

Radiation and Mortality of Workers at Oak Ridge National Laboratory: Positive Associations for Doses Received at Older Ages

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We examined associations between low-level exposure to ionizing radiation and mortality among 14,095 workers hired at the Oak Ridge National Laboratory between 1943 and 1972. Workers at the facility were individually monitored for external exposure to ionizing radiation and have been followed through 1990 to ascertain cause of death information. Positive associations were observed between low-level exposure to external ionizing radiation and mortality. These associations were larger for doses received after 45 years of age, larger under longer lag assumptions, and primarily due to cancer causes of death. All cancer mortality was estimated to increase 4.98% [standard error (SE) = 1.5] per 10-mSv cumulative dose received after age 45 under a 10-year lag, and 7.31% (SE = 2.2) per 10-mSv cumulative dose received after age 45 under a 20-year lag. Associations between radiation dose and lung cancer were of similar magnitude to associations between radiation dose and all cancers except lung cancer. Nonmalignant respiratory disease exhibited a positive association with cumulative radiation dose received after age 45, whereas ischemic heart disease exhibited no association with radiation dose. These findings suggest increases in cancer mortality associated with low-level external exposure to ionizing radiation and potentially greater sensitivity to the carcinogenic effects of ionizing radiation with older ages at exposure. **Key words:** epidemiology, ionizing radiation, Oak Ridge National Laboratory. *Environ Health Perspect* 107:649–656 (1999). [Online 29 June 1999] <http://ehpnet1.niehs.nih.gov/docs/1999/107p649-656richardson/abstract.html>

People are exposed to ionizing radiation from a wide range of occupational and environmental sources. The effects of these exposures remain a topic of substantial concern and interest. Studies of atomic bomb survivors and patients receiving medical irradiation have provided widely cited epidemiologic evidence about the effects of external exposure to ionizing radiation (1–4). Epidemiologic studies of workers in the nuclear industry, however, offer potentially valuable information about the effects of long-term, low-level ionizing radiation exposures; such studies may be particularly relevant to evaluations of the effects of the low dose rate exposures typically received in environmental and occupational settings.

In this paper we describe associations between external exposure to ionizing radiation and mortality among workers employed at the Oak Ridge National Laboratory (ORNL; Oak Ridge, TN), a United States Department of Energy (DOE) facility. Workers at the ORNL have been involved in research and production of nuclear materials since the facility's construction in 1943 as part of the U.S. government's World War II program to develop atomic weapons. These workers have relatively complete external radiation dosimetry data and vital status follow-up (5,6). Previous studies of this workforce have reported excess leukemia mortality as compared to the general population (7,8) and positive associations between cumulative external ionizing radiation dose and cancer mortality among white males at the ORNL

who had not been employed at other DOE facilities (8,9). Subsequent analyses found that these dose–response associations were primarily due to the association between cancer mortality and radiation doses received at older ages (10,11). In contrast to previous studies, which focused on radiation–mortality associations among white males at the ORNL who had not been employed at other DOE facilities (7–9), we describe analyses that include all ORNL workers for whom data were adequately complete. We examined associations between external radiation dose and several specific causes of death and evaluated the sensitivity of these associations to assumptions about the latency between exposure and mortality.

Materials and Methods

This study included all employees hired at the ORNL between 1943 and 1972 who worked 30 or more days; for whom there was complete information on sex, race, dates of birth and hire; and who had no more than 2 years of missing annual whole-body dosimetry data from employment at other DOE facilities ($n = 14,095$). In contrast to previous studies of radiation–cancer associations among workers at the ORNL, the cohort included women, nonwhite workers, and workers who were also employed at other DOE facilities (primarily other DOE facilities located in Oak Ridge, TN).

Vital status was ascertained through 1990 by the use of records from the Social Security Administration, the National Death

Index, and employers. Information on underlying cause of death, as well as contributory causes of death related to cancer, was abstracted from death certificates and coded to the *International Classification of Diseases*, 8th Revision (ICD-8) adapted for the United States. Comparisons of mortality of workers to the general population are usually based only on underlying causes of death information; however, characterization of deaths by a single underlying cause leads to loss of information for decedents with multiple morbid conditions. Therefore, in this study, similar to previous analyses that have compared mortality of ORNL workers with different dose levels, we used both underlying and contributory cause of death information to define cancer death (8,12).

We examined deaths due to all causes (any worker identified as deceased) because this outcome is of broad public health significance and is not dependent on the accuracy of information about causes of death. All cancer mortality (any worker who had an underlying or contributory cause of death assigned ICD-8 codes 140–209) was examined because radiation-induced cancers may occur at most, if not all, sites following whole-body exposure to ionizing radiation and because death certificate data may be more accurate for identifying all cancers as a group than for identifying specific types of cancer (2,13). The category of all causes except cancer (any worker who did not have an underlying or contributory cause of death assigned ICD-8 codes 140–209) was examined to assess whether radiation–mortality associations were specific to malignant diseases. Lung cancer (any worker who had an underlying or contributory cause of death

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assigned ICD-8 code 162) was examined because this was the most common cancer cause of death in the cohort and this cancer site is most strongly related to cigarette smoking, which potentially may confound studies of radiation–cancer associations (14). All cancer mortality except lung cancer (any worker who had an underlying or contributory cause of death assigned ICD-8 codes of 140–209 except 162) was examined to assess the specificity of radiation–cancer association to lung cancer. Ischemic heart disease (any worker who had an underlying cause of death assigned ICD-8 codes 410–414) was examined because it was a leading noncancer cause of death, it was expected to be associated with cigarette smoking, and it was potentially indicative of bias due to selection of healthier workers into exposed jobs. Nonmalignant respiratory disease (any worker who had an underlying cause of death assigned ICD-8 codes 460–519) was examined as a non-cancer outcome expected to be associated with cigarette smoking.

