

Analysis of the Mortality Experience amongst U.S. Nuclear Power Industry Workers after Chronic Low-Dose Exposure to Ionizing Radiation

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Workers employed in 15 utilities that generate nuclear power in the United States have been followed for up to 18 years between 1979 and 1997. Their cumulative dose from whole-body ionizing radiation has been determined from the dose records maintained by the facilities themselves and the REIRS and REMS systems maintained by the Nuclear Regulatory Commission and the Department of Energy, respectively. Mortality in the cohort from a number of causes has been analyzed with respect to individual radiation doses. The cohort displays a very substantial healthy worker effect, i.e. considerably lower cancer and noncancer mortality than the general population. Based on 26 and 368 deaths, respectively, positive though statistically nonsignificant associations were seen for mortality from leukemia (excluding chronic lymphocytic leukemia) and all solid cancers combined, with excess relative risks per sievert of 5.67 [95% confidence interval (CI) –2.56, 30.4] and 0.506 (95% CI –2.01, 4.64), respectively. These estimates are very similar to those from the atomic bomb survivors study, though the wide confidence intervals are also consistent with lower or higher risk estimates. A strong positive and statistically significant association between radiation dose and deaths from arteriosclerotic heart disease including coronary heart disease was also observed in the cohort, with an ERR of 8.78 (95% CI 2.10, 20.0). While associations with heart disease have been reported in some other occupational studies, the magnitude of the present association is not consistent with them and therefore needs cautious interpretation and merits further attention. At present, the relatively small number of deaths and the young age of the cohort (mean age at end of follow-up is 45 years) limit the power of the study, but further follow-up and the inclusion of the present data in an ongoing IARC combined analysis of nuclear workers from 15 countries will have greater power for testing the main hypotheses of interest. © 2004 by Radiation Research Society

INTRODUCTION

Many individuals are routinely exposed to low doses of low-LET whole-body ionizing radiation received at low dose rates by virtue of occupation. In this context, the terms “low dose” and “low dose rate” generally refer to equivalent doses of the order of several millisieverts (mSv) received during a working year. This definition is used in this paper for convenience since it describes the experience of typical nuclear workers.

Currently, standards for limiting the amount of such exposure are based on cancer risk estimates obtained by extrapolating data from epidemiological studies of individuals exposed on average to much higher doses at higher dose rates, for example, the study of the atomic bomb survivors (1). Such extrapolation involves uncertainty in terms of factors such as the shape of the dose–response relationship at low doses and whether, as some suggest, there is a threshold effect for the induction of cancer, the primary stochastic outcome associated with radiation exposure. It is therefore desirable to study directly disease risks, especially cancer risk, amongst cohorts of occupationally exposed individuals, both to directly estimate those risks and to compare them with risks extrapolated from higher-dose studies (1).

One of the largest groups occupationally exposed to low doses consists of workers in the nuclear power industry. In this context, the mortality experience between 1957 and 1994 of a cohort of 45,468 Canadian nuclear power industry workers and workers at Atomic Energy of Canada Limited (a research organization) has been reported (2). In this paper, the mortality experience between 1979 and 1997 of a cohort of 53,698 U.S. workers in the U.S. nuclear power industry is reported. Dose–response analyses are presented examining radiation-related risks of various cancer and noncancer outcomes with the primary *a priori* hypotheses of an association between dose and risk of leukemia, excluding chronic lymphocytic leukemia, and between dose

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TABLE 1
U.S. Nuclear Power Industry Workers Study: Characteristics of the Cohort, 1979–1997

	Male	Percentage	Female	Percentage	All	Percentage
Total	47,311	88.1	6,387	11.9	53,698	100.0
Ethnicity						
White non-Hispanic	39,176	82.8	5,098	79.8	44,274	82.4
Other	8,135	17.2	1,289	20.2	9,424	17.6
Socioeconomic status (code) ^a						
1	8,343	17.6	1,324	20.7	9,667	18.0
2	5,902	12.5	763	11.9	6,665	12.4
3	9,224	19.5	991	15.5	10,215	19.0
6	7,406	15.7	1,156	18.1	8,562	15.9
7	8,762	18.5	1,210	18.9	9,972	18.6
8	4,633	9.8	467	7.3	5,100	9.5
9	3,041	6.4	476	7.5	3,517	6.5
Mean age at start of monitoring, years	30.5		30.4		30.5	
Mean year at start of monitoring	1982		1986		1983	
Mean duration of monitoring, years	12.4		7.7		11.9	
Mean age at end of follow-up, years	45.8		42.1		45.2	
Mean cumulative dose, mSv	28.5		4.6		25.7	

^a Codes 1–3 were used for education levels recorded in personnel files; codes 6–8 indicate education levels estimated from worker job title description. Facilities used either codes 1–3 or 6–8, depending on the availability of information. Code 1 or 6: high school diploma or GED; code 2 or 7, Associate degree or equivalent; code 3 or 8, baccalaureate degree and above; code 9, unknown. Codes 4 and 5 were not used.

and all solid cancers combined. Other analyses are regarded as being more exploratory, based on the existing epidemiological evidence. Comparisons are made with other epidemiological studies of whole-body ionizing radiation.

