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Uranium Dust Exposure and Lung Cancer Risk in Four Uranium Processing Operations

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We examined the relation between uranium dust exposure and lung cancer mortality among workers employed in four uranium processing or fabrication operations located in Missouri, Ohio, and Tennessee. Among workers who had at least 30 years of potential follow-up, we identified 787 lung cancer cases from death certificates and matched one control to each case. Health physicists estimated individual annual lung doses from occupational exposure primarily to insoluble uranium compounds, using contemporary monitoring data. With a 10-year lag, cumulative lung doses ranged from 0 to 137 centigrays (cGy) for cases and from 0 to 80 cGy for controls. Health physicists assigned annual external radiation doses to workers having personal monitoring records. Archivists collected smoking information from occupational medical records. Odds ratios for lung cancer mortality for seven cumulative internal dose groups did not demonstrate increasing risk with increasing dose. We found an odds ratio of 2.0 for those exposed to 25 cGy and higher, but the 95% confidence interval of 0.20 to 20 showed great uncertainty in this estimate. There was a suggestion of an exposure effect for workers hired at age 45 years or older. Further analyses for cumulative external doses and exposures to thorium, radium, and radon did not reveal any clear association between exposure and increased risk, nor did dichotomizing workers by facility. (Epidemiology 1995;6:370–375)

Keywords: ionizing radiation, lung neoplasms, radium, radon, smoking, thorium, uranium, occupation.

Four studies of workers in the Department of Energy (DOE) nuclear complex investigated the health effects of exposure to uranium dust in uranium processing and fabrication operations.[1–4] All but one of these studies[3] reported an excess of lung cancer deaths among selected subgroups of workers. A study of 18,869 white males employed at a uranium processing plant between 1943 and 1947[1] found that lung cancer standardized mortality ratios (SMRs) for workers with the greatest potential uranium dust exposure were not higher than SMRs for unexposed workers. Risk was increased, however, among potentially exposed workers hired at age 45 years or older. A nested case-control study of 330 lung cancer cases among this cohort[2] confirmed the increased risk in this age group among workers with a cumulative lung dose of 20 centigrays (cGy) or more. A study of 6,781 white males employed at a nuclear weapons fabrication plant between 1947 and 1979[4] reported an elevated risk for lung cancer. A dose-response trend with increasing cumulative external dose was reported among those workers with a cumulative lung dose of 5.0 centisieverts (cSv) or more, but small numbers and the diminishing of this trend with a 10-year lag made this result equivocal.

Subjects and Methods

Study Facilities

To investigate the relation between lung cancer and uranium dust exposure, we identified eligible workers from four uranium processing or fabrication operations. Two of the operations were located at the Y-12 facility in Oak Ridge, TN, during two nonoverlapping time periods. The first was the uranium enrichment operations run by Tennessee Eastman Corporation (TEC) between 1943 and mid-1947. The second, which operated from mid-1947 through the end of the study, was a materials processing and fabrication operation. The operations from 1943 to 1947 will be referred to as TEC and those from 1947 onward as Y-12. Both operations have been described elsewhere.[1,4] The third operation was Mallinckrodt Chemical Works' Uranium Division (MCW), located at two different sites in Missouri from 1942 to shutdown in 1966. The Feed Materials Production Center (FMPC) in Fernald, OH, the fourth operation, came on-line in 1951 and concluded production in

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1989. Both FMPC and MCW processed ore concentrate into uranium metal. MCW also processed pitchblende ores between 1947 and 1955.

The primary radiation hazard in these facilities was alpha radiation resulting from airborne exposure to dust of mainly insoluble natural uranium compounds. External radiation was of secondary concern. Only TEC had enriched uranium present; all sites except TEC processed thorium. Because MCW processed radium-bearing pitchblende ores, exposure to radium and radon daughters was possible.

Study Population

Eligible cases were employed at least 183 days at any of these facilities and died before January 1, 1983, with lung cancer listed anywhere on the death certificate (that is, *International Classification of Diseases*, revision 8A, codes 162.0–163.9). Inclusion of deaths through 1982 allowed over 30 years of observation at each facility. We chose one control for each case, matching on race, gender, and birth and hire dates within 3 years. Controls had to have worked at least 183 days at the same facility as the case and in at least one other Department of Energy facility if the case had done so.

