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Greater sensitivity to ionizing radiation at older age: follow-up of workers at Oak Ridge National Laboratory through 1990

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Background Workers at Oak Ridge National Laboratory (ORNL) were individually monitored for whole body exposure to ionizing radiation. Studies of these workers may provide valuable information about the long-term effects of occupational exposure to ionizing radiation. Since biological changes occur as adults age, a potentially important question in these investigations is whether sensitivity to the carcinogenic effects of ionizing radiation changes with age at exposure.

Methods Vital status and cause of death were ascertained through 1990 for 8307 white males hired at ORNL from 1943 through 1972. Associations between whole body ionizing radiation dose and all-cancer mortality were quantified using life table regression methods for time dependent exposures. Analyses focused of differences in radiation-cancer associations with age at exposure. Length of follow-up, period of hire, and age at risk were considered as alternative explanations for effects of age at exposure.

Results Cumulative radiation dose was associated with a 1.8% (SE = 0.9) increase in all-cancer mortality per 10 mSv, assuming a 10-year lag between exposure and mortality. However, radiation doses received at older ages exhibited larger associations with cancer mortality than doses received at younger ages. Doses received after age 45 were associated with a 5.9%(SE = 1.7) increase in cancer mortality per 10 mSv, adjusted for doses received before age 45. Dose-response associations between cancer mortality and doses received after age 45 appeared consistent across periods of follow-up, periods of hire, and ages at risk.

Conclusions Findings suggest that sensitivity to the carcinogenic effects of ionizing radiation may increase with older ages at exposure. More attention should be given to the role of age at exposure in studies of the health effects of low-level exposure to ionizing radiation, and to efforts to limit exposure to ionizing radiation.

Keywords Cancer, ionizing radiation, Oak Ridge National Laboratory

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The effects of low-level exposure to ionizing radiation are of concern to a large number of people, including workers receiving radiation exposure on the job.[1–3] One way to investigate the effects of low-level exposure to ionizing radiation is to study the mortality of workers in the nuclear industry, such as those employed at the US Department of Energy's (DOE) Oak Ridge National Laboratory (ORNL). Workers employed at ORNL have been individually monitored for whole body exposure to ionizing radiation and have been followed in order to ascertain information about causes of death. No associations between external penetrating radiation and mortality from all cancers were reported in follow-up of ORNL workers through 1977.[4,5] However, with follow-up through 1984, positive associations were reported by a number of investigators.[6–10] Radiation-mortality associations were primarily attributable to cancer causes of death.[6] Although the number of cancer deaths was too small to permit separate dose-response analyses for many specific types of cancer, positive associations were observed for broad groups of cancers.[11] Data from this occupational cohort allow not only examination of the magnitude of radiation-cancer associations, but also investigation of possible modifiers of these associations.

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This paper gives particular attention to possible changes in workers' vulnerability to the carcinogenic effects of ionizing radiation with older ages at exposure. As people age, they experience declines in the efficiency of their immune system and biological repair processes.[12–15] Since these processes may play an important role in mitigating the effects of exposure to ionizing radiation, we investigated whether associations between cancer mortality and radiation differed for doses received at different ages.

Interpretation of differences in radiation-cancer associations with age at exposure, however, is complicated by the fact that age at exposure is correlated with other factors which change over time.[16–18] Consequently, a series of analyses examined the consistency of results across periods of hire, periods of follow-up, and ages at risk. In order to give detailed attention to these investigations of time-related factors, this report focuses on all-cancer mortality.

Methods

Similar to previous reports, this study included 8307 white males hired from 1943 through 1972, employed at least 30 days at ORNL, and not employed at another Department of Energy facility prior to 1978.[4,6] These workers have been selected for previous studies because they have more complete dosimetry records and vital status follow-up than the ORNL cohort as a whole. Vital status through 1990 was ascertained through Social Security Administration, National Death Index, and employer records.