The data from both the Canadian and U.S. studies will contribute to a combined analysis of nuclear workers from 15 countries currently being coordinated by the International Agency for Research on Cancer (IARC). Both studies conform to the protocol requirements of the IARC analysis.

METHODS

The Cohort

A total of 15 U.S. nuclear power utilities (52 nuclear plants) contributed workers to the study (see Appendix Table 1). To be eligible, a subject had to have been employed by one of these utilities at some time between January 1, 1979 and December 31, 1997, and to have been monitored for at least 1 year during that employment for exposure to ionizing radiation. The 1-year minimum monitoring was used to exclude individuals with very short-term employment, who have been shown to demonstrate irregular mortality patterns (3). Contractor employees were not included in the cohort because of the difficulty in ensuring complete dosimetric records for such individuals. The years 1979–1997 were set to correspond with the period when mortality could be ascertained through the National Death Index (see below). Each utility provided data on identifying information such as name, date of birth, gender and ethnicity, as well as most recent occupation and socioeconomic status (SES) based on either recorded education or an assessment of the typical educational requirements for a given occupation (three categories of SES were used). The data were assembled centrally by researchers at Columbia University and Battelle Laboratories who thus constituted a scientific team which was independent of the facilities and was responsible for data collection, checking, analysis, interpretation and report writing. Their work was subject to evaluation and approval by the Institutional Review Board with regard to confidentiality and privacy act considerations.

In total, the cohort contained 53,896 individuals, of whom 198 were

eliminated because of irresolvable inconsistencies in their data records, leaving a final cohort of 53,698 for analysis.

Dosimetry

Dose monitoring records for all individuals in the cohort were supplied by the utilities where they were employed, including records for doses received prior to 1979. This dose information was supplemented by the dose records maintained by the Nuclear Regulatory Commission (NRC) and the Department of Energy (DOE) and was summarized for analysis to provide annual doses for each worker. The NRC system, the Radiation Exposure Information Record System (REIRS), contains dose information since the mid-1960s for all employees of facilities licensed by the NRC. The DOE system, Radiation Exposure Monitoring Systems (REMS), contains records for all DOE workers, again since the mid-1960s. The combination of these three sources (facility records, REIRS and REMS) provided an essentially complete dosimetric history for all cohort subjects. The records from NRC and DOE for the subjects in this study were obtained under a collaborative agreement among NRC, DOE, the IARC and Battelle. The DOE provided what is called a Center for Epidemiologic Research (CER) number to anonymize records. This also enabled the identification of a few individuals who had worked at DOE sites in addition to their experience in the nuclear power industry, and these individuals were removed from the cohort. This exclusion was carried out because cohorts from DOE facilities had been and are being reported separately and will contribute independently to the IARC combined analysis.

It is believed that this is the first time that all three sources (facilities, REIRS and REMS) have been used in an attempt to provide as complete a dose history as possible, and it underscores the desirability of a single depository for all occupation-related radiation doses received by U.S. workers in general.

The great majority of recorded doses came from external penetrating high-energy low-LET radiation (>100 keV), and a negligible amount of dose came from other sources (e.g., only 4.4% of the cohort had some neutron dose, and for these individuals, the average percentage of total dose from neutron dose was 1.7%). The few workers with more than 10% of their total dose from neutrons were excluded. Those monitored for internal depositions (again, a very small number) were also excluded

from the cohort analyzed. Doses from neutrons and internal contamination are subject to considerably more uncertainty than those from external low-LET radiation. In addition, the numbers of workers with neutron and internal doses were too small to evaluate their mortality experience separately.

Doses below the threshold level were recorded as zero dose. No attempts were made to correct for the potential underestimation of dose where the doses were recorded as zero. It is planned to evaluate the impact of measurement error in dosimetry as part of the IARC analysis.

Mortality Assessment

The identifying data for the cohort were supplied to the National Death Index for linkage to U.S. National death records between 1979 and 1997 (4). The study satisfied the privacy act requirements of the U.S. National Death Index (NDI) and additional requirements imposed by some states and cities for access to vital status information. The NDI has been reported to provide very high sensitivity and specificity for identifying deaths in various U.S. cohorts with similar amounts of identifying information as the present cohort (e.g. refs. 5, 6).

After the receipt of all possible links from the NDI based on deterministic rules of linkage, (i.e. agreement on various combinations of specified sets of identifying items), these links were further subjected to a probabilistic record linkage process (7, 8). This resolved the multiple possible links for an individual and gave the link with the greatest likelihood of being true. For a few links with some remaining uncertainty in their validity, manual examination of the data not available to the computerized processes allowed such links to be resolved.

A total of 1,190 deaths were identified in the cohort with data available on the date of death, the underlying cause of death coded to the 9th revision of the International Classification of Diseases (ICD), and up to three contributory causes, again coded to the 9th revision of the ICD.

In a separate exercise, the death certificates for all those identified as dying of leukemia were reviewed blindly by trained nosologists, and the degree of agreement with the underlying cause as coded on the death certificate was found to be 100%.

