

Cancer Mortality through 2005 among a Pooled Cohort of U.S. Nuclear Workers Exposed to External Ionizing Radiation

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Nuclear workers worldwide have been studied for decades to estimate associations between their exposure to ionizing radiation and cancer. The low-level exposure of these workers requires pooling of large cohorts studied over many years to obtain risk estimates with appropriate latency and good precision. We assembled a pooled cohort of 119,195 U.S. nuclear workers at four Department of Energy nuclear weapons facilities (Hanford site, Idaho National Laboratory, Oak Ridge National Laboratory and Savannah River site) and at the Portsmouth Naval Shipyard. The cohort was followed at the start of the workers beginning their radiation work (at earliest, between 1944 and 1952) through 2005, and we compared its mortality to that of the U.S. population. We also conducted regression-modeling analysis to evaluate dose-response associations for external radiation exposure and outcomes: all cancers, smoking- and nonsmoking-related cancers, all lymphatic and hematopoietic cancers, leukemia (excluding chronic lymphocytic), multiple myeloma, cardiovascular disease and others. The mean dose observed among the cohort was 20 mSv. For most outcomes, mortality was below expectation compared to the general population, but mesothelioma and pleura cancers were highly elevated. We found an excess relative risk (ERR) per 10 mSv of 0.14% [95% confidence interval (CI): -0.17%, 0.48%] for all cancers excluding leukemia. Estimates were higher for nonsmoking-related cancers (0.70%, 95% CI: 0.058%, 1.5%) and lower for smoking-related cancers (-0.079%, 95% CI: -0.43%, 0.32%). The ERR per 10 mSv was 1.7% (95% CI: -0.22%, 4.7%) for leukemia, which was similar to the estimate of 1.8% (95% CI: 0.027%, 4.4%) for all lymphatic and hematopoietic cancers. The ERR per 10 mSv for multiple myeloma was 3.9% (95% CI: 0.60%, 9.5%). The ERR per 10 mSv for cardiovascular disease was 0.026% (-0.25%, 0.32%). Little evidence of heterogeneity was seen

by facility, birth cohort or sex for most outcomes. The estimates observed here are similar to those found in previous large pooled nuclear worker studies and also (with the exception of multiple myeloma) to those conducted in the Life Span Study of Japanese atomic bomb survivors. The tendency of observed risks to persist many years after exposure for most outcomes illustrates the importance of continued follow-up of nuclear worker cohorts. © 2015 by Radiation Research Society

INTRODUCTION

Studies of workers exposed to ionizing radiation have provided many insights on the risks of cancer associated with low-dose exposure. While occupational radiation protection standards are based largely on studies of acute exposure, such as the Life Span Study (LSS) of Japanese atomic bomb survivors (1, 2), studies of workers and others exposed to more protracted radiation doses are able to directly assess the effects of low-dose and low-dose-rate exposures. For example, recent meta-analyses of solid cancers (3) and leukemia (4) suggest that risks per unit dose of low, protracted exposures are similar to those found in the LSS (5). While studies of U.S. workers in the nuclear industry have been conducted for several decades (e.g., 6–16), they have been limited by the relatively short follow-up time (e.g., fewer than 25% deceased) and small sizes of some of the cohorts, making it difficult to analyze rare diseases or those with long latency, such as leukemia, solid cancers or lymphomas. Recent publications on updated mortality from pooled national cohorts in France (17, 18) and the United Kingdom (19) have evaluated elevations in risk of certain cancers in these cohorts with extended follow-up. Although U.S. cohorts have been included in pooled analyses previously [e.g., in the 15-country study (20)], no comparable extended follow-up and analysis of a large group of cancers yet exists for a pooled U.S. cohort of nuclear industry workers at facilities with largely external ionizing radiation dose. A recent National Academies review of studies of U.S. nuclear workers (21) recommend-

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ed extension of the follow-up of the pooled U.S. cohorts previously included in the 15-country study and inclusion of additional cohorts with predominantly external exposure.

This article reports on a pooled analysis of five cohorts from the U.S. Department of Energy (DOE) and Department of Defense (DOD), comprised of workers monitored for external ionizing radiation exposure. The cohorts were selected based on either their inclusion in the 15-country study (20) or their predominantly external radiation dose and lack of substantial exposure to high-linear energy transfer radiation. We also required availability of identifiable information on workers and relatively complete external dosimetry information. We updated the mortality experience of the pooled cohort through a common date (2005) and here assess the associations between external ionizing radiation (primarily gamma) and a number of cancer and non-cancer causes of death.

MATERIALS AND METHODS

This study was conducted under the review and approval of the Institutional Review Boards of the National Institute for Occupational Safety and Health and the U.S. Department of Energy.

Cohort Assembly and Follow-Up

The pooled U.S. nuclear worker cohort was assembled from five previously studied cohorts meeting study inclusion criteria. They are: 1. Hanford (8, 13); 2. Idaho National Laboratory (INL) (16); 3. Oak Ridge National Laboratory (ORNL) (9); 4. Portsmouth Naval Shipyard (PNS) (6); and 5. Savannah River Site (SRS) [see ref. (10) and expanded in ref. (14)]. Hanford, INL, ORNL and SRS were managed by DOE, and PNS was managed by DOD. Each cohort consisted of workers who were employed for at least 30 days at one of these facilities and were ever monitored for external ionizing radiation. Workers included in the cohorts were hired between the facility startup date (or at the time work history records became available, for PNS) and the late 1970s (for Hanford, ORNL and PNS) or later (1989 for SRS and 1991 for INL). Work history was combined for cohort members employed at more than one facility to determine the first and last dates of employment at any of the studied facilities. Mortality and cause-of-death ascertainment from previous studies was used and was extended through December 31, 2005, using information from the National Death Index (NDI). The Social Security Death Master File was also used to confirm vital status. Newly identified deaths were coded to the International Causes of Disease (ICD) revision in effect at the time of death. Deaths identified in previous studies of these cohorts were coded in a variety of ways, but in all cases the pertinent ICD revision was available and was used to identify the death category of interest. We also confirmed whether nondecedents were still alive by linking their information to the Internal Revenue Service, which indicated whether a subject was alive in 2007.