Personal monitoring data for whole-body exposure to external penetrating ionizing radiation (primarily gamma rays) were available for the period 1943–1985 from records at the ORNL. External ionizing radiation exposure monitoring began at the ORNL in February 1943; by 1948 over 98% of the employed workers were monitored, and by November 1951 all ORNL workers were required to have a radiation dosimeter, which was later incorporated into a security badge required to be worn at all times (5,6). Annual external radiation doses were estimated for work-years at the ORNL with missing dose data by using dose estimates in adjacent time periods and average values for similar workers (15). Radiation dosimetry data from other facilities, including Y-12 (Oak Ridge, TN), K-25 (Oak Ridge, TN), Hanford (Richland, WA), and the Savannah River Site (Aiken, SC), were merged with the ORNL records; workers who had more than 2 years of missing external radiation dose data during employment at other DOE facilities were excluded from analyses.

Statistical methods. Statistical analyses of radiation–mortality associations were conducted using the Poisson regression method (16,17). Person-time and events were allocated in tables stratified by all covariates and cumulative radiation dose (18). Age at risk was classified in 5-year intervals from < 25 years to ≥ 90 years. Birth cohort was classified as births before 1905, between 1905 and 1915, between 1915 and 1925, or after 1925. Sex was included with two levels; race indicated whether or not a worker was classified as white. Paycode, which was used to control for socioeconomic differences in cancer mortality, was based on the worker's pay

schedule when hired and indicated whether a worker was paid monthly, weekly, or hourly. Employment status, which indicated whether or not a worker had been employed within the last 2 years, was used to control for mortality differences between actively employed and terminated workers (19–21). Internal exposure to radionuclides has been monitored since 1951. Internal monitoring status was lagged the same number of years as external dose and indicated whether a worker was employed during those years when monitoring for internal radionuclide contamination was conducted, and if so, whether the worker had ever been monitored. Facility of employment was examined as a covariate that indicated whether or not the ORNL was the only DOE facility at which the worker was employed.

After evaluation of the data, we determined that a single term could be used to adjust for age at risk centered at 52.5 years in a log–log relationship for cancer causes of death and in a log–linear relationship for noncancer causes (22). This is similar to previous analyses of mortality of workers at the ORNL and has been demonstrated to be an efficient method for adjusting for age at risk (23,24). Other covariates were included using indicator terms. Terms were included to describe interactions between birth cohort and paycode, changes with age at risk in the association between cancer mortality and employment status, and differences by sex in the effects of race and birth cohort. Due to the limited number of lung cancer deaths among female workers, analyses of lung cancer mortality could not support interactions between race or cohort and sex. Similarly, analyses of nonmalignant respiratory disease do not include a race–sex interaction term.

Cumulative external ionizing radiation doses were classified in seven 20-mSv categories from 0 mSv to ≥ 100 mSv. To consider a lag between exposure and mortality, deaths and person-time were classified according to the cumulative external radiation dose received 5, 10, and 20 years earlier. In regression analyses, cumulative dose was evaluated as a continuous variable, providing an estimate of the percent change in mortality per 10-mSv cumulative dose (see Appendix). We previously demonstrated that white male ORNL workers show substantial heterogeneity in radiation–cancer associations with age at exposure (10,11) and that the best fitting model was produced when cumulative dose was partitioned at 45 years of age. In the analyses reported here, a regression model with separate terms for doses received before and after age 45 was compared to a nested regression model with a single term for all ages of exposure combined (see Appendix). Results include an

indication of the change in deviance on inclusion of a dose term in the regression model. This value is referred to as likelihood ratio test (LRT) statistic and can be interpreted using a chi-square distribution with one degree of freedom (*df*); larger values indicate a better fit of the regression model to the observed data (16).

Results

Vital status was ascertained for 94% of the cohort in follow-up through 1990 (Table 1). Of the 14,095 workers in the cohort, 3,269 (23%) were deceased at the end of follow-up. Death certificates were retrieved for 97% of the decedents, from which 879 deaths due to cancer were identified. The follow-up period includes 425,486 person-years. The distribution of person-time and deaths by study factors is described in Table 2.

Lifetime cumulative dose was positively associated with all cancer mortality under 5-, 10-, and 20-year lag assumptions (Table 3). However, radiation–cancer associations were of larger magnitude and better fit when radiation doses received after age 45 were examined than when associations with lifetime cumulative dose were examined (Table 3). Cumulative dose received after 45 years of age was positively associated with all cancer mortality under a 5-year lag assumption (4.39%/10 mSv), 10-year lag assumption (4.98%/10 mSv), and 20-year lag assumptions (7.31%/10 mSv). The LRT statistic for the association between doses received after age 45 and all cancer mortality was marginally larger under a 10-year lag assumption (LRT = 9.4; 1 *df*) than under a 5-year lag assumption (LRT = 8.7; 1 *df*) or 20-year lag assumption (LRT = 8.4; 1 *df*). We used a nested regression model to compare the fit of the dose–response model for lifetime cumulative dose to the fit of the model that allowed the association to differ for exposures received before and after age 45 (Table 3). The change in deviance between nested regression models provided an LRT of the heterogeneity in dose–response associations for exposures received before and after 45 years of age; the results indicate substantial improvement under the assumption that the dose–response association differed for

Table 1. Vital status of the study cohort of Oak Ridge National Laboratory workers as of 31 December 1990.