Statistical Analysis

Poisson regression techniques were used to analyze the cohort data (9). All individuals contributed person-years at risk from the date when they had completed 1 year of monitoring or January 1, 1979, whichever was later, until their date of death or December 31, 1997, whichever occurred earlier. Person-years were cross-classified by gender, ethnicity (non-Hispanic whites or other), 5-year intervals of age at risk, 5-year intervals of the calendar year at risk, facility (six groupings), SES (seven categories), cumulative radiation dose, and monitoring status (still being monitored or no longer monitored). There were too few individuals other than non-Hispanic whites to sensibly subdivide other ethnic groups. Facilities were grouped by geographic location to reduce the degree of stratification. Dose was categorized into four categories (0-, 1-, 50-, ≥ 100 mSv) for purposes of categorical analysis, or into 12 categories when dose was treated as a quasi-continuous variable in the analysis. The latter 12 categories were chosen (apart from the <1 mSv dose category) to give approximately equal numbers of the outcome under consideration in each dose category. The mean dose in each cell of the cross-classification table was estimated as the person-year weighted mean, and these values were used in the regression analysis when dose was treated as a quasi-continuous variable. Dose was lagged by 2 years for all leukemia and for 10 years for analysis of all other causes.

Two approaches were taken to the analysis of the data, i.e. categorical and linear analyses, for the following reasons. A categorical analysis allows the examination of data for indications of a dose-response relationship, i.e. generally higher risk with categories of higher dose. This is done without imposing any form of specific dose-response relationship on the data. However, of course, this approach lacks power compared to the linear analysis. The linear analysis gives greater power and yields a parameter (the excess relative risk) that has become the standard param-

eter for presenting the results of radiation studies, and thus this approach permits ready comparison with results from other studies. However, outliers can produce an artificially high or low ERR. The use of both methods allows for the assessment of the possible contribution of chance to study results (preferably based on the linear model) and the existence of a dose-response relationship (based on the categorical approach) and produces a parameter that is the most directly comparable to that of other studies. For these reasons, the results of both approaches are presented for the analyses reported in this paper, with the interpretation of results taking into account the relative contributions of the two different models to assessing the reality of any observed association.

"Person-years" were actually calculated as person-days, and time-dependent variables such as age at risk and dose were computed for the particular day at risk under consideration. For this calculation, it was assumed that annual doses were received in equal amounts on each day of that year; this technique allowed the use of exact dates for variables such as birth date.

The observed deaths in the cohort were classified in the same way as the person-years at risk using all solid cancers combined (defined by ICD-9 codes 140.0-199.9) (10), 10 individual cancer causes of death, all non-cancers combined (ICD-9 1.0-139.9 and 209.0-999.9), and seven individual noncancer causes. The choice of individual cancer and noncancer causes of death was based primarily on available numbers of deaths, with a minimum of five observed deaths, and also from consideration of the potential radiosensitivity of the various causes.

External comparisons were made with U.S. population rates. For any particular analysis, the relevant person-years at risk in the cohort or subgroup of the cohort were multiplied by the gender-, age-, calendar year- and cause-specific death rates for the U.S. population between 1979 and 1997 to yield the expected number of deaths. The standardized mortality ratio (SMR) was calculated as the ratio of the observed deaths to those expected. Confidence intervals (CI) were calculated and tests of significance were conducted by treating the observed number of deaths as a Poisson-distributed variable (9).

Quantification of the relationship between risk of cancer and radiation dose was carried out by conducting internal comparisons with the use of Poisson regression models for grouped data.

The general model used to estimate relative risk was the linear excess relative risk model (11). This model takes the form

$$R_D = R_0(1.0 + \beta D), \quad (1)$$

where R_D is the rate at dose D , R_0 is the background rate (stratified to adjust for potential confounders), β is the excess relative risk, and D is the cumulative lagged dose. Thus any risk associated with dose multiplies the background rate, and the relationship between risk and dose is linear.

It was assumed for analyses that a linear dose-response function applied. This has been demonstrated for many higher-dose epidemiological studies (1). Although leukemia appears to follow a linear-quadratic dose-response relationship, at doses of the order of those experienced by nuclear workers, this effectively reduces to linearity. The present study did not have sufficient power to investigate alternative forms of dose-response relationship, in common with other nuclear worker studies (12).

Maximum likelihood point and interval estimates were obtained using the module AMFIT from the software package EPICURE (11). Tests of significance were based on the likelihood ratio test. The trend tests for categorical analyses were based on the significance of a single variable with values of 1, 2, 3 and 4 corresponding to the four categories of dose. For continuous analyses, the P value was based on the significance of the continuous dose variable in the model. All tests are two-sided unless otherwise specified. Because of the form of Eq. (1), the possible values of β are limited by the requirement that the corresponding relative risk should not be negative. The minimum value for β is given by $-1/D_{\max}$ where D_{\max} is the maximum individual cell dose. If the likelihood being sought for a point or bound estimate requires a β less than this value, no convergence will be obtained, and the estimate is shown as $< \beta_{\min}$ (see for example Table 4).