The following outcomes, selected to be compatible with planned analyses of the International Nuclear Workers Study (INWORKS), to which the pooled U.S. cohort will contribute,² were examined (Supplementary Table S1; <http://dx.doi.org/10.1667/RR13988.1.S1>): all cancers excluding leukemia (summarized below as "all cancers"), all smoking-related cancers excluding leukemia [as defined in IARC Monograph Volume 100E (22)], all nonsmoking-related cancers, all

"radiogenic" cancers excluding leukemia [cancers determined to have "sufficient" evidence of etiologic association with external radiation, as defined in IARC Monograph 100D (23)], lung cancer, all lymphatic and hematopoietic cancers, lymphoma, multiple myeloma, chronic lymphocytic leukemia (CLL), leukemia excluding CLL, mesothelioma, chronic obstructive pulmonary disease (COPD), cardiovascular disease and cirrhosis of liver. "All cancers" are of interest as a broad cause-of-death category used for radiation protection purposes and less likely than specific cancer causes to suffer from outcome misclassification. Leukemia is of interest because it typically exhibits relatively large excess relative risks (ERRs) after ionizing radiation exposures. CLL's radiogenicity may differ in magnitude from that for acute and myeloid forms of leukemia (as well as exhibit a more protracted induction and latency period). Lymphomas are of interest as a disease of potentially long latency that can be assessed given the updated periods of follow-up. Multiple myeloma was observed to be elevated in the 15-country study (20), in incidence analyses of the UK nuclear worker cohort (19), and among older workers in a nested case-control study conducted at four U.S. DOE facilities [including three studied here, with follow-up through 1986 or 1990 (24)]. Mesothelioma was analyzed to evaluate potential confounding of the radiation-lung cancer association by exposure to asbestos. We analyzed cirrhosis as an indirect indicator of confounding by alcohol consumption. To examine potential confounding by smoking, we separated the "all cancers" group into two groups (smoking-related as defined above and nonsmoking-related), analyzed nonsmoking-related radiogenic cancers (i.e., cancers of bone, skin, breast, brain and central nervous system and thyroid), and evaluated COPD.

Radiation Dosimetry

For this study, doses from the studied facilities, as well as other DOE sites and nuclear power facilities where participants were employed before or after the studied facilities, were incorporated into the analyses. Ionizing radiation dosimetry data were obtained from exposure databases compiled for previous studies by investigators from the National Institute for Occupational Safety and Health (NIOSH) and elsewhere, supplemented by linkage of the cohort to two external databases assembled by the U.S. DOE (the Radiation Exposure Monitoring System database) and the U.S. Nuclear Regulatory Commission (the Radiation Exposure Information Reporting System database) (25). Potentially overlapping doses among all data sources were resolved by manual review, with preference given to individual facility records over national databases. In this study, "dose" refers to measurements of whole-body penetrating radiation and tritium assimilation, expressed in mSv, abstracted from available dosimetry records. Recorded doses included adjustments for the relative biological effectiveness of the incident radiation (e.g., average quality factor of 10 for fast neutrons). Under most exposure conditions, these recorded doses reasonably approximate the whole-body equivalent dose from gamma, X rays, tritium assimilation and neutrons, however, some overestimation of absorbed dose to deep tissue or organs (as used in some previous studies) is likely from attenuation, and the varied use of adjusting factors adds to the uncertainty in dose estimates. Cumulative dose values were calculated by summing annual values from age at first exposure to attained age minus any exposure lag period. The dose from internally deposited radionuclides (other than tritium) was not quantified, however, workers who had records of committed dose or who had bioassay data indicating a positive uptake of radionuclides were flagged as potentially internally exposed. The number of persons flagged was used to qualitatively assess the potential influence on risk estimates from not including dose from internal emitters.

Statistical Analysis

Standardized mortality ratio (SMR) analyses comparing the cohort's mortality to that of the U.S. population were conducted

² Hamra GB, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan J, et al. Cohort profile: the International Nuclear Workers Study (INWORKS). (Unpublished data)

using the NIOSH Life Table Analysis System for Windows, LTAS.net (26). Person-time at risk began at the latest of: 1. thirty days after the worker's date of first employment at one of the studied facilities; 2. the worker's date of first monitoring for external radiation exposure; and 3. for PNS workers, the start date of available work history records (January 1, 1952). Person-time ended at the earliest of: 1. the worker's date of death; 2. December 31, 2005 (for workers last observed alive on or after January 1, 1979, the date the NDI began); and 3. the last employment date (for workers last observed alive before January 1, 1979). Comparison rates were based on the U.S. population, which were available from January 1, 1940 through December 31, 2005. SMRs were indirectly standardized based on sex, race (white, all other races) and age and calendar period (in five-year intervals). Cause-of-death categories were as described elsewhere (27). For each outcome, SMR analyses were stratified by duration of employment (0–<5, 5–<15, 15–<25 and ≥25 years) and into periods of active and inactive employment. We lagged inactive employment by one year, so that deaths occurring within a year of leaving employment would be accrued to the active category, thus accounting for health-related departure from the workforce. We evaluated the inactive employment follow-up period to emphasize patterns in SMRs by duration, while controlling to some degree for the healthy worker survivor bias (HWSB) (28).

Cox regression analyses were conducted to evaluate the association of radiation with cause-specific mortality, by creating risk sets for each outcome of interest, matched on attained age. Thus, a potential risk set member was required to have been under observation and alive at the age of death of the case. We selected 200 risk set members at random per case for each outcome (29).

The dose metric used in all modeling analyses was total equivalent external (gamma rays and neutrons) and tritium dose. A 10-year dose lag was used for all cancers, all lymphatic and hematopoietic cancers, lymphoma, and non-cancer outcomes. A 7-year lag was used for leukemia excluding CLL, and a 20-year lag was used for CLL, based on previous pooled studies of leukemia in U.S. nuclear workers (11, 12, 16, 25).

A linear ERR model was preferred, given its frequent use in previous studies (1). The general model form is $\lambda[t, Z, d(t)] = \lambda_0(t)[1 + \beta d(t)] \exp(\sum_{i=1}^P \alpha_i Z_i)$, where λ is the death rate, $\lambda_0(t)$ is the baseline death rate for attained age t , $d(t)$ is the time-dependent cumulative dose, the Z_i represents the i th covariate of a list of $i = 1$ to P covariates and regression parameters to be estimated are indicated by α , and β . We also evaluated a log-log (power) dose-response model because risk attenuation at high-dose exposure is often seen in occupational cancer studies (12, 25, 30, 31). The dose function of the log-log model follows the form $[d(t) + k]^\beta = \beta * \ln [d(t) + k]$ [where $d(t)$ and β are defined as before and k represents a small value added to each person's cumulative dose to avoid taking the log of zero]. We express risk as ERR percentage per 10 mSv, to emphasize the dose range most relevant for the cohort while easing comparison to results from high-dose studies (generally expressed as ERR/Sv). Fit was compared for each dose-response model form, using the Akaike Information Criterion (AIC) value. An AIC value within 2 units was considered equivalent. Visual inspection of the dose-response shape was realized by overlay plots of both models and a model using restricted cubic splines with three knots at the 10th, 50th and 90th percentile of the exposure distribution among risk sets. Model estimates included likelihood-based, two-sided 95% confidence intervals. In linear models, confidence interval estimates were not calculable when the estimate was on the boundary of the parameter space.

