doses ranged from 0.0004 to 12.5 Gy, and a linear dose–response function provided an adequate fit to the data.

With regard to external radiation exposure, recent analyses of both mortality and incidence data on A-bomb survivors have demonstrated a dose response for liver cancer (22–24). Thus it is reasonable to think that external exposure would contribute to liver cancer risks in Mayak workers, and analyses in which the ERR/Sv was assumed 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 female plutonium plant workers who were not monitored for plutonium (where adjustments for plutonium burden could not be made).

Analyses addressing both internal and external exposure result in larger relative risks for females than for males. This is due at least in part to differences in baseline risks, which are smaller for females than males and which are probably affected by differences in alcohol consumption. Only two liver cancers occurred in females without detectable plutonium burdens, making it impossible to adequately evaluate the relationship of risks from exposure to baseline risks. A contributor to the larger female risks resulting from plutonium exposure and shown in Tables 4 and 5 may be that females in the plutonium plant had larger body burdens and liver doses than males (Table 1). Among workers with body burdens exceeding 7.4 kBq, the average burden for males was 20 kBq, whereas that for females was 46 kBq. However, differences in relative risks persisted in continuous analyses that adjusted for the magnitude the body burden, although the evidence of a difference between the sexes was lessened when a quadratic rather than a linear function was used. In the Thorotrast studies, absolute risks were larger for males than for females in the German study (18). However, in a study conducted in Denmark (25), absolute

risks for the two sexes were similar and relative risks were larger in females. In the most recent analysis of liver cancer incidence data from the A-bomb survivor study, the sex-specific relative risk estimates of the ERR/Sv were nearly identical (24) even though these are larger for females than for males for most other cancer types (22, 23).

We did not attempt to perform detailed analyses for specific histological types of cancers. However, examination of Table 2 suggests that hemangiosarcoma exhibits a particularly strong relationship with plutonium exposure. According to London and McGlynn (9), Thorotrast exposure is a major risk factor for hemangiosarcoma, and also increases the risk of cholangiocarcinoma and hepatocellular carcinoma, a pattern that appears consistent with the findings in Mayak workers. In the A-bomb survivors exposed externally, only one hemangiosarcoma was reported. Also, the A-bomb survivors showed no difference in the dose response for hepatocellular carcinoma compared to cholangiocarcinoma, although this may have been because the number of cancers of the latter type was small.

In the future, better plutonium dosimetry that includes data from more workers than currently is expected to become available. This will include improved estimates of doses to the liver along with the pattern of accumulation over time. Although it will never be possible to obtain precise estimates of liver dose for all workers in the Mayak cohort, it is hoped that improved plutonium dosimetry will allow better quantification of liver cancer risks from both plutonium and external exposure than is currently possible.