Consistent with previous analyses of this cohort, all-cancer mortality was defined to include any death for which an International Classification of Diseases adapted for the United States (Eighth Revision) code of 140–209 appeared as an underlying or contributory cause.[6,9,10] All-cancer mortality was chosen as the outcome of interest for these investigations since radiation-induced cancers may occur at most, if not all, sites following whole body exposure to ionizing radiation.[19] Previous analyses have shown that associations between cumulative whole body radiation dose and mortality in this cohort are primarily due to cancer causes of death.[6] Although the observed number of leukaemia deaths in this cohort has been elevated compared to the number expected based on national mortality data, the small number of leukaemia deaths precluded separate dose-response analyses.[20] Analyses examining associations among ORNL workers between radiation dose and cause-specific mortality under varying lag assumptions are reported elsewhere.[20,21]

Personal monitoring data for whole body exposure to ionizing radiation (primarily gamma rays) were available for the period 1943–1985 from records at ORNL. Monitoring began at ORNL in February 1943; by 1948 over 98% of the employed workers were monitored,[22] and by November 1951 all ORNL workers were required to have a film badge which was later incorporated into a security badge required to be worn at all times.[23] Pocket ionization chambers were used from February 1943 through May 1944, film badge dosimeters were used from June 1944 through December 1975, and thermoluminescent dosimeters have been used since January 1976. Whole body radiation doses were estimated for work-years at ORNL with missing dose data using dose estimates in adjacent time periods and average values for similar workers.[24]

Statistical methods

Poisson regression methods were used to examine associations between cumulative radiation doses and cancer mortality, adjusted for other demographic and occupational variables.[25–27] Person-time and events were allocated in tables stratified by covariates and cumulative radiation doses.[27,28] Age at risk was categorized in 5-year intervals from <25 years to $\geqslant 90$ years. Year of birth was categorized as prior to 1905, 1905–1915, and after 1915. 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 or not a worker had been hired on a monthly pay schedule. 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.[29,30] Associations between these variables and mortality through 1990 were similar to those reported previously in follow-up through 1984.[31] Internal contamination from radionuclides has been monitored since 1951.[32] Internal monitoring status was lagged the same number of years as external radiation 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.[9,23,32]

Similar to previous analyses of mortality among workers at ORNL, a single term was included for age at risk centred at 52.5 years, in a log-log relationship with all-cancer mortality.[33] Use of a single regression parameter, rather than a vector of indicator terms for categories of age at risk, facilitated inspection of age-mortality associations and has been demonstrated to be an adequate method for adjusting for age at risk in this cohort.[8,20,31] Other covariates were included using indicator terms. In addition to including terms for all main effects of covariates, interaction terms were included to describe differences between birth cohorts in the effect of paycode, and changes with age at risk in the effect of employment status.[6]

Associations between radiation and cancer mortality are described as the per cent increase in all-cancer mortality per 10 mSv cumulative dose. The change in deviance upon inclusion of a dose term in the regression model, described as a likelihood ratio test (LRT) statistic, can be interpreted using a χ^2 distribution with one degree of freedom; larger values indicate a better fit of the regression model to the observed data. In all analyses person-time and deaths were classified in eight 20 mSv dose categories (0, >0–<20, 20–<40, 40–<60, 60–<80, 80–<100, 100–<120, and $\geqslant 120$ mSv), under specified lag assumptions. While cumulative dose had to be categorized to generate person-time tables, the quantitative values used for regression analyses were the person-year weighted mean values for each dose group cross-classified by all covariates.[26,34] Use of these cell-specific mean doses minimizes the sensitivity of regression coefficients to decisions about dose categorization.[34] Graphs of observed versus expected numbers of cancer deaths by categories of cumulative dose were created using cell-specific mean doses over broad enough ranges of dose to include at least one cancer death in each dose group. Expected counts were calculated for each cell of the person-time table using a regression model that included all variables except the dose term.