Data Collection

All data collection and dose calculations were done blinded to case-control status. Data collected on all study members included smoking history, first pay code, which was a surrogate for socioeconomic status, complete work history from each of these facilities, and occupational radiation monitoring records. Archivists recorded the earliest date of either a positive smoking history or of nonsmoking status in plant medical records, when available. Only data that predated the death of a case were used to assign the smoking status to the control. Smoking information was available in medical records at each facility, but level of detail was not standard. Consequently, we included smoking as a dichotomous variable (never/ever smoked) in the analysis. Work history included dates of hire and termination, and each job title/department combination with associated pay code and start and stop dates.

Exposure Assessment

Health physicists estimated annual radiation lung doses from deposited uranium for each study member. Because quantity and quality of radiologic monitoring data varied among study sites, different methodologies were used. For FMPC, MCW, and TEC, uranium air monitoring data were the basis for internal radiation doses. TEC data consisted of several hundred general area air results, identified by date and location. At FMPC and MCW, time-weighted job summaries of uranium dust exposure had been made for jobs in specific areas at specific points in time during facility operation. For these three facilities, we divided an employee's total work experience into periods, which were linked to appropriate average uranium dust concentrations. We multiplied these exposure concentrations by days worked and accumulated the results for an annual integrated activity in the lung. We converted this activity to a dose using the appropriate S-factor.[5] Annual lung dose estimates for Y-12 workers were based on uranium whole body counting and urinalysis results from personal monitoring. A report by Crawford-Brown *et al*[6] details methods used to calculate these doses.

Health physicists determined annual external whole body doses from gamma radiation for FMPC, MCW, and Y-12 workers who had personal monitoring data available. Cases and controls had 53.5% and 54.1%, respectively, of their employment years monitored for external radiation. These data were not assessed for completeness or quality, and none was available for TEC. Health physicists also assigned indices of likely exposure to thorium, radium, and radon. Radon has been identified as a lung cancer hazard.[7]

Statistical Analysis

We used conditional logistic regression[8,9] to obtain maximum conditional likelihood estimates of odds ratios. We categorized cumulative internal lung doses and external radiation doses into seven groups, chosen to accommodate the heavy skewing to the right, and collapsed dose groups in selected analyses when data became sparse. We defined exposure to thorium, radium, and radon as never/ever. All doses and indices were lagged 10 years.

In addition to the matching factors, we considered as potential confounders smoking status (never/ever smoked) and pay code (nonmonthly/monthly). Because lung dose estimates at TEC were based on very limited data, we analyzed data for all workers combined and dichotomized by employment only at TEC. We controlled for pay code as the numbers available permitted, not including this covariate in analyses restricted to the TEC group, in which there were only six pairs discordant for pay code. Analyses that included smoking status were based on 166 pairs for which both members had known smoking status; therefore, odds ratios with and without adjustment for smoking were not comparable. If lagging resulted in a date before first hire, we set doses to zero because of the small likelihood of occupational radiation exposure before employment.

Results

Seven hundred eighty-eight deceased workers met the criteria defining a case. We excluded one case who received an acute external whole body dose of 339 cGy in a 1958 Y-12 accident,[10] because we were interested in studying the effects of exposure to internal ionizing radiation. Of the remaining 787 cases, 567 were first employed at TEC, 142 at Y-12, 51 at FMPC, and 27 at MCW. Only 61 were not white males: 44 white females, 13 black males, and 4 black females. The median age at hire was 36 years. On average, cases died in 1973 at age 62 after 26 years of follow-up.