	No. men (%)	No. women (%)	Total no. (%)
Alive	7,399 (69.1)	2,568 (75.8)	9,967 (70.7)
Dead	2,890 (27.0)	379 (11.2)	3,269 (23.2)
Unknown	417 (3.9)	442 (13.0)	859 (6.1)

exposures received at older and younger ages (Table 3). Adjustment of dose–response associations for doses received before age 45 had little effect on the estimated associations between doses received after age 45 and all cancer mortality. When we did not adjust

for associations between all cancer mortality and radiation doses received before age 45 in the model, we estimated a 4.54% (SE = 1.33) increase in all cancer mortality per 10 mSv dose received after age 45 under a 10-year lag assumption.

Table 2. Distribution of person-years and deaths by study factors among Oak Ridge National Laboratory (ORNL) workers.

	All cause deaths	All cancer deaths	Lung cancer deaths	Ischemic heart disease deaths	Nonmalignant respiratory deaths	Person-years of follow-up
Age						
<30	59	6	1	0	0	52,693
30–50	475	98	23	100	9	214,198
50–70	1,684	519	156	543	63	140,007
70+	1,051	256	65	333	95	18,589
Sex						
Male	2,890	750	219	913	150	326,767
Female	379	129	26	63	17	98,718
Race						
White	2,961	819	235	906	156	398,674
Other	308	60	10	70	11	26,812
Facility of employment						
ORNL only	2,576	693	189	781	135	334,318
Other	693	186	56	195	32	91,168
Pay code						
Hourly	690	181	67	209	40	65,706
Weekly	1,706	442	134	493	91	214,684
Monthly	873	256	44	274	36	145,096
Birth cohort						
<1905	778	162	38	306	49	22,902
1905–1915	985	252	68	318	77	55,968
1915–1925	1,017	321	105	263	35	139,233
1925+	489	144	34	89	6	207,383
Employment status						
Employed within last 2 years	536	162	41	146	8	169,816
Not employed	2,733	717	204	830	159	255,670
Internal radiation monitoring						
Not monitored	2,202	565	150	669	116	91,619
Monitored	1,002	304	92	297	50	273,513
Not eligible to be monitored	65	10	3	10	1	60,354
Total	3,269	879	245	976	167	425,486

Table 3. Estimated percent increase in all cancer mortality among Oak Ridge National Laboratory (ORNL) workers per 10-mSv cumulative external ionizing radiation dose under 5-, 10-, and 20-year lag assumptions.

	Model 1: Partitioned cumulative dose		Model 2: Lifetime cumulative dose	Model 1 versus Model 2
	Cumulative dose received before age 45	Cumulative dose received after age 45	Cumulative dose received after age 16	LRT ^a
5-year lag				
Percent increase	-0.86	4.39	1.06	
SE	1.05	1.36	0.61	
LRT, 1 df	0.7	8.7	2.7	6.22
10-year lag				
Percent increase	-0.69	4.98	1.21	
SE	1.05	1.48	0.65	
LRT, 1 df	0.5	9.4	3.0	6.62
20-year lag				
Percent increase	0.24	7.31	1.73	
SE	1.12	2.24	0.86	
LRT, 1 df	0.05	8.4	3.5	5.79

Abbreviations: *df*, degree of freedom; LRT, likelihood ratio test; SE, standard error. Adjusted for age, race, sex, birth cohort, employment status, paycode, internal radionuclide monitoring, and the interaction between race and sex, sex and birth cohort, paycode and birth cohort, and employment status and age.

^aLRT comparing Model 1 to Model 2, which has a chi-square distribution with 1 *df*.

The fit of these regression models to the observed data was examined graphically, evaluating associations between radiation dose and all cancer mortality under a 10-year lag assumption (Figure 1). Figure 1 shows the relationship between all cancer mortality and lifetime cumulative dose (Figure 1A), cumulative dose received before age 45 (Figure 1B), and cumulative dose received after age 45 (Figure 1C). There do not appear to be any systematic departures from linearity.

These radiation–cancer dose–response associations were based on a multiplicative relative risk model in which mortality is described as increasing on a natural log scale with increasing cumulative radiation dose. However, within the range of observed cumulative doses, the magnitude of association between all cancer mortality and radiation doses received after 45 years of age was similar when estimated using an additive relative risk model. Under an additive relative