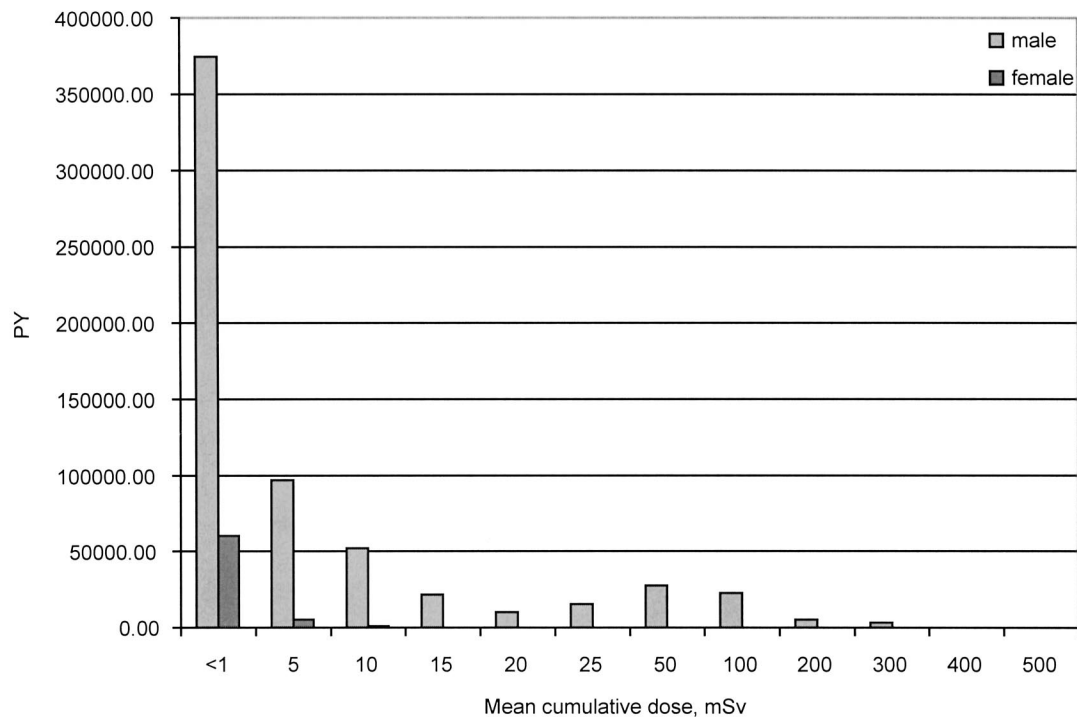


FIG. 1. Distribution of person-years in the cohort of U.S. nuclear power industry workers by 12 dose groups and gender.

RESULTS

A total of 698,051 person-years (PY) at risk were accumulated by the 53,698 members of the cohort. Table 1 shows the demographic, follow-up and dose characteristics of the cohort. The cohort consists predominantly of men, and the ethnic composition is substantially non-Hispanic white. The average period of monitoring is 11.9 years, and the average length of follow-up (i.e. from 1979 or completion of 1 year of monitoring) is 13.0 years. Workers who died from solid cancers accumulated 6,092 PY-Sv (with a 10-year lag), and those who died from leukemia 14,025 PY-Sv (with a 2-year lag).

The mean total cumulative equivalent dose is 25.7 mSv for the whole cohort and is 30.7 mSv among those with some recorded dose. The distribution of person-years at risk by dose category and gender is shown in Fig. 1 and shows the approximately lognormal distribution typical for this type of cohort. Except for the first dose group (<1.0 mSv), the contribution of women to the follow-up was negligible. Further analyses are based on the total cohort.

The results of the SMR analysis are given in Table 2. The cohort displays a very substantial healthy worker effect, i.e. considerably lower mortality than the general population, with an SMR for all causes of 0.41. The SMR for all noncancer causes (0.34) is substantially less than the SMR for all cancers (0.65). This observation too is consistent with the healthy worker effect, which generally is stronger for noncancer causes than cancer causes (3).

Consideration of individual causes shows that the SMRs are generally below unity. Because many factors differ be-

tween the general population and an employed cohort, interpretation of these observations is obviously very limited.

The remainder of the analyses involve internal comparisons, i.e. only within the cohort. All analyses were adjusted by stratification for age at risk, ethnic group, gender and calendar year at risk. Other potential confounders investigated included facility, duration of monitoring (as a surrogate for employment), and socioeconomic status. Stratification variables for each analysis were selected based both on *a priori* considerations and empirical results, i.e. the change in the point estimate of the excess relative risk. Only variables that had a nontrivial effect on the point estimate of the dose parameter(s) for any particular cause were included as covariates to minimize stratification and thus maximize statistical efficiency.

For all solid cancers as the outcome, under the excess relative risk model, the estimate of the excess relative risk (ERR) per sievert was adjusted for the four potential confounding variables (age, gender, ethnic group and calendar year) and, in addition, for duration of monitoring and facility. Analyses for leukemia used only the four potential confounding variables, and analyses of noncancer outcomes used the four potential confounding variables together with facility, duration of monitoring and SES.