Covariates included in each analysis were sex, race, birth cohort (modeled using restricted cubic splines) (32), socioeconomic status based generally on first job type (professional and technical, skilled nonmanual, skilled manual, unskilled or partly skilled, missing), employment facility (first employment was used for workers employed at more than one facility) and employment duration (based on restricted cubic splines) as a means of controlling for the HWSB.

Knots for all restricted cubic spline models were placed at the 10th, 50th, and 90th percentiles of the distribution.

We evaluated the interaction between attained age and dose for each outcome, as a test of the proportional hazards assumption. We evaluated temporal variation in risk after the exposure, both to assess our choice of dose lag value and to determine the likely value of additional follow-up in the pooled U.S. cohort. We therefore evaluated radiation dose effect modification using dose in time windows of 10–<20, 20–<30 and ≥30 years (before the occurrence of the death) for all outcomes except leukemia. We used 7–<10, 10–<20, 20–<30 and ≥30 year windows for leukemia excluding CLL and we used 20–<30, 30–<40 and ≥40 for CLL. The linear ERR dose-response form was preferred for these temporal analyses.

In sensitivity analyses, we evaluated heterogeneity in associations between dose and each outcome of interest by employment facility, and by strata defined by birth cohort (in 3 groups defined as <1915, 1915–<25 and 1925+). For all cancers, radiogenic cancers, lung cancer and all lymphatic and hematopoietic cancers we also evaluated effect modification by sex. Subgroup-specific estimates are reported only when significant heterogeneity or effect modification was observed ($P < 0.05$). We also evaluated the impact of excluding neutrons and tritium from the total dose, for all-cancers and all lymphatic and hematopoietic cancers. We evaluated the effect of using a 2-year lag for non-CLL leukemia. We evaluated the effect of using just a single cutpoint for duration of employment (at 1 year) rather than splines, to determine if the fine spline adjustment for employment duration reduced the magnitude of the dose-response relationship due to the correlation between employment duration and radiation dose. Lastly, we tested the sensitivity for two outcomes (all cancers and all leukemia excluding CLL) of choice of regression model (matching only on age and adjusting for main effects of other confounders compared to background stratification by matching on most confounders, including age, sex, race, birth year within 2.5 years and facility). The latter approach may be preferred, because it allows for all interaction forms to be implicitly controlled, among the matched variables. All sensitivity analyses were based on the linear ERR model.

RESULTS

Information about the cohorts is summarized in Table 1 and Fig. 1. Approximately 5% were employed at more than one facility, with the greatest overlap among the DOE sites. The mean cumulative dose for the pooled U.S. nuclear worker cohort was 20.2 mSv (median 1.8 mSv; interquartile range: 0.12–12.6 mSv) and was highly right-skewed. The vast majority of external dose arose from photon exposure. Across the pooled cohort, 1.9% had a confirmed internal radionuclide deposition. Nineteen percent of the cohort received a dose at more than one facility (including other DOE sites and nuclear power plant facilities). We found that 1.1% of the cohort members were lost to follow-up and that cause of death was unavailable for 1.1% of decedents. We observed 41,508 deaths among 4,019,065 person-years in the pooled U.S. nuclear worker cohort.

Standardized Mortality Ratio Analysis

We observed 11,332 cancer deaths in the cohort (Table 1 and Supplementary Table S2; <http://dx.doi.org/10.1667/RR13988.1.S1>). The SMRs for all causes and all cancers were far lower for follow-up associated with active employment periods (including within one year of leaving

TABLE 1
Pooled U.S. Cohort Characteristics

Attribute	Portsmouth Naval Shipyard	Hanford site	Oak Ridge National Laboratory	Savannah River site	Idaho National Laboratory	Total cohort
Period of employment eligibility	1952-1977	1944-1978	1944-1978	1952-1989	1949-1991	-
Cohort size ^a	9,625	34,278	18,830	22,485	33,978	119,196
Percent male	99.6%	74.7%	75.5%	80.6%	83.4%	80.4%
Median duration employed (years)	23.8	6.2	4.0	10.4	7.5	8.0
Median year of birth	1926	1928	1930	1937	1942	1934
Last previous year of follow-up for all-cancer dose-response analyses (reference)	1996 (45)	1994 (13)	1984 (9)	2002 (14)	1999 (16)	-
Socioeconomic status ^b						
Professional and technical	1,423 (15%)	13,899 (41%)	9,520 (51%)	7,079 (31%)	13,165 (39%)	45,086 (38%)
Skilled nonmanual	44 (0%)	7,098 (21%)	3,710 (20%)	2,882 (13%)	4,281 (13%)	18,015 (15%)
Skilled manual	7,145 (74%)	11,630 (34%)	2,417 (13%)	10,099 (45%)	7,015 (21%)	38,306 (32%)
Partly skilled and unskilled	960 (10%)	1,650 (5%)	2,753 (15%)	2,389 (11%)	5,064 (15%)	12,816 (11%)
Missing	53 (1%)	1 (0%)	430 (2%)	36 (0%)	4,453 (13%)	4,973 (4%)
Number with internal radionuclide deposition	0	476 (1.4%)	572 (3.0%)	871 (3.9%)	367 (1.1%)	2286 (1.9%)
Mean dose (median), mSv						
Gamma	24.6 (3.6)	25.7 (3.4)	13.7 (0.9)	21.8 (2.5)	15.8 (0.7)	20.2 (1.9)
Neutron	0.0 (0)	0.7 (0)	0.4 (0)	1.5 (0)	0.2 (0)	0.6 (0)
Tritium	0.0 (0)	0.1 (0)	0.1 (0)	1.0 (0)	0.0 (0)	0.2 (0)
Number of person-years of follow-up	303,290	1,269,928	717,789	752,989	975,069	4,019,065
Average length of follow-up (years)	31.5	37.0	38.1	33.5	28.7	33.7
Number of all-cause deaths (percentage deceased)	4,973 (52%)	15,296 (41%)	7,079 (38%)	6,275 (28%)	7,885 (23%)	41,508 (35%)
Number of cancer deaths	1,499	3,971	1,916	1,772	2,174	11,332
Standardized mortality ratio for cancer (95% CI)	1.09 (1.04, 1.15)	0.86 (0.84, 0.89)	0.78 (0.74, 0.81)	0.85 (0.81, 0.89)	0.78 (0.74, 0.81)	0.85 (0.84, 0.87)

Note. CI = confidence interval.