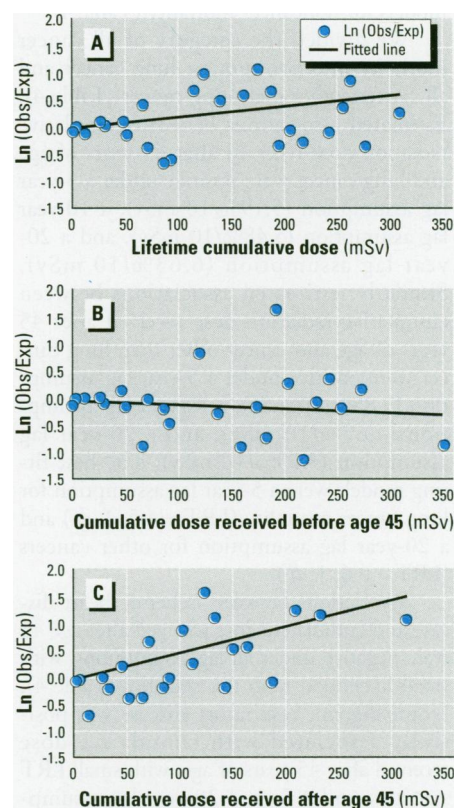


Figure 1. Ratio of observed (Obs) to expected (Exp) number of all cancer deaths by cumulative dose under a 10-year lag. (A) Association with lifetime cumulative dose. (B) Association with cumulative dose received before the age of 45 years. (C) Association with cumulative dose received after the age of 45 years. Points represent the ratio of observed cancer deaths to the number expected in each cumulative dose category based on the covariate-specific distribution of person-time. Solid lines represent the estimated percent increase in cancer mortality with increasing cumulative dose.

risk model, cumulative dose received after age 45 was associated with a 6.85% (SE = 3.10; LRT = 8.6; 1 *df*) increase in all cancer mortality per 10 mSv under a 10-year lag assumption.

All cause mortality was also positively associated with cumulative radiation dose received after 45 years of age; associations increased in magnitude under longer lag assumptions, from 1.10%/10 mSv under a 5-year lag assumption to 3.54%/10 mSv under a 20-year lag assumption (Table 4). However, associations between cumulative dose received after age 45 and cancer mortality were of substantially larger magnitude and better fit than associations with all cause mortality (Table 4). Associations between radiation dose received after age 45 and all causes of death except cancer were negative under 5- or 10-year lag assumptions and positive under a 20-year lag assumption. Likelihood ratio tests indicate relatively little contribution of the dose term to fit of the models for noncancer mortality (Table 4).

We divided the category of all cancer mortality into two groups: lung cancer and all cancers other than lung cancer (Table 4). Estimated associations between cumulative radiation dose received after 45 years of age and lung cancer were positive under a 5-year lag assumption (5.19%/10 mSv), a 10-year lag assumption (5.48%/10 mSv), and a 20-year lag assumption (6.63%/10 mSv). Similarly, estimated associations between cumulative radiation dose received after 45 years of age and cancer other than lung cancer were positive under a 5-year lag assumption (3.88%/10 mSv), a 10-year lag assumption (4.67%/10 mSv), and a 20-year lag assumption (7.69%/10 mSv). The best fitting models were a 5-year lag assumption for lung cancer mortality (LRT = 4.5; 1 *df*) and a 20-year lag assumption for other cancers (LRT = 6.6; 1 *df*).

Associations between ischemic heart disease and cumulative dose received after age 45 were negative under all lag assumptions, with small likelihood ratio test statistics (Table 4). Nonmalignant respiratory disease was positively associated with cumulative dose received after 45 years of age, with small LRT statistics under 5- and 20-year lag assumptions. The magnitude (5.66%/10 mSv) and goodness of fit (LRT = 3.2; 1 *df*) of the association between nonmalignant respiratory disease and radiation dose was largest under a 10-year lag assumption. There were few deaths at higher doses when the association between nonmalignant respiratory disease and doses received after 45 years of age were examined under a 20-year lag assumption.

To further describe the fit of these models for radiation-cancer dose-response associations to the observed data, ratios of observed

Table 4. Estimated percent increase in cause-specific mortality among Oak Ridge National Laboratory workers per 10-mSv cumulative external radiation dose received after age 45, under 5-, 10-, and 20-year lag assumptions.

	5-Year lag	10-Year lag	20-Year lag
All cause mortality			
Percent increase per 10 mSv	1.10	1.19	3.54
SE	0.87	0.96	1.42
LRT, 1 <i>df</i>	1.5	1.5	5.5
All cancer mortality			
Percent increase per 10 mSv	4.39	4.98	7.31
SE	1.36	1.48	2.24
LRT, 1 <i>df</i>	8.7	9.4	8.4
All causes except cancer			
Percent increase per 10 mSv	-0.30	-0.44	2.04
SE	1.12	1.25	1.81
LRT, 1 <i>df</i>	0.1	0.1	1.2
Lung cancer ^a			
Percent increase per 10 mSv	5.19	5.48	6.63
SE	2.21	2.45	4.18
LRT, 1 <i>df</i>	4.5	4.1	2.0
All cancers except lung			
Percent increase per 10 mSv	3.88	4.67	7.69
SE	1.74	1.87	2.64
LRT, 1 <i>df</i>	4.2	5.2	6.6
Ischemic heart disease			
Percent increase per 10 mSv	-2.39	-2.86	-0.16
SE	1.81	2.06	2.99
LRT, 1 <i>df</i>	1.9	2.1	0.0
Nonmalignant respiratory disease ^a			
Percent increase per 10 mSv	4.55	5.66	3.57
SE	2.79	2.93	4.95
LRT, 1 <i>df</i>	2.3	3.2	0.5

Abbreviations: *df*, degree of freedom; LRT, likelihood ratio test; SE, standard error. Adjusted for cumulative dose received before age 45, age, race, sex, birth cohort, employment status, paycode, internal radionuclide monitoring, and the interaction between race and sex, sex and birth cohort, paycode and birth cohort, and employment status and age.