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REFERENCES

1. N. A. Koshurnikova, M. G. Bolotnikova, L. A. Ilyin, I. B. Keirim-Markus, Z. S. Menshikh, P. V. Okatenko, S. A. Romanov, V. I. Tsvetkov and N. S. Shilnikova, Lung cancer risk due to exposure to incorporated plutonium. *Radiat. Res.* **149**, 366–371 (1998).
2. Z. B. Tokarskaya, N. D. Okladnikova, Z. D. Belyaeva and E. G. Drozhko, Multifactorial analysis of radiation and nonradiation factors on the lung cancer incidences among workers of the Mayak Nuclear Enterprise. *Health Phys.* **69**, 356–366 (1997).
3. M. Kreisheimer, N. A. Koshurnikova, E. Nekolla, V. F. Khokhryakov, S. A. Romanov, M. E. Sokolnikov and A. M. Kellerer, Lung cancer mortality among nuclear workers of the Mayak facilities in the former Soviet Union. *Radiat. Res.* **154**, 3–11 (2000).
4. N. A. Koshurnikova, E. S. Gilbert, M. Sokolnikov, V. F. Khokhryakov, S. Miller, D. L. Preston, S. A. Romanov, N. S. Shilnikova, K. G. Suslova and V. V. Vostrotin, Bone cancers in Mayak workers. *Radiat. Res.* **154**, 229–236 (2000).
5. V. V. Dvoirin, V. V. Starinsky and N. N. Trapeznikov, *Information Provision of Planning and Estimating of Russian Anti-cancer Program*, p. 154. ONC RAMN, Moscow, 1992. [in Russian]
6. E. M. Asked, V. V. Dvoirin and N. N. Trapeznikov, *Malignant Neoplasm Statistics in Russia and other CIS Countries in 1980–1991*, p. 299. CRC RAMS, Moscow, 1993. [in Russian]
7. V. V. Dvoirin, E. M. Aksel and N. N. Trapeznikov, *Morbidity and Mortality from Malignant Neoplasms in Russian Population and some other CIS Countries in 1993*, p. 231. CRC RAMS, Moscow, 1995. [in Russian]
8. V. V. Dvoirin, E. M. Aksel and N. N. Trapeznikov, *Malignant Neoplasm Statistics in Russia and other CIS Countries in 1994*, p. 193. CRC RAMS, Moscow, 1995. [in Russian]
9. W. T. London and K. A. McGlynn, Liver cancer. In *Cancer Epidemiology and Prevention* (D. Schottenfeld and J. F. Fraumeni, Jr., Eds.), pp. 772–793. Oxford University Press, New York, 1996.
10. D. L. Preston, J. H. Lubin and D. A. Pierce. *EPICURE User's Guide*. HiroSoft International, Seattle, 1991.
11. L. D. Wiggs, E. R. Johnson, C. A. Cox-DeVore and G. L. Voelz, Mortality through 1990 among white male workers at the Los Alamos National Laboratory: Considering exposures to plutonium and external ionizing radiation. *Health Phys.* **67**, 577–588 (1994).
12. G. S. Wilkinson, G. L. Tietjen, L. D. Wiggs, W. A. Galke, J. Acquavella, M. Reyes, G. L. Voelz and R. J. Waxweiler, Mortality among plutonium and other radiation workers at a plutonium weapons facility. *Am. J. Epidemiol.* **125**, 231–259 (1987).
13. R. Z. Omar, J. A. Barber and P. J. Smith, Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. *Br. J. Cancer* **79**, 1288–1301 (1998).
14. E. S. Gilbert, G. R. Petersen and J. A. Buchanan, Mortality of workers at the Hanford site: 1945–1981. *Health Phys.* **56**, 11–25 (1989).
15. A. M. Granov and N. N. Petrovichev, *Pervichnyi Rak Pecheni (Primary Liver Cancer)*, p. 244. Medicina, Leningrad, 1977. [in Russian]
16. G. L. Voelz and J. N. P. Lawrence, A 42-y medical follow-up of Manhattan Project plutonium workers. *Health Phys.* **61**, 181–190 (1991).
17. United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation*. United Nations, New York, 1994.
18. G. van Kaick, A. Dalheimer, S. Hornik, A. Kaul, D. Liebermann, H. Luhrs, A. Spiethoff, K. Wegener and H. Wesch, The German Thorotrast study: Recent results and assessment of risks. *Radiat. Res.* **152** (Suppl.), S64–S71 (1999).
19. G. N. Taylor, R. D. Lloyd, C. W. Mays, W. Angus, S. C. Miller, L. Shabestari and F. F. Hahn, Plutonium- or americium-induced liver tumors and lesions in beagles. *Health Phys.* **61**, 337–347 (1991).
20. J. F. Park, R. L. Buschbom, G. E. Dagle, E. S. Gilbert, C. R. Watson and R. E. Weller, Inhaled plutonium in dogs. In *Pacific Northwest Laboratory Annual Report for 1994 to the DOE Office of Energy Research*, Part 1, pp. 1–9. PNL-10500, National Technical Information Service, Springfield, VA, 1995.
21. E. S. Gilbert, W. C. Griffith, B. B. Boecker, G. E. Dagle, R. A. Guilmette, F. F. Hahn, B. A. Muggenburg, J. F. Park and C. R. Watson, Statistical modeling of carcinogenic risks in dogs that inhaled ²³⁸PuO₂. *Radiat. Res.* **150**, 66–82 (1998).
22. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ochikubo, S. Sugimoto, T. Ikeda, M. Teraski and D. L. Preston, Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat. Res.* **137** (Suppl.), S17–S67 (1994).
23. D. A. Pierce, Y. Shimizu, D. L. Preston, M. Vaeth and K. Mabuchi, Studies of the mortality of atomic bomb survivors. Report 12, Part I, Cancer: 1950–1990. *Radiat. Res.* **146**, 1–27 (1996).
24. J. B. Cologne, S. Tokuoka, G. W. Beebe, T. Fukuhara and K. Mabuchi, Effects of radiation on incidence of primary liver cancer among atomic bomb survivors. *Radiat. Res.* **152**, 364–373 (1999).
25. M. Andersson and H. Storm, Cancer incidence among Danish Thorotrast-exposed patients. *J. Natl. Cancer Inst.* **84**, 1318–1325 (1992).