^a Workers employed at multiple facilities were assigned to the facility of first employment.

^b Based on longest (Hanford) or first (all other sites) job title.

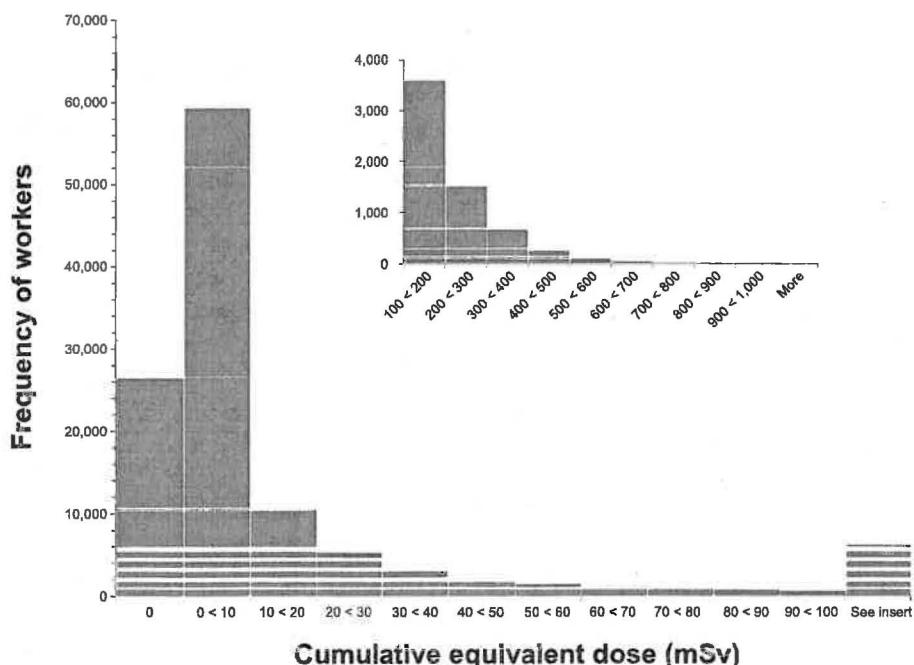


FIG. 1. External cumulative dose distribution in the pooled U.S. cohort.

TABLE 2
Standardized Mortality Ratios and 95% Confidence Intervals by Duration of Employment
for Causes of Death of Interest, During Inactive Employment Periods^a

Disease grouping of interest	Deaths (n)	Standardized mortality ratios (95% confidence interval)				Overall
		0-<5 years	5-<15 years	15-<25 years	≥25 years	
Cohort person-years	—	1,526,070	629,057	249,285	260,369	2,664,782
All cause	37,852	0.83 (0.82, 0.85)	0.86 (0.84, 0.89)	0.92 (0.90, 0.95)	0.84 (0.82, 0.85)	0.85 (0.84, 0.86)
All cancer excluding leukemia	9,979	0.86 (0.83, 0.89)	0.88 (0.85, 0.92)	0.95 (0.90, 1.00)	0.92 (0.89, 0.96)	0.89 (0.87, 0.91)
All nonsmoking-related cancers ^b	2,855	0.94 (0.88, 1.00)	1.08 (1.00, 1.17)	1.04 (0.94, 1.14)	1.09 (1.01, 1.17)	1.02 (0.98, 1.04)
All smoking-related cancers excluding leukemia ^c	6,388	0.83 (0.80, 0.86)	0.81 (0.77, 0.86)	0.90 (0.85, 0.96)	0.86 (0.82, 0.90)	0.84 (0.82, 0.86)
Lung cancer	3,228	0.81 (0.77, 0.86)	0.81 (0.75, 0.88)	0.93 (0.85, 1.02)	0.87 (0.81, 0.93)	0.84 (0.81, 0.87)
All radiogenic cancers excluding leukemia ^d	6,091	0.85 (0.82, 0.89)	0.85 (0.80, 0.90)	0.93 (0.87, 0.99)	0.89 (0.84, 0.93)	0.87 (0.85, 0.89)
Radiogenic nonsmoking-related solid cancers	824	0.94 (0.85, 1.04)	1.04 (0.90, 1.19)	0.99 (0.81, 1.21)	0.99 (0.92, 1.06)	0.99 (0.92, 1.06)
All lymphatic and hematopoietic cancers	1,070	0.91 (0.82, 1.00)	1.03 (0.90, 1.17)	0.99 (0.84, 1.16)	1.02 (0.90, 1.16)	0.97 (0.92, 1.03)
Lymphoma	488	0.98 (0.85, 1.13)	1.10 (0.91, 1.32)	1.10 (0.86, 1.39)	0.98 (0.80, 1.19)	1.02 (0.93, 1.12)
Multiple myeloma	172	0.85 (0.66, 1.07)	0.75 (0.51, 1.06)	0.83 (0.53, 1.23)	1.06 (0.79, 1.40)	0.86 (0.74, 0.99)
Leukemia	410	0.85 (0.72, 1.00)	1.08 (0.88, 1.32)	0.96 (0.73, 1.23)	1.06 (0.86, 1.28)	0.96 (0.87, 1.06)
Mesothelioma and pleural cancer	96	1.63 (1.01, 2.51)	2.95 (1.83, 4.55)	3.23 (1.81, 5.41)	4.03 (2.87, 5.53)	2.80 (2.27, 3.42)
Chronic obstructive pulmonary disease	1,883	0.88 (0.82, 0.95)	0.89 (0.81, 0.99)	1.10 (0.99, 1.21)	0.71 (0.65, 0.79)	0.87 (0.83, 0.91)
Cardiovascular disease	12,178	0.77 (0.75, 0.79)	0.79 (0.76, 0.82)	0.84 (0.81, 0.88)	0.78 (0.75, 0.81)	0.79 (0.78, 0.80)
Cirrhosis of liver ^e	535	0.61 (0.53, 0.69)	0.73 (0.61, 0.86)	0.93 (0.75, 1.15)	0.82 (0.66, 1.01)	0.71 (0.65, 0.77)

^a Beginning one year after leaving employment.

^b Excludes 10 cases of endocrine cancer (other than thyroid) and cancer of "other specified sites", part of the original grouping.

^c Includes small intestine and anus, not part of the original grouping.

^d Includes gum and mouth and small intestine, not part of the original grouping.