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TABLE 1. Distribution of Matched Case-Control Pairs by Cumulative Internal and External Doses of Ionizing Radiation, in cGy, with a 10-Year Lag

A. Cumulative Internal Dose: All Pairs

	Controls							
Cases	<0.05	0.05–	0.25–	0.5–	2.5–	5.0–	25.0+	Total
<0.05	81	27	22	37	6	3	0	176
0.05–	26	55	28	70	21	8	0	208
0.25–	12	16	20	25	4	3	0	80
0.5–	26	53	36	75	22	16	0	228
2.5–	9	17	5	14	8	7	1	61
5.0–	5	7	5	8	4	1	0	30
25.0+	0	0	0	0	0	3	1	4
Total	159	175	116	229	65	41	2	787

B. Cumulative Internal Dose: Tennessee Eastman Company Workers Only

	Controls						
Cases	<0.05	0.05–	0.25–	0.5–	2.5–	5.0–	Total
<0.05	27	13	11	21	5	1	78
0.05–	8	35	19	42	14	3	121
0.25–	4	10	7	12	4	1	38
0.5–	13	36	20	46	14	5	134
2.5–	9	10	3	10	7	3	42
5.0–	4	3	1	5	1	1	15
Total	65	107	61	136	45	14	428

C. Cumulative Internal Dose: All Except Tennessee Eastman Company Workers

	Controls							
Cases	<0.05	0.05–	0.25–	0.5–	2.5–	5.0–	25.0+	Total
<0.05	54	14	11	16	1	2	0	98
0.05–	18	20	9	28	7	5	0	87
0.25–	8	6	13	13	0	2	0	42
0.5–	13	17	16	29	8	11	0	94
2.5–	0	7	2	4	1	4	1	19
5.0–	1	4	4	3	3	0	0	15
25.0+	0	0	0	0	0	3	1	4
Total	94	68	55	93	20	27	2	359

D. Cumulative External Dose: All Except Tennessee Eastman Company Workers*

	Controls							
Cases	<0.05	0.05–	0.25–	0.5–	2.5–	5.0–	25.0+	Total
<0.05	22	4	2	5	1	0	0	34
0.05–	7	11	5	8	3	1	0	35
0.25–	0	3	5	8	2	1	0	19
0.5–	5	7	4	15	2	1	0	34
2.5–	0	4	0	5	2	2	1	14
5.0–	1	1	1	1	1	2	0	7
Total	35	30	17	42	11	7	1	143

* Including only pairs for which both case and control had personal external monitoring data available.

One hundred eighty cases worked at more than one Department of Energy facility, primarily at both TEC and Y-12. Excluding case-control pairs employed only at TEC, the median employment duration was over 8 years for both cases and controls. About 80% of cases and controls were nonmonthly workers. We obtained smoking data for 48% (N = 377) of the cases and 39% (N = 305) of the controls, with 91% (N = 344) of these cases and 75% (N = 228) of these controls identified as smokers. Less than 30% of the study population was monitored for external radiation.

Table 1 shows distributions of matched pairs by cumulative internal and external radiation dose categories. Table 2 displays odds ratios with 95% confidence intervals for univariate analysis of factors other than internal or external radiation. Compared with nonsmokers, smokers had a distinctly elevated odds ratio. The odds ratios for monthly paid workers were no greater than those for nonmonthly paid workers. The odds ratio for exposure to thorium was 1.06. Based on only 23 pairs, radon exposure doubled the lung cancer risk, whereas radium exposure decreased it by one-third.

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TABLE 2. Univariate Odds Ratios (OR) and 95% Confidence Intervals (CI) for Selected Factors among All Study Members and Two Mutually Exclusive Subgroups Delineated by Employment Only at Tennessee Eastman Company (TEC)

	All Pairs		TEC Only Pairs		All Pairs Except TEC Workers	
Variable	No. of Pairs	OR (95% CI)	No. of Pairs	OR (95% CI)	No. of Pairs	OR (95% CI)
Smoking ever *vs* never	166	4.33 (2.10–8.94)	94	2.71 (1.14–6.46)	72	10.00 (2.34–42.78)
Paycode: monthly *vs* nonmonthly	787	0.69 (0.38–1.26)	428	1.00 (0.20–4.96)	359	0.65 (0.34–1.25)
Thorium*: exposed *vs* not exposed					335	1.06 (0.55–2.01)
Radon*,†: exposed *vs* not exposed	23	2.00 (0.37–10.92)				
Radium*,†: exposed *vs* not exposed	23	0.67 (0.11–4.00)				

* With 10-year lag.
† Mallinckrodt Chemical Works only.

Table 3 presents odds ratios for cumulative internal lung dose. There was no indication of increased risk for workers exposed below 25 cGy. The elevated odds ratio for the highest dose group came from cases other than TEC and had a wide confidence interval. Although analyses confined to cases age 45 years or older at hire showed elevated odds ratios for exposed workers, no trend was evident with increasing dose.