^aThere is no race-sex interaction in the model for nonmalignant respiratory disease, and no race-sex or sex-cohort interactions in the model for lung cancer.

to expected cancer deaths were tabulated by categories of cumulative dose received after 45 years of age under 5-, 10-, and 20-year lag assumptions (Table 5). This table also provides a description of the distribution of person-time and deaths by level of cumulative external radiation dose received after age 45. The ratio of observed to expected deaths tended to increase with increasing dose received after age 45 for each of the three categories of death examined (Table 5). As longer lag assumptions were evaluated and deaths and person-years shifted to lower cumulative dose groups, the ratio of observed to expected deaths tended to increase for the highest cumulative dose categories.

Discussion

Epidemiologic studies of badge-monitored workers in the nuclear industry provide a potentially important source of evidence about the health effects of low-level exposure to ionizing radiation. Studies of workers employed at the ORNL allow examination of a cohort with a long duration of follow-up, nearly complete external radiation dosimetry records, and a high level of vital status follow-up.

Previous analyses determined that, overall, workers at the ORNL have low mortality

rates in comparison to the general population (8,12). This observation is consistent with other studies of DOE workers and typical of mortality patterns for well-paid, highly educated workers in the United States (25). An exception to the low overall mortality rates among ORNL workers as compared to the general population, however, is the observed excess mortality due to leukemia and ill-defined causes (7,8). Previous investigations of radiation-cancer associations among ORNL workers have focused on white male ORNL workers who were not employed at other DOE facilities. These workers have the most complete radiation dosimetry data and vital status follow-up. In that subcohort, positive associations between cumulative whole-body ionizing radiation dose and mortality, primarily due to cancer, were reported with follow-up through 1984 (8). Subsequent analyses of that subcohort reported that associations between radiation dose and cancer mortality were primarily due to radiation doses accrued at older ages (10,11,24).

In this paper, we examine an expanded cohort of ORNL workers, with follow-up through 1990. Given this expanded cohort and additional period of follow-up, these analyses include twice as many deaths as previous reports on radiation-cancer associations

Table 5. Ratio of observed to expected deaths for cancer causes of death and observed deaths (shown in parentheses) by lag period and grouped dose received after the age of 45 years.

Cause of death	Dose received after age 45						
	0 mSv	0–20 mSv	20–40 mSv	40–60 mSv	60–80 mSv	80–100 mSv	100+ mSv
All cancer							
5-year lag	0.99 (561)	0.96 (237)	1.12 (32)	1.24 (17)	0.83 (8)	1.26 (5)	1.88 (19)
10-year lag	0.99 (593)	0.97 (217)	0.99 (25)	1.09 (13)	1.18 (10)	0.92 (3)	2.22 (18)
20-year lag	1.00 (703)	0.91 (135)	1.35 (20)	0.78 (5)	1.03 (4)	3.27 (5)	2.68 (7)
All cancer except lung							
5-year lag	0.99 (411)	0.99 (174)	0.97 (19)	1.22 (11)	0.78 (5)	0.78 (2)	1.88 (12)
10-year lag	1.00 (436)	0.97 (155)	0.94 (16)	1.16 (9)	1.08 (6)	0.47 (1)	2.14 (11)
20-year lag	1.00 (508)	0.93 (100)	1.29 (13)	0.70 (3)	0.37 (1)	3.70 (4)	2.76 (5)
Lung cancer							
5-year lag	0.98 (150)	0.90 (63)	1.43 (13)	1.27 (6)	0.92 (3)	2.08 (3)	1.85 (7)
10-year lag	0.98 (157)	0.96 (62)	1.09 (9)	0.96 (4)	1.37 (4)	1.73 (2)	2.33 (7)
20-year lag	1.01 (195)	0.83 (35)	1.51 (7)	0.98 (2)	2.54 (3)	2.25 (1)	2.57 (2)
Person-years 10-year lag	387,873	31,881	27,497	1,228	748	323	686

Adjusted for age, race, sex, birth cohort, employment status, paycode, internal radionuclide monitoring, and the interaction between race and sex, sex and birth cohort, paycode and birth cohort, and employment status and age.

among white male ORNL workers followed through 1984 (8). With these data we investigated associations between age-specific cumulative radiation doses and cause-specific mortality. Cumulative doses received after age 45 were associated with all cancer mortality under a range of lag assumptions and were associated with lung cancer mortality as well as mortality from cancers other than lung cancer (Table 4).

We evaluated age at exposure using a single critical age value. However, this should not be interpreted as suggesting that sensitivity to radiation changes abruptly at a particular age. Previous analyses demonstrated that the magnitude of association between cancer mortality and external radiation dose increased as critical ages between 40 and 55 years were considered (11,24), although age 45 yielded the best fitting model. In these analyses, there was little evidence of associations between cancer mortality and doses accrued at younger ages (Table 3). This may be a consequence of smaller magnitude associations between radiation doses accrued at younger ages and cancer mortality; additionally, selection of young, healthy workers into jobs with higher radiation exposures due, for example, to occupational health screening might have led to a downward bias in dose–response associations for exposures accrued at younger ages.