The results for lymphopioietic cancers are shown in Table 3. For all leukemias, there is some evidence of a positive trend, both for the categorical analysis and for the ERR analysis. The trend test for the categorical results is not statistically significant ($P = 0.25$), whereas, based on the ERR analysis, the tests almost achieve conventional levels

TABLE 2
U.S. Nuclear Power Industry Workers Study: Standardized Mortality Ratios (SMRs) by Cause of Death, 1979–1997

Cause	Observed	Expected ^a	SMR	95% CI
All causes	1,190	2922.4	0.41	0.38, 0.43
All solid cancers	368	564.3	0.65	0.59, 0.72
Stomach cancer	16	19.7	0.81	0.47, 1.32
Colon cancer	36	47.8	0.75	0.53, 1.04
Pancreatic cancer	18	29.0	0.62	0.37, 0.98
Lung cancer	125	210.4	0.59	0.49, 0.71
Prostatic cancer	14	23.2	0.60	0.33, 1.01
Kidney cancer	14	17.7	0.79	0.43, 1.32
Brain and other CNS ^b cancer	23	27.0	0.85	0.54, 1.28
All lymphopoietic cancer	49	75.7	0.65	0.48, 0.86
Multiple myeloma	6	9.5	0.63	0.23, 1.37
Leukemia	29	27.2	1.07	0.71, 1.53
All noncancers	773	2282.3	0.34	0.32, 0.36
Nervous system diseases	20	39.9	0.50	0.31, 0.77
Circulatory system diseases	350	832.7	0.42	0.38, 0.47
Arteriosclerotic heart disease including CHD ^c	248	524.6	0.47	0.42, 0.54
All vascular lesions of CNS	24	89.5	0.27	0.17, 0.40
All respiratory diseases	37	129.1	0.29	0.20, 0.40
All pneumonia	8	48.1	0.17	0.07, 0.33
Digestive system diseases	32	148.9	0.21	0.15, 0.30

^a Expected number of deaths based on age-, gender-, calendar year- and cause-specific mortality rates for the U.S. population during 1979–1997.

^b Central nervous system.

^c Coronary heart disease.

of statistical significance using a one-sided test ($P = 0.053$). When the three deaths from chronic lymphocytic leukemia are excluded, the results are similar but are somewhat less positive, with an ERR of 5.67 (95% CI –2.56, 30.4) with a (one-sided) P value of 0.14.

Although there is a monotonic increase in risk with dose category for non-Hodgkin’s lymphoma, there is only a single death in each of the top two dose categories. The ERR is again large, but the P values achieve conventional levels of statistical significance.

TABLE 3
U.S. Nuclear Power Industry Workers Study: Categorical and Linear Excess Relative Risks for Lymphopoietic Cancers^a

Cause	Dose group, mSv				P value ^b	ERR ^c	P value ^d
	<1	1–49	50–99	100–			
Leukemia ^e							
RR ^f	1.00	1.48	0.65	2.54	0.25	8.89	0.11
95% CI		0.63, 3.44	0.08, 5.16	0.77, 8.44		–1.04, 36.4	
n	10	14	1	4		29	
Leukemia excluding CLL ^{e,g}							
RR	1.00	1.27	0.65	1.95	0.49	5.67	0.28
95% CI		0.53, 3.04	0.08, 5.20	0.52, 7.37		–2.56, 30.4	
n	10	12	1	3		26	
Non-Hodgkin’s lymphoma ^h							
RR	1.00	1.31	2.53	6.25	0.22	61.3	0.076
95% CI		0.39, 4.33	0.26, 24.43	0.49, 79.05		–2.51, 313	
n	7	5	1	1		14	

^a Background rate stratified for gender, age, calendar year and ethnicity.

^b P value of the trend test for categorical analysis, two-sided.

^c Excess relative risk per sievert.

^d P value of the ERR estimate, two-sided.

^e Doses lagged by 2 years.

^f Relative risk.

^g Chronic lymphocytic leukemia.

^h Doses lagged by 10 years.

TABLE 4
U.S. Nuclear Power Industry Workers Study: Categorical and Excess Relative Risks for Various Solid Cancers^a

Cause ^b	Dose group, mSv				<i>P</i> value ^c	ERR ^d	<i>P</i> value ^e
	<1	1–49	50–99	100			
All solid cancers							
RR ^f	1.00	0.96	0.72	1.14	0.86	0.51	0.75
95% CI		0.74, 1.24	0.38, 1.37	0.64, 2.05		–2.01, 4.64	
<i>n</i>	222	116	12	18		368	
Stomach cancer							
RR	1.00	2.27	3.66	5.17	0.091	19.5	0.14
95% CI		0.64, 8.00	0.54, 24.80	0.64, 41.83		–2.23, 141	
<i>n</i>	5	7	2	2		16	
Colon cancer							
RR	1.00	0.6	0.18		0.070	–2.28	0.52
95% CI		0.25, 1.42	0.02, 1.55			<–2.51, 10.5	
<i>n</i>	24	11	1			36	
Pancreatic cancer							
RR	1.00	1.17	1.58		0.65	9.38 ^g	0.32
95% CI		0.37, 3.72	0.22, 11.22			<–2.5, 89.7	
<i>n</i>	11	5	2			18	
Lung cancer							
RR	1.00	1.03	0.61	1.44	0.76	0.246	0.93
95% CI		0.67, 1.60	0.20, 1.85	0.58, 3.52		<–2.51, 8.44	
<i>n</i>	72	41	4	8		125	
Prostate cancer							
RR	1.00		0.68		0.53	–2.503 ^g	0.50
95% CI			0.20, 2.30			<–2.51, 26.4	
<i>n</i>	9		5			14	
Kidney cancer							
RR	1.00	1.11	16.03		0.057	48.8	0.075
95% CI		0.27, 4.66	2.33, 110.60			–1.77, 315	
<i>n</i>	8	3	3			14	
Brain and other CNS ^h cancer							
RR	1.00	0.6	0.41		0.27	–2.503 ^g	0.61
95% CI		0.20, 1.78	0.05, 3.74			<–2.51, 27.1	
<i>n</i>	16	6	1			23	