^e Includes chronic hepatitis and other nonalcoholic chronic liver disease, not part of the original grouping.

employment) than for inactive periods (Supplementary Table S3; <http://dx.doi.org/10.1667/RR13988.1.S1>). The SMR results below refer just to follow-up that occurred more than a year after leaving employment. For all cancers combined (excluding leukemia), a deficit in deaths was observed, compared to the general U.S. population (Table 2). This deficit was greatest among the short-term workers, and the SMR tended to increase with duration of employment. A similar pattern was observed for all smoking-related cancers and for lung cancer. For nonsmoking-related cancers, a slight deficit was observed in the shortest duration group, with slight excesses for longer-term workers. Standardized mortality ratios for all lymphatic and hematopoietic cancers and for lymphoma were generally near expectation, and did not vary substantially by employment duration. For leukemias, the SMR was lowest for the shortest employment duration category, and was near expectation for the higher duration categories. For multiple myeloma, the SMR was below expectation across the shortest three duration categories and higher for the longest duration group.

Pleural cancer combined with mesothelioma was substantially elevated in the pooled cohort, with a near threefold overall elevation compared to the general population. SMRs increased monotonically with employ-

ment duration, to a fourfold elevation among those working for 25 years or greater. Most of the increase in the SMRs for this outcome was related to the PNS cohort (Supplementary Table S4; <http://dx.doi.org/10.1667/RR13988.1.S1>), which exhibited an eightfold elevation in risk; the pooled DOE cohorts had a doubled rate compared to the general U.S. population. Among the non-cancer outcomes, COPD showed SMRs below unity for most employment duration categories (Table 2). For cardiovascular disease and liver cirrhosis, SMRs were substantially below unity for each duration category.

Regression-Modeling Analysis

For most outcomes, a power model and linear ERR model fit equally well (Supplementary Table S5; <http://dx.doi.org/10.1667/RR13988.1.S1>). The dose-response curves are shown (in comparison to the restricted cubic spline model) for all cancers, all smoking-related cancers, all nonsmoking-related cancers and leukemia excluding CLL (Fig. 2). The linear ERR model fit best for the lymphatic and hematopoietic cancers, except CLL. For cardiovascular disease, the power model fit best (Supplementary Table S5). However, the dose-response curves show that a linear ERR model fits best in the dose region (<500 mSv) of greatest interest and

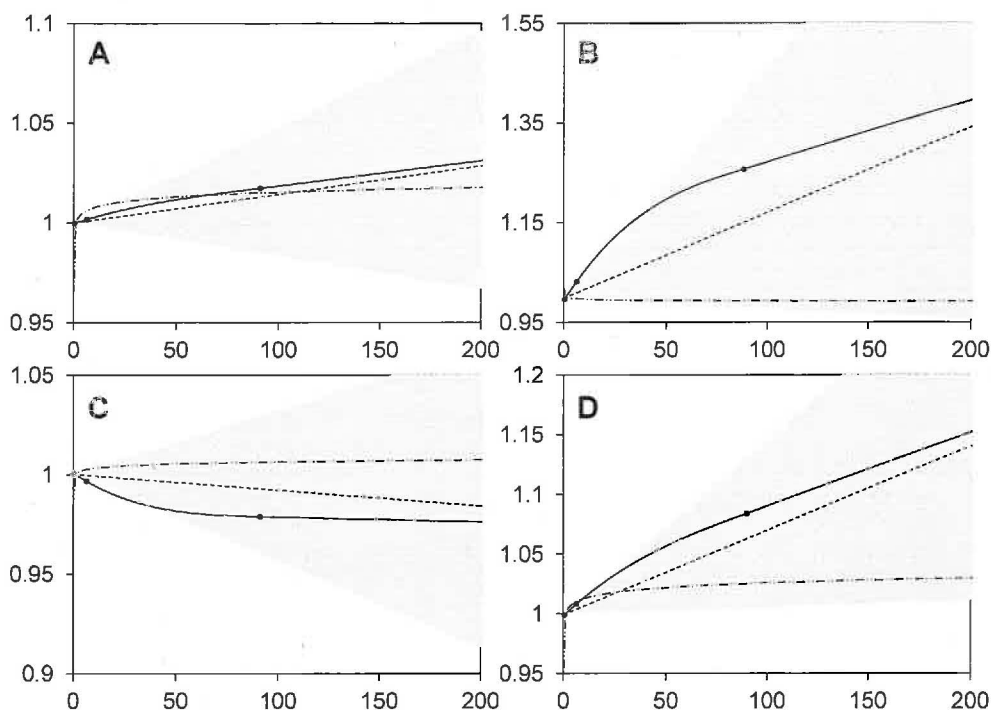


FIG. 2. Dose-response curves for: all cancers excluding leukemia (panel A); leukemia excluding chronic lymphocytic (panel B); all smoking-related cancers (panel C); and all nonsmoking-related cancers (panel D). Solid line indicates restricted cubic spline with knots indicated by black dots, dashed line indicates linear excess relative risk (ERR) model, and stippled line indicates log-log (power) model. The confidence interval is shown for the linear ERR model. Ordinate scale is rate ratio, and abscissa scale is dose in mSv. A value of 1 mSv was used as the baseline for all dose-response comparisons.

is represented by the majority of the data (Supplementary Fig. S1; <http://dx.doi.org/10.1667/RR13988.1.S1>). Therefore, descriptions below emphasize the linear ERR model for all outcomes.

The ERR per 10 mSv was 0.14% (95% CI: -0.17%, 0.48%) for all cancers combined, with 10,877 observed deaths, and was 0.70% (95% CI: 0.058%, 1.5%) for nonsmoking related cancers, with 3,140 deaths. The estimate was negative, but with wide confidence intervals, for all smoking-related cancers excluding leukemia. ERR estimates were slightly positive for all radiogenic cancers excluding leukemia and for lung cancer. For nonsmoking-related radiogenic cancers, the ERR per 10 mSv was 0.40% (95% CI: -0.70%, 2.0%). For mesothelioma and pleura cancers combined, the ERR per 10 mSv was positive, but with very wide confidence intervals (Table 3). The ERR per 10 mSv for all lymphatic and hematopoietic cancers was 2.0% (95% CI: 0.71%, 3.5%). ERR per 10 mSv estimates for lymphoma and for leukemia excluding CLL were similar, at 1.7 and 1.8, respectively. The ERR estimate for CLL, in contrast, was negative (Table 3). For non-cancer outcomes (Table 3), cirrhosis of the liver showed an ERR per 10 mSv similar to that for all cancers. The estimates for cardiovascular disease and COPD were close to zero, with wide confidence intervals. No evidence of a dose-attained age interaction was observed for all outcomes except

nonsmoking-related cancers (Table 3). For that group, ERR per 10 mSv estimates increased with age (Supplementary Fig. S2; <http://dx.doi.org/10.1667/RR13988.1.S1>).