Although this study included more workers than previous studies of radiation–cancer associations among ORNL workers, the study still had a limited ability to examine associations between radiation and many

specific cancers, in part because of the cross-classification of events by younger and older age exposures. Consequently, these analyses focused on all cancer, lung cancer, and all cancers except lung cancer because there were adequate data to support investigations of dose–response associations for these causes of death. Leukemia mortality, while of potential interest, occurred too infrequently in this cohort to allow investigation of associations with radiation doses received after 45 years of age; only one leukemia death was observed among workers who received > 40 mSv cumulative dose after age 45 (24).

Radiation–cancer associations may differ between men and women; however, there were insufficient data to evaluate differences in radiation–cancer associations between male and female workers in this cohort. These analyses included 3,389 women, among whom 129 deaths due to cancer were identified (Table 2). Deaths occurred primarily among weekly paid women who tended to have relatively low cumulative recorded external radiation doses. We considered separate analyses of radiation–cancer associations among women; however, only 16 cancer deaths occurred among women with cumulative external doses of ≥ 10 mSv, and there was only one cancer death among women who received > 50 mSv.

We examined demographic and employment variables in these analyses for two reasons: to investigate whether mortality patterns for workers in this occupational cohort conformed to expectations from the epidemiologic literature, and to adjust for

potential confounding of radiation–mortality associations. Given observations of changes in age-specific cancer mortality rates between historical periods, we adjusted for potential confounding by birth cohort. We examined paycode as a measure of socioeconomic status; workers who were paid monthly tended to be employed in higher socioeconomic jobs, whereas workers who were paid either hourly or weekly were typically employed in lower socioeconomic status jobs. We adjusted for employment status in order to evaluate potential confounding due to health-related selection of people out of the workforce (described as a “healthy worker survivor effect”) (19,21). Some previous analyses that examined data for ORNL workers did not adjust for employment status (23,26). Dropping the employment status terms from our model yielded an estimated 5.36% (SE = 1.46) increase in all cancer mortality per 10 mSv cumulative dose received after 45 years of age under a 10-year lag, as compared to the 4.98%/10 mSv estimate derived after adjustment for employment status (Table 4). We found that with the exception of age at risk, adjustment for these demographic and employment factors exerted little influence on our estimates of associations between external radiation dose and cancer mortality.

For the ORNL workers included in this study, there was little quantitative information about individual exposure to agents other than external ionizing radiation. There is the potential for confounding, or modification, of radiation–mortality associations by chemical and internal radionuclide exposures. In previous analyses of white male ORNL workers, however, neither examination of job titles, which were used as an indicator of occupational exposures other than external ionizing radiation, nor evaluation of potential exposure to beryllium, lead, and mercury substantially changed estimates of the association between radiation and cancer mortality (9). Although data from internal exposure monitoring provided only a poor indicator of exposure from internally deposited radionuclides, radionuclide contamination was not considered to be a major hazard among workers at the ORNL.

Cigarette smoking has also been considered as a possible confounder of radiation–cancer dose–response relationships at the ORNL (8,27,28). Historical smoking data were not available for these workers; consequently, we evaluated the plausibility of confounding by cigarette smoking indirectly. Radiation dose–response relationships were compared between causes of death with different magnitudes of association with smoking (8,27–29). Lung cancer is the primary component of associations between smoking and cancer mortality; the excess relative risk

for smoking and lung cancer is approximately one order of magnitude greater than for smoking and other cancers (14). If cigarette smoking were positively associated with radiation dose, observed associations between radiation and lung cancer would be much larger than associations between radiation and cancers other than lung cancer. However, we found that radiation–cancer dose–response associations were not substantially stronger for lung cancer than for other cancers; in fact, the radiation–cancer dose–response relationship was of smaller magnitude for lung cancer than for other cancers under a 20-year lag assumption (Table 4). Among other smoking-related causes of death, associations with radiation doses received after the age of 45 years were positive for nonmalignant respiratory disease and negative for ischemic heart disease, but imprecise in both cases (Table 4). These findings, which provide little suggestion of confounding by cigarette smoking, conform to expectations from the literature. General discussions about occupational epidemiology studies that use internal rather than external referent groups (29,30), empirical investigations in other worker studies (31–33), and simulations (34) suggest that confounding by cigarette smoking would be “relatively modest in most situations” (34). In addition, if smoking is the reason for the observed associations, smoking patterns would have to be positively associated with cumulative doses received at older ages, but not associated with cumulative doses received at younger ages. Furthermore, this age at exposure-related association must occur within strata of age at risk, sex, birth cohort, paycode (a marker of socioeconomic status), and period of hire (9,24).

This study used annual external ionizing radiation dosimetry records as a measure of the primary exposure of interest. A substantial amount of attention has been given to evaluations of ORNL dosimetry data. While the external dosimetry records for ORNL workers are relatively complete, attention has been given to the issue of missing annual external dosimetry records. As an alternative to the assumption that values for missing annual external dosimetry records were zero, we estimated doses for years of employment at ORNL with missing records (15). Attention has also been given to potential underestimation of doses due to the practice of recording zeros for dosimetry readings that were less than the minimum detectable level of the dosimeters used at the ORNL (6,35–37). However, in previous evaluations of an adjustment method for dose underestimation, little influence on dose–response estimates was found (12).