A multiplicative relative risk model of the form $\lambda(Z,x) = e^{Z\alpha + \beta x}$ was used in the main regression analyses, where the

cancer mortality rate λ was considered in terms of a vector of covariates (Z) and radiation dose (x).[26,35] A vector of parameter estimates, α, was associated with the covariates, and the parameter estimate β represented the association between radiation dose and cancer mortality. In order to evaluate the sensitivity of our findings to assumptions about regression model form, estimates were also calculated using an additive relative risk model of the form $\lambda(Z,x) = e^{Z\alpha}(1 + \beta x)$.[20]

In order to investigate differences in the effects of radiation doses with age at exposure, person-time and deaths were classified according to the level of cumulative dose received during specified ranges of age.[16] Person-time and deaths were cross-classified in separate strata according to the level of dose accrued before and after a specified age; by using this method we examined the effect of doses received at older ages adjusted for the effect of doses received at younger ages.[20] Analyses that considered the effect of doses received at older ages adjusted for doses received at younger ages included separate terms for doses received at older and younger ages. This model was of the form $\lambda(Z,x,y) = e^{Z\alpha + \beta x + \delta y}$, where ($x$) represented the radiation dose accumulated at older ages, (y) represented the radiation dose accumulated at younger ages, and β and δ represented their associated parameter estimates. This model was compared to a nested model that included a single parameter estimate for the sum of the age-specific doses, $\lambda(Z,x,y) = e^{Z\alpha + \beta(x + y)}$.

Several alternative explanations for results pertaining to the effects of doses received at older ages were evaluated. For example, workers were hired at older ages between 1943 and 1947 and potentially suffered poorer health than workers hired later because of the military's selection of young, healthy men out of the workforce;[7,36] these workers also tended to receive higher whole body radiation doses, and were monitored with less sensitive exposure measurement methods.[20,22] In order to investigate whether dose-response associations differed for workers hired in these early years, radiation-cancer dose response relationships were evaluated separately for workers hired before and after 1947.

The possibility that the effects of doses received at younger ages may occur after longer latency periods than the effects of doses received at older ages was also investigated. Associations between cancer mortality and radiation doses received at younger ages were examined under a range of lag assumptions, using a regression model that included separate terms for doses received at older and younger ages at exposure.

Associations between cumulative radiation dose and cancer mortality among workers at ORNL have previously been reported to increase in magnitude with older ages at risk.[8] Age at risk and age at exposure are related, since as workers reach older ages at risk doses may be accrued at older ages at exposure. In order to examine dose response associations separately for deaths occurring among older and younger workers, associations were evaluated separately for ages at risk less than, and greater than, 70 years.[8,37]

Finally, the stability of dose response estimates with the inclusion of additional years of follow-up was examined. Differences in dose-response associations for this population have previously been attributed to longer follow-up.[6] To evaluate the effect of the end-date of follow-up, the magnitude of dose-response associations was compared in analyses that included follow-up through 1980, 1982, 1984, 1986, 1988, and 1990.

Table 1 Distribution of person-years and cancer deaths by study factors among white male workers employed at Oak Ridge National Laboratory

	All-cancer deaths	Person-years
Age at risk		
<30	4	27 311
30–50	55	128 728
50–70	316	86 596
>70	186	11 771
Paycode		
Monthly	204	118 920
Non-monthly	357	135 486
Birth cohort		
<1905	115	15 670
1905–1914	184	35 927
1915–	262	202 809
Employment status		
Employed within last 2 years	112	104 832
Not employed	449	149 574
Internal monitoring status		
Not monitored	358	177 587
Monitored	197	64 169
Not eligible to be monitored (person-time and events prior to 1951)	6	12 650

Results

At the close of follow-up, 5879 (70.8%) members of the cohort were still alive, 2110 (25.4%) members had died, and 318 (3.8%) members had been lost to follow-up. Death certificates were retrieved for 98% of those known to have died, from which 561 cancer deaths were identified. The distribution of cancer deaths and person-time by study factors is presented in Table 1.