^a Background rate stratified for gender, age, calendar year, ethnicity, facility and duration of monitoring.

^b Doses lagged by 10 years.

^c *P* value of the trend test for categorical analysis, two-sided.

^d Excess relative risk per sievert.

^e *P* value of the ERR estimate, two-sided.

^f Relative risk.

^g Estimate may not be a maximum likelihood estimate; see Methods section.

^h Central nervous system.

Although multiple myeloma is of interest, in view of the somewhat mixed evidence from other studies of those exposed occupationally (12), the number of deaths ascribed to multiple myeloma with a total cumulative dose of 1 mSv or more was too small ($n = 2$) to permit a sensible evaluation in the present data.

In Table 4, all solid cancers combined do not show any obvious pattern of increasing risk with increasing dose in the categorical analysis, and there is no indication of a positive trend ($P = 0.86$). The excess relative risk is positive with an estimate of 0.51, though, again, this is nowhere near statistically significant ($P = 0.75$).

Of the individual solid cancers, stomach cancer demonstrates a monotonically increasing risk with dose category, though there are only two cases in each of the two top-dose categories. The ERR is large but with wide CIs (ERR = 19.5, 95% CI –2.23, 141).

Apart from kidney cancer, which shows a substantial elevation in the highest-dose category (though again this is based on only three deaths), the other individual cancers shown in Table 4 display no meaningful evidence of a positive association.

Table 5 shows the results for noncancer outcomes based on the underlying cause of death and excluding contrib-

TABLE 5
U.S. Nuclear Power Industry Workers Study: Categorical and Linear Excess Relative Risks for Noncancers
(Underlying Causes of Death Only)^a

Cause ^b	Dose group, mSv				P value ^c	ERR ^d	P value ^e
	<1	1–49	50–99	100–			
Noncancer							
RR ^f	1.00	0.73	1.49	1.36	0.73	6.40	0.001
95% CI		0.60, 0.88	1.04, 2.12	0.88, 2.11		2.29, 12.2	
n	459	225	51	38		773	
Nervous system diseases							
RR	1.00	1.08	3.25		0.38	46.8	0.031
95% CI		0.33, 3.54	0.52, 20.29			1.51, 242	
n	13	5	2			20	
Circulatory system diseases							
RR	1.00	0.87	1.98	1.57	0.11	8.32	0.002
95% CI		0.66, 1.15	1.22, 3.20	0.86, 2.84		2.30, 18.2	
n	185	114	29	22		350	
Arteriosclerotic heart disease including CHD^g							
RR	1.00	0.70	1.76	1.65	0.36	8.78	0.004
95% CI		0.50, 0.97	1.00, 3.11	0.82, 3.33		2.10, 20.0	
n	141	72	20	15		248	
All vascular lesions of CNS^h							
RR	1.00	1.89	3.27		0.21	–2.05	0.69
95% CI		0.52, 6.83	0.48, 22.26			<–2.06, 353	
n	9	4	0			24	
Respiratory system diseases							
RR	1.00	1.09	2.10	0.43	0.93	–2.05	0.57
95% CI		0.44, 2.68	0.46, 9.49	0.04, 4.72		<–2.06, 14.8	
n	20	12	4	1		37	
Pneumonia							
RR	1.00		3.08		0.22	–2.05 ⁱ	0.43
95% CI			0.53, 17.98			<–2.06, 22.8	
n	3		5			8	
Digestive system diseases							
RR	1.00	0.89	2.44	1.05	0.67	17.8	0.29
95% CI		0.33, 2.37	0.51, 11.70	0.10, 1.24		<–2.06, 110	
n	17	11	3	1		32	

^a Background rate stratified for gender, age, calendar year, ethnicity, SES, facility and duration of monitoring.

^b Doses lagged by 10 years.

^c P value of the trend test for categorical analysis, two-sided.

^d Excess relative risk per sievert.

^e P value of the ERR estimate, two-sided.

^f Relative risk.

^g Coronary heart disease.

^h Central nervous system.

ⁱ Estimate may not be a maximum likelihood estimate; see Methods section.

utory causes. The categorical analysis generally shows irregular patterns with two-sided P values all in excess of 0.11. However, the ERR analysis shows positive and statistically significant trends for all noncancer causes, diseases of the nervous system, diseases of the circulatory system, and deaths from arteriosclerotic heart disease including coronary heart disease (CHD). It appears as though the all noncancer causes and all circulatory diseases associations are driven primarily by the association for CHD.