Current understanding of the biologic processes involved in carcinogenesis supports

the conclusion that age at exposure may play an important role in modifying radiation–cancer associations (38–41). Ionizing radiation is a well-established carcinogen known to cause aberrations and point mutations in human chromosomes (2). Fortunately, the body has mechanisms for identifying and destroying damaged cells, and mechanisms for repairing radiation-induced damage to chromosomes (2). However, with increasing age, the accuracy and efficiency of these cellular-repair processes, and of immune responses, declines (42–45). This is one reason why associations between radiation doses and cancer might be larger for ionizing radiation doses received at older ages. Theoretical models of a multistage process of carcinogenesis also suggest that the effect of a carcinogenic exposure may depend upon the age at which exposure was received (38,46).

The conclusion that sensitivity to external ionizing radiation increases with age among adults, however, is at odds with conclusions drawn from the Life Span Study (LSS) of atomic bomb survivors, which has played an influential role in radiation risk estimation (2,47). When considering atomic bomb survivors who were adults at the time of the attack, radiation–cancer associations show different trends with age at exposure for different causes of death. The excess relative risk for cancers of the trachea, bronchus, and lung has been reported to increase with older age at exposure (47), and the excess risk for leukemia was larger for atomic bomb survivors who were over 40 years of age at the time of bombing than for adults 20–40 years of age (48). In contrast, associations between radiation and breast cancer, for example, have been reported to decline substantially with age at exposure in the LSS (47); similar findings have been reported in studies of medical irradiation (49). Such observations suggest the need to consider variation in patterns of radiation risk with age at exposure by cancer type. This study of ORNL workers provided insufficient data to examine radiation–cancer associations separately for many types of cancer. There are also other possible explanations for differences in findings between the LSS and this study. This study of ORNL workers investigates the effects of long-term, low-level external radiation exposure among relatively healthy workers. In contrast, it has been suggested that patterns of selective survival following acute high-level radiation exposure may have obscured evidence of age-related differences in radiation sensitivity among atomic bomb survivors. Mortality due to the acute effects of the atomic bombing (from radiation exposure, as well as physical injuries from the explosion and environmental deprivation) among residents in Hiroshima and

Nagasaki, Japan, may have led to selective survival and a lack of comparability in sensitivity to the carcinogenic effects of ionizing radiation between the higher and lower exposed survivors (50–52).

Some previous studies of workers exposed to low-level ionizing radiation have shown no evidence of differences in radiation–mortality associations with age at exposure (23,26), whereas other studies have reported stronger dose–response associations with older ages at exposure (10,11,45,53). When contrasting findings from this study of ORNL workers with other studies, it is important to recognize the differences in the patterns of exposure, study populations, sources of data, and follow-up. This study includes 14,095 workers; although this is a sizable epidemiologic cohort, the study includes substantially fewer people than recent pooled analyses of nuclear workers (12,26,53). However, although a larger sample size increases the precision of risk estimates, it does not reduce bias. Inclusion of a large number of workers with incomplete or inaccurate exposure information, for example, may produce biased findings rather than increase the ability of a study to detect an association. One recent pooled analysis of DOE workers suggested that pooling ORNL cohort data with data for the Oak Ridge Y-12 facility could obscure radiation–mortality associations because exposure information was less complete for Y-12 workers (12). In occupational cohort studies of nuclear workers at several DOE facilities, Stewart and Kneale (45,53) reported that the magnitude of radiation–cancer associations increased with older age at exposure. Stewart and Kneale (45,53), however, also reported that evidence of heterogeneity in radiation–cancer associations between cohorts suggests that pooling data may be inappropriate. In a study that pooled data from four uranium processing facilities, Dupree et al. (54) also reported that positive associations between external radiation and lung cancer were observed only among workers first hired after 45 years of age.

An estimated 600,000 workers have been employed by the DOE (55), with millions more people worldwide exposed to low-level ionizing radiation through occupational and environmental releases from commercial nuclear facilities and medical and industrial sources. Recent initiatives to fund independent investigations into the health effects of low-level radiation, to provide more open communication about research findings, to allow public access to epidemiologic data, and to offer information about environmental sources of radiation exposure are intended to help open discussions and increase public participation in decisions about the

uses of nuclear technologies (55–57). The data used in these analyses are publicly available via the Comprehensive Epidemiological Data Resource (57). This is encouraging because the involvement of labor organizations and community groups in epidemiologic research, in the scrutiny of findings, and in the use of studies for advocacy has been central to achieving the public health goals of occupational and environmental protection (58,59).

While there are acknowledged limitations to the available data for studying workers in the nuclear industry, such studies offer one approach to addressing concerns about long-term, low-level exposures to ionizing radiation that are typical of occupational and environmental settings (60). The magnitudes of the radiation–cancer associations observed in these analyses are substantially larger than estimates derived from the LSS; these differences are important to consider because the LSS has served as a quantitative basis for current radiation protection standards (2,4). The observed effect of age at

exposure in these analyses suggests that further attention should be given to factors that influence sensitivity to the carcinogenic effects of ionizing radiation. A more complete understanding of the effects of ionizing radiation exposures, however, also requires consideration of a wider range of health outcomes. Although exposures received at older adult ages may be important for cancer mortality, exposures received at younger ages may be important for other biologic effects of ionizing radiation (such as nonfatal diseases and reproductive effects). A better understanding of variation in radiation sensitivity among individuals, and investigations of other potential biologic effects of radiation exposure, should inform and support efforts to protect workers' health and to minimize unnecessary environmental exposures to ionizing radiation.