All models adjusted for the same set of covariates, as noted in Table 3. In the main dose-response models, we observed that, for outcomes strongly related to smoking, alcohol consumption or occupational exposure to asbestos, covariates with significant main effects tended to include birth cohort, employment duration, SES and facility. For other outcomes (lymphatic and hematopoietic cancers as well as nonsmoking-related cancers), most of these covariates were not important risk predictors (Supplementary Table S6; <http://dx.doi.org/10.1667/RR13988.1.S1>).

Evaluating risk within time windows of exposure (Table 4) gave ERR per 10 mSv estimates that did not exhibit statistically significant heterogeneity, except for multiple myeloma, for which risks were highest 10–20 years after exposure and declined thereafter. For other outcomes, risks tended to persist with long periods of follow-up.

In sensitivity analyses, no significant effect modification by sex was observed for any outcome (P values ranged from 0.39–0.97). Heterogeneity in risk by facility was observed only for lung cancer ($P = 0.0022$) and for COPD ($P = 0.0011$). The ERR per 10 mSv estimates for lung cancer and COPD, respectively, were 1.1 and 3.8% at ORNL, 0.28 and 0.56% at Hanford, -1.3% and -1.0% at INL, 1.6 and

TABLE 3
Results of Dose-Response Analyses for Health Outcomes of Interest, Based on Total (Gamma, Neutron, Tritium) Dose, in a Linear Excess Relative Risk Model^a

Outcome	Deaths (n)	ERR % per 10 mSv (95% CI) ^b	Age ^c dose interaction (<i>P</i> value)
All cancers excluding leukemia	10,877	0.14 (-0.17, 0.48)	0.161
All nonsmoking related cancers ^d	3,140	0.70 (0.058, 1.5)	0.011
All smoking-related cancers excluding leukemia ^d	6,950	-0.079 (-0.43, 0.32)	0.520
Lung cancer	3,514	0.069 (-0.43, 0.66)	0.839
All "radiogenic" cancers excluding leukemia	6,596	0.086 (-0.30, 0.52)	0.724
Radiogenic nonsmoking-related cancers (bone, skin, breast, brain and CNS, thyroid)	925	0.40 (-0.70, 2.0)	0.295
All lymphatic and hematopoietic cancers	1,194	2.0 (0.71, 3.5)	0.452
Lymphoma	551	1.8 (0.027, 4.4)	0.442
Multiple myeloma	188	3.9 (0.60, 9.6)	0.226
Chronic lymphocytic leukemia (CLL)	128 ^e	-0.30 (-2.0, 3.6)	0.391
Leukemia excluding CLL	369	1.7 (-0.22, 4.7)	0.948
Mesothelioma and pleural cancer	99	2.5 (-1.3, 10)	0.427
Chronic obstructive pulmonary disease	1921	-0.0054 (-0.63, 0.78)	0.417
Cardiovascular disease	13,514	0.026 (-0.25, 0.32)	0.231
Cirrhosis of liver	498	0.16 (-1.3, 2.4)	0.169

Note. CI = confidence interval; CNS = central nervous system.

^a All models adjust for sex, race, birth cohort (in splines), employment duration (in splines), socioeconomic status, and facility of first employment. Dose lagged for 10 years for all outcomes except leukemia excluding CLL (lagged 7 years) and CLL (lagged 20 years).

^b Excess relative risk (ERR) is defined as the hazard ratio calculated at 10 mSv minus 1.

^c Excludes cancers of indeterminate site.

^d Includes nonunderlying cause.

-2.1% at PNS and 0.43% and -1.6% at SRS. For lymphoma and for mesothelioma and pleura cancer combined, a significant interaction was observed with birth cohort. For lymphoma, the ERR per 10 mSv showed a pattern of increasing magnitude across birth cohorts. For mesothelioma and pleura cancer, the highest dose-related risk was seen in the early and later birth cohorts. No

significant heterogeneity by facility or birth cohort was observed for other outcomes (*P* values ranged from 0.060-0.97).

The ERR per 10 mSv estimates were 0.18% (95% CI: -0.14%, 0.53%) and 2.0% (95% CI: 0.73%, 3.7%), respectively, for the all-cancer and lymphatic and hematopoietic cancer models when excluding neutron and tritium

TABLE 4
Results of Dose-Response Analyses Across Exposure Time Windows, Based On Total (Gamma, Neutron, Tritium) Dose, for Outcomes of Interest other than Leukemia and Leukemias

Outcome	Minimum no. exposed cases ^a	<i>P</i> (heterogeneity)	Excess relative risk (ERR) % per 10 mSv (95% confidence interval) by dose time windows ^b				
			7-<10 years	10-<20 years	20-<30 years	≥30 years	≥40 years
All cancers excluding leukemia	3,918	0.903					
All nonsmoking related	1,049	0.202					
All smoking-related	2,612	0.519					
All "radiogenic" cancers excluding leukemia	2,462	0.451					
Radiogenic nonsmoking-related cancers (bone, skin, breast, brain and CNS, and thyroid)	309	0.426					
Lymphoma	193	0.664					
Multiple myeloma	64	0.047					
Cardiovascular disease	5,092	0.261					
Chronic lymphocytic leukemia (CLL)	40	0.481					
Leukemia excluding CLL	81	0.978	4.7 (-1.3, 38)	2.8 (NC, 13)	0.82 (NC, 7.7)	1.9 (-1.3, 6.9)	4.6 (NC, 22)

^a Minimum number of cases with positive dose in each time window category.

^b Based on linear ERR dose-response model.

^c NC: not calculable.

dose. The model fit slightly more poorly (AIC of 3,921.5 vs. 3,921.1) and the ERR per 10 mSv was 1.6% (95% CI: -0.29%, 4.4%) when lagging by 2 years instead of 7. We also evaluated the potential attenuation of the radiation dose-response relationship by the fine (spline) adjustment for duration of employment, by replacing the spline with a covariate for just a single cutpoint at 1 year of employment. The only outcome that exhibited an increase in the ERR per 10 mSv with this adjustment was leukemia excluding CLL, which showed a relative increase of less than 10%. The ERR estimates for the other lymphatic and hematopoietic outcome categories decreased by 20–67%. The estimate for all radiogenic nonsmoking-related cancers did not change. For the smoking- and alcohol-related outcomes, the ERR per 10 mSv decreased twofold or more. The estimate for mesothelioma and pleura cancer decreased by less than 10%.