Our analyses were based on the underlying causes of

death. Inclusion of contributory causes of death did not significantly change the total number of deaths attributed to cancer, because when cancer is present, it is usually recorded as the underlying cause. However, for noncancer outcomes, inclusion of contributory causes increased the total number of deaths by 33% for a total of 1,160 deaths. Analysis of noncancer outcomes including contributory causes in general gave results similar to those shown in Table 5 (results not shown). Again, however, none of the corresponding categorical analyses give statistically significant associations.

DISCUSSION

This is the first analysis of mortality among U.S. nuclear power industry workers. The two primary objectives of the present study were the direct estimation of disease risks in workers employed in the U.S. nuclear power industry and the comparison of these estimates to those derived either by extrapolation from higher-dose studies or from other estimates based on low-dose exposure. The two main hypotheses investigated were those of a positive association between cumulative radiation dose and all leukemias (excluding CLL) and all solid cancers combined.

The overall mortality of the cohort was substantially reduced compared to the U.S. general population. This was not unexpected and is likely due to the healthy worker effect (3). A similar reduction was seen in a parallel Canadian cohort of nuclear workers (2). The possibility of underascertainment of mortality seems most unlikely as all subjects had a Social Security number together with a substantial amount of other identifiers. The National Death Index provides essentially complete coverage of deaths in the U.S., and linkages to the NDI have been shown to have high sensitivity and specificity (5, 6).

Associations with the two main outcomes of interest were both positive, though neither achieved conventional levels of statistical significance with ERRs of 5.67 (95% CI -2.56, 30.4) for leukemia, excluding CLL and 0.51 (95% CI -2.01, 4.64) for all solid cancers combined. There was some evidence of positive associations amongst several of the individual cancers considered, specifically stomach cancer, kidney cancer, and non-Hodgkin's lymphoma, but, given the number of comparisons made, considerable caution must be applied in the interpretation of these findings.

Among noncancer outcomes, these as a whole had a positive and highly statistically significant association, both when analyses were based on the underlying cause of death and also when they included the contributory causes of death. This association appears to be driven primarily by a positive association with arteriosclerotic heart disease including coronary heart disease, with an ERR of 8.78 (95% CI 2.10, 20.0) (underlying causes only). However, for the latter association, the categorical analysis does not provide strong support for a positive monotonic dose response. The appropriate interpretation could be to interpret the categorical analysis as providing the best evidence for the existence of a dose-response relationship, whereas the continuous analysis provides the best evidence regarding the strength of association. These are important criteria of the causality of a statistical association, and the fact that they yield somewhat contradictory results suggests cautious interpretation of these observations.

We did not explore the effects of possible effect-modifying factors such as gender on our estimates of effect due to lack of statistical power. Meaningful interpretations of interaction effects in the data were prevented by the instability of the ERR models.

The strengths of the study include the availability of several sources of dose records (the facilities, and REIRS and REMS systems for the first time) and the fact these doses were estimated with accuracy and precision (13). The cohort was sizable and was followed for up to 18 years. Deaths were ascertained from the NDI, which is known to have a high specificity and sensitivity from other studies with similar amounts of identifying data (5, 6).

The major limitation of the study was the lack of statistical power due to the relatively low doses of radiation involved and the consequent wide CIs. This limitation is inherent in low-dose studies in general. Our power was further limited by a relatively small number of deaths and the young age of the cohort (mean age at end of follow-up was 45 years). In addition, the unavailability of potentially important confounders such as smoking and the fact that SES could be based only on occupational classification also places limits on the interpretation of results. However, there was no strong evidence that diseases such as lung cancer were associated with radiation, which suggests that in this cohort smoking may not have been an important confounder. This is particularly relevant when considering the association with coronary heart disease, for which smoking is also a risk factor.

The highly statistically significant positive ERR for all noncancers combined and, in particular, for arteriosclerotic heart disease including coronary heart disease, was somewhat unexpected. However, the evidence from the corresponding categorical analysis is much less supportive of a positive association, which suggests that the positive ERR could be due to "outliers".

Comparisons between the present results and those from several other studies of whole-body exposure to ionizing radiation are shown in Table 6. The comparative studies include the atomic bomb survivors study, where average doses were much higher than in the present study and which is used as the source for most risk estimates obtained by extrapolation (1). The other studies are those of Canadian nuclear power industry workers (2) and a previously conducted IARC coordinated analysis of nuclear workers from Canada, the UK and the U.S. (12). Subjects in the present study were not included in the previous IARC coordinated analysis, except for a few individuals who may have worked previously at DOE sites.