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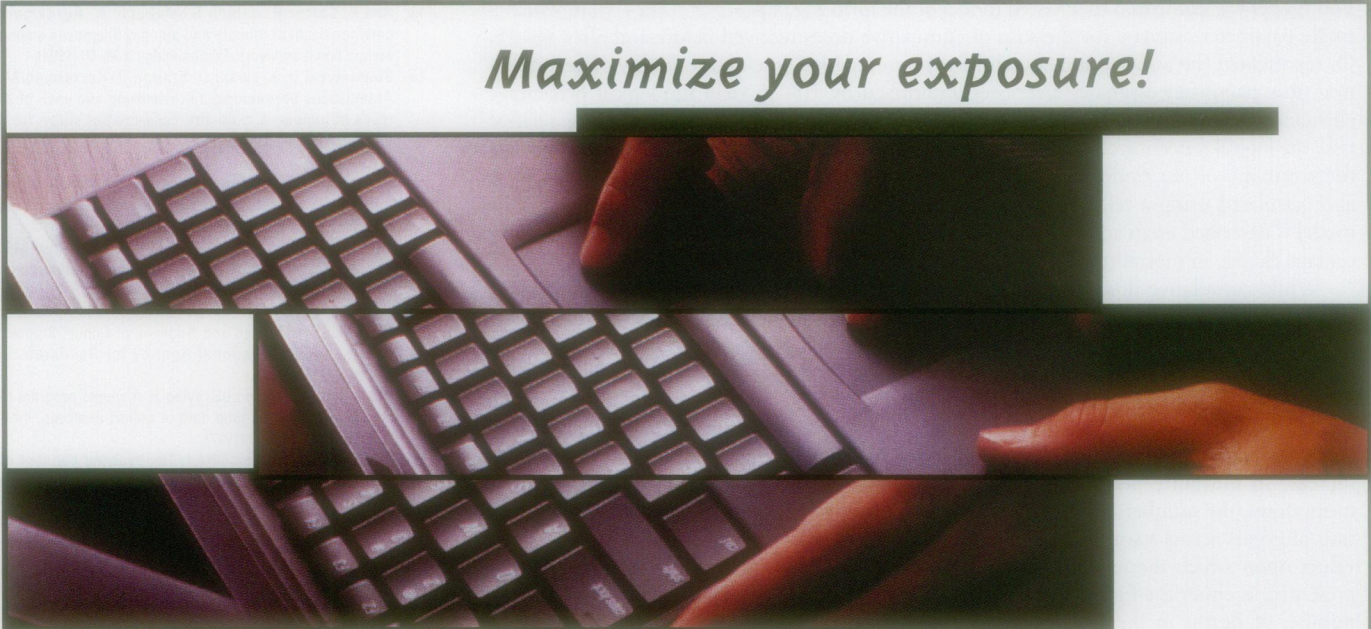
Appendix

In the analyses presented in this paper, we examined a relative risk model of the form $\lambda(Z, x, y) = e^{Z\alpha + \beta x + \delta y}$, where the mortality rate (λ) was considered in terms of a vector of covariates (Z), the radiation dose accumulated before age 45 (x), and the radiation dose accumulated after age 45 (y) (16,17). A vector of parameter estimates, α , was associated with the covariates, and the parameter estimates β and δ represented the change in the log of the relative risk per 10-mSv cumulative radiation doses accrued before and after age 45. This regression model was compared to a nested model of the form $\lambda(Z, x, y) = e^{Z\alpha + \Phi(x + y)}$, in which a single parameter estimate for the sum of cumulative doses received before and after age 45, Φ , represented the association between lifetime cumulative dose and mortality. These radiation dose parameter estimates have been multiplied by 100 to yield the logical percentage change in mortality per 10-mSv cumulative dose (61). For small increases in excess relative risk, the logical percentage change approximates the absolute percentage change. To evaluate the sensitivity of our findings to assumptions about regression model form, estimates were also calculated using a relative risk model of the form $\lambda(Z, x, y) = e^{Z\alpha} (1 + \beta x + \delta y)$. This model is described as an additive relative risk model and yields estimates of the absolute percentage change in mortality per 10-mSv dose (16).

While cumulative dose and age at risk had to be categorized to generate person-time tables, dose groups and age at risk groups were assigned quantitative values. We calculated the cell-specific person-year weighted mean values for radiation doses and age at risk (16,62). The use of cell-specific mean doses minimized the sensitivity of our findings to decisions about dose categorization (62).

We created a table and graphs of the ratios of observed to expected deaths to allow further examination of the data (Table 5, Figure 1A–1C). Although estimates of the percent increase in mortality per 10-mSv dose were based on cell-specific person-year weighted mean doses, the number of observed and expected counts in Table 5 represent the distribution of events across a smaller number of dose categories. There was a greater range of dose values upon which the regression parameters were based than the number of dose groups presented in either the figures or tabulations of observed and expected events. However, the number of deaths in these tables allows consideration of the distribution of events upon which regression analyses were based. The ratios presented in these tables allow comparison of the occurrence of cancer deaths among the population with higher levels of dose received after age 45 with those who received lower levels of dose after age 45; by comparing observed-to-expected counts, these ratios adjust for differences in the distribution of covariates between dose groups, as well as any association between dose received before age 45 and mortality.

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