In a model that matched on most covariates (age, race, sex, birth year within 2.5 years and facility), the estimate for all lymphatic and hematopoietic cancers was unchanged, at 2.0% per 10 mSv (95% CI: 0.72%, 3.5%), and that for all cancers excluding leukemia changed very little, at 0.11% per 10 mSv (95% CI: -0.19%, 0.45%).

DISCUSSION

Cancer risks from low and protracted doses of ionizing radiation have been the subject of intense interest for a number of years (1). Workers at the U.S. DOE complex were among the earliest worldwide to be exposed in large numbers to monitored external radiation. With over 100,000 workers who have been followed for mortality for up to 60 years, this pooled cohort is potentially highly informative on the risks for a broad group of cancers that may be associated with ionizing radiation exposure. With follow-up through 2005, the percentage of deceased individuals varied substantially by facility, from 23% at the facility with most recent enrollment (INL) to 52% for that with the earliest enrollment (PNS), and represents a substantial increase over most previous studies of these cohorts for outcomes other than leukemia (25). The low percentage of loss-to-follow-up and high percentage of death certificate availability indicate that follow-up mechanisms were adequate for the pooled cohort.

In this study, we observed positive (though imprecise) associations between occupational exposure to ionizing radiation and risk of a number of cancers. The 95% confidence interval excluded the null only for the group of nonsmoking-related cancers, for lymphatic and hematopoietic cancers combined, for lymphoma and for multiple myeloma. The ERR per 10 mSv tended to be smallest for the all-cancer group (at 0.14%), particularly for smoking-related cancers (which had a negative estimate), and largest for multiple myeloma (at 3.9%). The estimates were quite similar for individual cancers within the group of lymphatic and hematopoietic cancers, with the exception of CLL,

which showed little evidence of dose-related increases in risk, consistent with some studies of leukemia in pooled nuclear worker cohorts (e.g., 12, 33), but not in others (34). For the group of nonsmoking-related cancers, the ERR per 10 mSv estimate was intermediate at 0.70% and was statistically significant.

With more than three times the number of cancer deaths for the same cohorts included in the 15-country pooled international study, the estimates of risk in the current study demonstrate substantially improved precision over estimates from the much earlier follow-up in that study (20, 35). The estimate and upper 95% confidence limit for all cancers is lower than that found in the 15-country study (0.97% per 10 mSv). However, the current estimate is substantially larger than the negative estimate that was observed among all U.S. cohorts participating in that study (ORNL, INL and Hanford, as well as U.S. nuclear power plant workers). The estimate for all nonsmoking-related cancers is, however, quite similar to the all-cancer estimate in the 15-country study. The leukemia (excluding CLL) ERR per 10 mSv estimate we observed in our study (1.7%) was very similar to that found in the 15-country study overall (1.9%) and was based on a much larger number of cases (369 vs. 196). Our estimate is larger than that observed in the U.S. cohorts included in that study (1.2%) and is twice as high as the estimate observed by Daniels *et al.* (25) in a pooled study based on the same cohorts and follow-up period but excluding Hanford and ORNL workers hired before 1951 and SRS workers hired after 1974. Our estimate is also very similar to the value of 0.19 at 100 mGy derived from a recent meta-analysis of risk of leukemia from protracted, low-dose exposure to ionizing radiation (4) and to the expected ERR at 10 mSv of 1.4% (95% CI: 0.1–3.4%) from the Japanese LSS study, for males exposed as adults (20). It is also similar to the value observed in a recent follow-up of the UK National Registry of Radiation Workers (NRRW).

The risk estimate we found for lymphoma (1.8% per 10 mSv) is higher than, but statistically compatible with, the estimate of 0.46 per Gy found for non-Hodgkin lymphoma among men in the most recent follow-up of the LSS (36). It is, however, very similar to the 1.12 per Gy observed among men who were of working age at exposure (37). Elevations in lymphoma risk (some significant and some not) were observed in many other radiation-exposed populations, including SRS workers, the NRRW cohort, Chernobyl liquidators and several medically exposed populations [summarized in ref. (23)]. The ERR per 10 mSv estimate observed for multiple myeloma in this pooled study (3.9%/10 mSv) is substantially higher than that observed in the LSS (36). However, our estimate is very similar to that found in the 15-country study, and for incident cases among the UK NRRW cohort (3.6%/10 mSv) (19), although the UK mortality estimates were considerably lower. Our multiple myeloma ERR estimates were consistent across facilities and appear to indicate a period of highest risk between 10 and 20 years after exposure, which previous

studies of these and other U.S. nuclear worker cohorts (16, 24) may have had insufficient follow-up to detect. Our results, taken together with other recent studies, add substantially to the evidence base for the radiogenicity of both lymphoma and multiple myeloma, which were previously deemed to have "limited" evidence in the recent re-evaluation of the carcinogenicity of ionizing radiation by the International Agency for Research on Cancer (23). The dose-response curves and AIC values indicate that both the power model and the linear ERR model fit equally well for most outcomes except all nonsmoking-related cancers and lymphatic and hematopoietic cancers, for which a linear ERR model fit substantially better. This finding suggests that no substantive attenuation of risk is seen at higher exposure levels, in contrast to some previous leukemia studies among U.S. nuclear workers (11, 25).

We observed little evidence of heterogeneity by facility, birth cohort or sex in risk estimates for all cancers or leukemia. The heterogeneity in time since exposure was not statistically significant for these outcomes, and the patterns we observed suggest that excess risk remains decades after exposure for both outcomes. Furthermore, we observed a significant interaction of attained age and dose for nonsmoking-related cancers, in which the ERR per 10 mSv was negative at younger ages and became positive at older ages (Supplementary Fig. S2; <http://dx.doi.org/10.1667/RR13988.1.S1>). This is consistent with the observation that risks tended to be highest for this outcome with lengthy time since exposure (Table 4). We plan to explore this finding in greater detail in future studies. Continued follow-up of this pooled cohort is therefore important, particularly for cancers other than leukemia, because examination of the person-year distribution shows that 41% of the person-time at risk occurred among living subjects who were within 20 years of last employment, before the peak in radiation-associated risk we observed here. Continued study of the French and UK nuclear worker cohorts demonstrates the importance of extending follow-up of young cohorts, as the radiation-related risk of cancer has increased with longer follow-up (17–19).

Despite the large cohort size and lengthy follow-up, studies of U.S. nuclear workers are subject to some key limitations. These include the low average doses received in the cohorts (20 mSv), dose measurement error, the potential for positive or negative confounding by cigarette smoking or exposure to other carcinogenic agents and (perhaps most importantly) the existence of a very strong healthy worker bias (HWB) and HWSB.