With respect to leukemia excluding CLL, the ERRs from the present study are very similar to those estimated from the atomic bomb survivors study, are much lower than those estimated from the Canadian study, and are about twice as high as those estimated from the IARC analysis. However, the confidence intervals show that all the studies are statistically compatible with each other; i.e., the apparent difference could well have arisen by chance. A similar pattern is seen for all solid cancers combined, with the present results being very similar to those for the atomic bomb survivors study and lying between the estimates from the Canadian study and the IARC analysis, again with overlap-

TABLE 6
Comparison of ERR Estimates per Sievert between the Present Study, the Atomic Bomb Survivors Study, the Canadian Nuclear Power Industry Workers Study, and the First IARC Combined Analysis of Nuclear Workers

	Leukemia excluding CLL ^a	Solid cancers	Noncancer
U.S. nuclear power industry workers study			
Number of cases (<i>n</i>)	26	368	773 ^b
ERR ^c	5.67	0.51	6.40
90% CI	-1.84, 24.5	-1.70, 3.85	2.86, 11.2
95% CI	-2.56, 30.4	-2.01, 4.64	2.29, 12.2
Canadian nuclear power industry workers study ^d			
Number of cases (<i>n</i>)	18	474	NA ^e
ERR	52.5	2.80	
90% CI	3.97, 225	0.334, 6.32	
95% CI	0.205, 291	-0.038, 7.13	
Atomic bomb survivors (linear model)			
Number of cases (<i>n</i>)	132 ^f	9,335 ^g	31,881 ^g
ERR	4.55	0.29	0.14
90% CI		0.21, 0.39	0.09, 0.19
95% CI	2.83, 7.07		
First IARC combined analysis of nuclear workers ^h			
Number of cases (<i>n</i>)	119	3,976	NA
ERR	2.18	-0.07	
90% CI	0.13, 5.7	-0.39, 0.30	

^a Chronic lymphocytic leukemia.

^b Underlying causes of death only.

^c Excess relative risk per sievert.

^d Zablotska *et al.*, simple time- and age-constant linear ERR model; estimates are equal in males and females (2).

^e Not estimated in the original study.

^f Pierce *et al.*, bone marrow dose; weighted average of more specific risks based on the number of deaths in age categories; males only (20).

^g Preston *et al.*, colon dose; sex-averaged estimate using age at exposure model applied to the average age at exposure in the current cohort (14).

^h Cardis *et al.*, ERR model for the whole population (12).

ping confidence intervals. Finally, the results for all non-cancers combined are much higher than those for the atomic bomb survivors study; neither the Canadian study nor the previous IARC analysis reported noncancer risk estimates. However, it should be noted that the point estimate for coronary heart disease in the atomic bomb survivors study [ERR = 0.17, 95% CI 0.08, 0.26 (14)] lies below the lower bound of the ERR in the present study, and the confidence intervals do not overlap.

Currently, there are no occupational radiation studies which show a convincing association between noncancer mortality and low-dose, low-dose-rate radiation exposures, except for the study of occupationally exposed workers at the Sellafield plant (15). In the follow-up studies of that cohort, however, the association was no longer present (16). Increased risks of cardiovascular diseases were reported in a study of Chernobyl liquidators. However, all findings, except for essential hypertension, were not statistically significant (17). A previous IARC combined analysis of nuclear workers in Canada, the UK and the U.S. (12) produced some evidence for an association with circulatory diseases including heart diseases, and workers in the Canadian National Dose Registry (NDR) experienced a large

but nonsignificant increase in the risks of infectious diseases and endocrine and metabolic diseases (18). The only significant finding was an increase in the risk of circulatory diseases (ERR = 2.3 per Sv, 90% CI 0.9, 3.7). Analysis of incidence in the same cohort did not present results for noncancer incidence (19).

In summary, the results of the present cohort study provide estimates of the ERR for leukemias (excluding CLL) and all solid cancers combined that are very similar to the point estimates found in the atomic bomb survivors study, the study now generally used for setting occupational standards based on extrapolation to low doses. However, the confidence intervals are wide and are consistent with no risk at all or with much higher risks. The strong positive ERR for noncancer outcomes combined, particularly arteriosclerotic heart disease including coronary heart disease, is an unexpected finding that merits further follow-up of the present cohort and examination in other low-dose studies. Continued follow-up of this cohort and the ongoing combined analysis of data from nuclear workers in 15 countries being coordinated by the IARC, to which the present cohort will contribute, will provide a further opportunity and greater power to evaluate the present findings.

APPENDIX TABLE 1
U.S. Nuclear Power Industry Workers Study: Distribution of Workers by Utilities, 1979–1997

Utility	Number of workers	Percentage
Arizona Public Service (APS)	3,275	6.1
Commonwealth Edison (ComEd)	11,037	20.6
Consolidated Edison on New York (ConEd)	1,757	3.3
Detroit Edison (Detroit Ed)	1,346	2.5
Duke Energy Corporation	10,256	19.1
First Energy	3,287	6.1
GPU Nuclear Inc. (GPUN)	3,170	5.9
Florida Power and Light (FP&L)	4,387	8.2
AmerGen Clinton Power Station (Illinova)	1,352	2.5
Southern California Edison (SCE)	4,097	7.6
TU Electric (TXU)	1,361	2.5
Dominion Resources Services, Inc.	4,073	7.6
Wisconsin Electric Power Corporation (WepCo)	1,011	1.9
Wisconsin Public Service Corporation (WPS)	561	1.0
PECO Energy	2,728	5.1

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