Odds ratios for cumulative external dose presented in Table 4 showed no exposure effect overall but indicated increased risk among exposed cases hired at age 45 years or older. Including cumulative internal and external dose separately or together in analysis models had no notable effect on the odds ratios.

Adding lung cancer deaths that occurred since the close of the study by Checkoway *et al*,[4] we performed an analysis similar to theirs using cumulative internal and external doses with a quality factor of 10 to convert to seiverts and including the Y-12 radiation accident worker. Compared with the estimates of Checkoway *et*

TABLE 3. Odds Ratios and 95% Confidence Intervals for Lung Cancer Mortality for Internal Radiation Lung Dose among All Study Members and Two Mutually Exclusive Subgroups Delineated by Tennessee Eastman Company (TEC) Employment Using Dose <0.05 cGy as Referent Group and a 10-Year Lag

A. No Exclusions

	All (787)		TEC Workers Only (428)		All Except TEC Workers (359)	
Dose (cGy)	OR	95% CI	OR	95% CI	OR	95% CI
0.05–	1.03	0.73–1.45	0.88	0.54–1.44	1.18	0.72–1.95
0.25–	0.57	0.38–0.85	0.49	0.28–0.86	0.64	0.36–1.15
0.5–	0.85	0.58–1.14	0.78	0.49–1.24	0.90	0.55–1.47
2.5–	0.82	0.52–1.30	0.76	0.42–1.35	0.86	0.39–1.88
5.0–	0.64	0.37–1.12	0.87	0.39–2.00	0.53	0.24–1.14
25.0+	2.05	0.20–20.70			1.80	0.17–19.27

B. Estimates Adjusted for Smoking among Case-Control Pairs for Whom Smoking Information Was Available

	All Pairs (166)		TEC Pairs Only (94)		All Pairs Except TEC (72)	
Dose (cGy)	OR	95% CI	OR	95% CI	OR	95% CI
0.05–	0.47	0.19–1.18	0.14	0.03–0.62	2.11	0.49–9.11
0.25–	0.46	0.16–1.28	0.44	0.09–2.08	0.49	0.09–2.72
0.5–	0.64	0.26–1.60	0.24	0.06–0.91	2.81	0.57–13.82
2.5–	0.34	0.12–1.02	0.15	0.03–0.71	1.17	0.17–8.06
5.0–	0.36	0.09–1.38	0.11	0.02–0.76	1.13	0.13–9.93
Smoking: ever/never	4.54	2.16–9.53	2.92	1.17–7.29	13.41	2.76–65.17

C. Cases Hired at Age 45 Years or Older

	All Pairs (135)		TEC Pairs Only (71)		All Pairs Except TEC (64)	
Dose (cGy)	OR	95% CI	OR	95% CI	OR	95% CI
0.05–	1.50	0.63–3.56	1.32	0.36–4.88	1.62	0.48–5.43
0.25–	1.04	0.36–3.05	0.70	0.16–3.16	2.04	0.50–8.29
0.5–	1.50	0.62–3.63	1.52	0.39–5.94	1.34	0.40–4.43
2.5–	0.87	0.28–2.67	1.00	0.24–4.13	0.39	0.03–4.44

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TABLE 4. Odds Ratios and 95% Confidence Intervals for Lung Cancer Mortality for External Radiation Dose Using a 10-Year Lag and Dose of <0.05 cGy as Reference Group*

	No Exclusions† (143 Pairs)		Cases Hired at Age ≥45 Years (64 Pairs)	
Dose (cGy)	OR	95% CI	OR	95% CI
0.05–	1.31	0.55–3.13	2.10	0.66–6.68
0.25–	1.21	0.41–3.51	0.33	0.03–3.20
0.5–	0.85	0.35–2.04	1.56	0.47–5.13
2.5–	1.41	0.44–4.50	2.09	0.31–14.11
5.0–	1.00	0.24–4.13		

* Including only pairs for which both case and control had personal external monitoring data available.
†No exclusions with respect to age at time of hire.

al, results in Table 5 indicated a more moderately increasing risk with increasing external dose among those in the highest internal dose group, without lagging doses. The model failed to converge lagging doses 10 years.