Dose measurement error is a limitation of all radiation epidemiology studies. Accounting for some uncertainties in the measured photon dose at ORNL was found to have only slight effects on the estimates of risk and their precision (38). PNS dosimetry data were not available beyond 1996. Because a minimum lag of 10 years was used for all cancers other than leukemia, and follow-up was conducted through

2005, this limitation should only affect leukemia, for which a minimum lag of 7 years was used. The impact on the leukemia findings should be minimal since most workers had left employment by the mid-1990s.

The mean absorbed tissue or organ dose is the preferred dosimetric quantity in most situations (39). Workers in the cohort were primarily exposed to external whole-body penetrating gamma rays. As such, dose values from personal dosimetry records reasonably approximate organ-absorbed dose, although attenuation of 30–50% occurs in deep tissues (e.g., red bone marrow). This could lead to dose overestimation for some outcomes (e.g., leukemia) and underestimates of risk per unit dose compared to other studies based on organ dose (e.g., 15-country study or LSS). Assumptions on relative biological effectiveness that have been incorporated in external dose estimates increase the uncertainty in doses for persons exposed to neutrons. Historically, estimates of neutron dose have been less reliable than for photon exposures. Although an effect on the dose response from poorly measured neutrons or the inclusion of mixed radiation fields cannot be ruled out, it is likely to be small given that neutron exposures contributed less than 2% to the average equivalent dose among all workers. We also did not account in this study for internal deposition of radionuclides, but this seems unlikely to have been a major influence, since only 1.8% of the cohort had a confirmed radionuclide deposition. Tritium contributed a small amount (<5%) to the total dose, and was most substantial at the SRS and ORNL facilities, particularly among workers who had positive gamma dose. Its inclusion or exclusion made little difference in the risk estimates for the evaluated outcomes.

The presence of a strong HWB and HWSB has been noted in the 15-country study (20) and in other nuclear worker cohorts [e.g., ref. (19)]. Methods for adjusting for these sources of bias include restricting follow-up to periods of inactive employment [e.g., ref. (28)] or stratifying on duration of employment in broad categories (15, 16, 20, 35). In the current study, we observed that restricting SMR analyses to periods of inactive employment (i.e., more than one year after leaving employment) resulted in much higher SMRs overall and for each cancer category, and greatly reduced attenuation in SMRs with duration of employment. Furthermore, there was a large increase in the ERR per 10 mSv estimates when we included a restricted cubic spline adjustment for employment duration, which further suggests a strong HWSB in this pooled U.S. nuclear worker cohort. The fact that this increase was greatest for smoking-related cancers suggests that the HWSB is strongest for lifestyle-related outcomes, such as smoking-related cancers and nonmalignant respiratory and cardiovascular diseases. However, the methodologies we employed provide incomplete adjustment for the HWSB, because they condition on a factor (employment duration) that is related to both exposure and the outcome, which leads to "collider-stratification bias" (40). A preferred approach may be the

use of G-estimation in cumulative failure-time models, which were recently shown to lead to a doubling in the excess hazard in ischemic heart disease among a cohort of truck drivers (41). It would be informative to explore the use of such models for the pooled U.S. cohort, in conjunction with those from France and the UK in the forthcoming INWORKS analyses.²

Confounding of the radiation-related dose-response relationship by cigarette smoking for smoking-related cancers may have been positive at ORNL and Hanford, as the (positive) ERR per 10 mSv was of greater magnitude for COPD than for lung cancer. For INL, it is likely that negative confounding occurred, since the negative ERR per 10 mSv estimate was similar for lung cancer and COPD. This is similar to previous findings at that site, which were based on follow-up through 1999 (16). For PNS and SRS, negative confounding by cigarette smoking may also have occurred, since the estimate was negative for COPD while positive for lung cancer. This possibility was previously suggested (14) for SRS, using more formal methods to indirectly quantify the potential for confounding by cigarette smoking through evaluation of outcomes, but such methods [further explicated by Richardson *et al.* (42)] were beyond the scope of the current analysis. The facility-specific findings for cardiovascular disease (data not shown) support the arguments above, since there was a positive ERR per 10 mSv estimate model for Hanford and ORNL, and negative estimates at PNS, SRS and INL.

Although we observed a large excess in the expected number of mesothelioma and pleura cancers, the overall number of cases was small. The radiation dose coefficient was positive, suggesting that exposure to asbestos may have been positively correlated with radiation dose within the pooled cohort. Most of the excess was related to the PNS site, which exhibited very large SMRs that increased monotonically with employment duration. This is consistent with observations in a study of mesothelioma risk in a group of U.S. Navy nuclear shipyards (43). A nested case-control study of lung cancer among PNS workers (44) found that adjustment for asbestos and welding fume decreased the ERR per 10 mSv estimate from 3.6% to 1.9%, therefore it appears that confounding by exposure to these agents is likely at the PNS site, for lung cancer. Among the DOE sites, an approximate doubling of the expected number of mesothelioma cases was observed. A detailed evaluation in the INL cohort (16) found that the cases were restricted to workers with jobs related to maintenance and construction activities, and were highest in the group of jobs suggestive of asbestos exposure. The finding here of more widespread excesses in asbestos-related cancer suggests an opportunity for intervention or possible early screening among workers in or retirees from certain jobs within the DOE complex.

In summary, the results of this study suggest small, dose-related increases in risk have occurred for a wide variety of cancers among U.S. nuclear workers. Of particular interest are the findings of statistically significant increases in risk

of nonsmoking-related cancers, lymphoma and myeloma, which were consistent across the studied facilities. For other cancers, the radiation-related risks reported here are consistent with those observed in previous studies of nuclear workers, and also with the expectation from studies of those exposed to higher levels of non-protracted radiation. We anticipate that information about these risks, in particular with respect to time patterns after exposure and after adjustment for the HWSB, will become more precise after pooling these data with those from nuclear workers in France and the UK as part of the INWORKS study.

SUPPLEMENTARY INFORMATION

Table S1. Definitions of causes of death evaluated in the pooled U.S. cohort.

Table S2. Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) for individual cancer sites, by facility of first employment.

Table S3. SMRs and 95% CIs by duration of employment for causes of death of interest, during active and inactive employment periods combined.

Table S4. SMRs and 95% CIs by duration of employment and facility of first employment for mesothelioma and pleura cancer, during inactive employment periods.

Table S5. Akaike Information Criterion values for the linear excess relative risk (ERR) model and for the power (log-log) model.

Table S6. Covariates with significant main effects in dose-response analyses for health outcomes of interest, based on total dose in a linear ERR model.

Fig. S1. Dose-response curves for models of different forms, for cardiovascular disease.

Fig. S2. Age-varying ERR percentage per 10 mSv estimate for nonsmoking-related cancers.

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