Discussion

The results of this study indicate no dose-response relation between risk of lung cancer death and lung dose resulting from internal exposure to uranium dust. We found a suggestion of an exposure effect from internal radiation lung dose and external radiation for workers hired after age 45 years. Among the subgroup of case-control pairs for whom smoking information was available for both members, we saw an exposure effect for workers not employed only at TEC. In both instances, however, not more than 20% of the 787 pairs were included in the analysis. Our findings are consistent with those reported by Polednak and Frome[1] and Cookfair *et al.*[2] Although the dose-response effect is much weaker than in the analysis by Checkoway *et al*,[4] risk estimates for each dose group are not inconsistent, given the wide confidence intervals reported by Checkoway and colleagues.

The current study differed from earlier ones[1–4] in a number of ways. The current incremental method used to calculate doses for TEC differed from the approach taken by Cookfair *et al*,[2] which estimated a 50-year lung dose commitment truncated at death or the end of the study and could include a dose received after the onset of disease. Our study required a minimum employment of 6 months as contrasted with 30 days for previous studies, and it included more than twice as many lung cancer cases. The results reported by Checkoway *et al*[4] were based on only 40 cases (27 in the highest internal dose group) rather than 105, as in our study (38 in the highest group).

Several shortcomings of this study, including possible dose misclassification and potential exposure to other lung carcinogens, might have precluded finding an association between radiation exposure and lung cancer risk. Dose estimates were the best possible, based on currently accepted procedures and all relevant information available for each worker.[5,6] No previous study has been based on individual annual lung doses calculated for each year of employment. Nevertheless, some potential for exposure misclassification still exists, particularly from the TEC workers, with only area air monitoring data available. To evaluate this possible misclassification, data for TEC workers were analyzed separately.

The decision to match one control for each case was prompted by practical constraints of estimating annual lung doses and collecting smoking data. Matching on birth year helped to control indirectly for differences in smoking habits among birth cohorts.[11]

Because of limited information available in the medical records, only 166 pairs were available to obtain odds ratio estimates adjusted for smoking. It is unlikely, however, that smoking was related to cumulative internal radiation dose. To check whether smoking status was a confounder for dose, we calculated odds ratios for these same 166 pairs without adjusting for smoking. The resulting odds ratios (0.51, 0.45, 0.59, 0.34, 0.38) were not notably different from those in Table 3 (0.47, 0.46, 0.64, 0.34, 0.36).

Matching on facility ensured the use of similar methods to estimate lung doses for each case and his control. In any given year within each operation, the actual doses varied widely among different jobs, with workers spread rather evenly across these jobs. Matching on operation by year of hire and by employment at another Department of Energy facility helped to control for exposure to nonradiation lung carcinogens not measured in the current study. Because of geographic dispersion of the operations, matching on facility minimized the effect of geographic variations in background radon exposure, a known risk factor for lung cancer. White and co-workers[12] reported a fivefold variation in maximum radioactivity level due to radon in houses across the three states.

TABLE 5. Odds Ratios and 95% Confidence Intervals for Lung Cancer Mortality According to Joint Cumulative Exposure, Assuming a 0-Year Lag and Quality Factor of 10 for Internal Exposure

External Radiation Exposure (cSv)	Internal Radiation Exposure (cSv) 0–0.99			1–4.99			≥5		
	No. of Deaths	OR	95% CI	No. of Deaths	OR	95% CI	No. of Deaths	OR	95% CI
0–0.99	45	1.00	Referent	17	0.71	0.30–1.69	15	0.64	0.30–1.39
1–4.99	0			5	0.75	0.18–3.10	20	1.03	0.40–2.66
≥5	0			0			3*	1.18	0.19–7.41

* Includes accident victim, who was included in the analysis by Checkoway *et al.*[4] but was excluded from all other analyses in the current study.

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The direction and strength of the association of lung cancer with smoking[11] and socioeconomic status were consistent with those reported in the literature. These findings reinforce the conclusion that there is no dose-response relation between risk of lung cancer and radiation dose to the lung at levels of occupational uranium dust exposure experienced by workers in these facilities.

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