Cumulative whole body radiation dose received at all ages was associated with an estimated 1.8% (SE = 0.9; LRT = 3.8, 1 d.f.) increase in cancer mortality per 10 mSv, under a 10-year lag assumption (Table 2). Associations between cancer mortality and cumulative whole body radiation dose were of larger magnitude and better fit for doses accrued at older ages than for doses accrued at all ages. Estimated associations ranged form 4.3% (SE = 1.3; LRT = 9.6, 1 d.f.) increase in all-cancer mortality per 10 mSv for doses received after age 40, to 9.9% (SE = 3.5; LTR = 5.9, 1 d.f.) increase in all-cancer mortality per 10 mSv for doses received after age 55. The best fitting model for the association between cumulative radiation dose and cancer mortality, indicated by the largest likelihood ratio test statistic, was for cumulative doses received after age 45 (5.9% per 10 mSv; LRT = 10.6, 1 d.f.).

The association between cancer mortality and cumulative dose received after age 45 was examined using a model that adjusted for the association between cancer mortality and cumulative dose received before age 45 (Table 3). Cumulative doses received before age 45 showed little association with all-cancer mortality (–0.7% per 10 mSv; LRT = 0.3, 1 d.f.), while cumulative doses received after age 45 showed a positive association with all-cancer mortality (5.9% per 10 mSv; LRT = 9.8, 1 d.f.). This heterogeneity in

Table 2 Estimated per cent increase in all-cancer mortality per 10 mSv dose received during specified periods of age.[a] Ten-year lag assumption

	Doses received				
	After age 16[b]	After age 40[b]	After age 45[b]	After age 50[b]	After age 55[b]
% increase	1.8	4.3	5.9	6.2	9.9
(SE)	(0.9)	(1.3)	(1.6)	(2.4)	(3.5)
LRT,[c] 1 d.f.	3.8	9.6	10.6	5.6	5.9

[a] Adjusted for age at risk, birth cohort, employment status, paycode, internal radionuclide monitoring, and the interaction between paycode and birth cohort, and employment status and age at risk.

[b] Cumulative occupational whole body penetrating radiation dose received after specified age at exposure. Minimal age of employment at ORNL was 16 years.

[c] Likelihood ratio test.

Table 3 Estimated per cent increase in all-cancer mortality per 10 mSv, for cumulative doses accrued before age 45 and after age 45.[a] Ten-year lag

	Doses received	
	Before age 45	After age 45
% increase	–0.7	5.9
(SE)	(1.2)	(1.7)
LRT,[b] 1 d.f.[c]	0.3	9.8

[a] Adjusted for age at risk, birth cohort, employment status, paycode, internal radionuclide monitoring, and the interaction between paycode and birth cohort, and employment status and age at risk.

[b] Likelihood ratio test.

[c] Likelihood ratio test statistic indicating the change in deviance after dropping parameter from a model which included terms for doses accrued before age 45 and after age 45.

dose-response associations with age at exposure was evaluated statistically by comparing a model that included separate terms for radiation doses accrued before, and after, age 45 to a nested regression model that included a single term for the sum of these age-specific cumulative doses. Compared to a model with a single term for cumulative dose received at all ages, a model with separate terms for associations between cancer mortality and doses received before, and after, age 45 showed a substantial improvement in fit (LRT = 7.9, 1 d.f).

Figures 1–3 show relationships between all-cancer mortality and cumulative radiation doses (10-year lag) received before age 45 (Figure 1), after age 45 (Figure 2), and at all ages (Figure 3). The horizontal axis in each figure indicates levels of cumulative dose. The vertical axis indicates the ratio of observed to expected cancer deaths plotted on a natural log scale. The points in each Figure represent the ratio of observed cancer deaths to the number expected in each category based on its covariate specific distribution of person-time. The solid line in each Figure represents the estimated per cent increase in cancer mortality per 10 mSv cumulative dose. There do not appear to be any systematic departures of the observed/expected ratios from the fitted dose response.

We next evaluated an additive relative risk model for the dose-response relationship. Under the additive relative risk model, cumulative dose received after age 45 (10-year lag) was associated with a 7.7% (SE = 3.7; LRT = 8.2, 1 d.f.) increase in all-cancer mortality per 10 mSv. Within the range of observed cumulative doses, results were similar to the multiplicative relative risk model; however, estimated associations under the additive relative risk model and multiplicative relative risk model diverge as higher cumulative doses are considered.

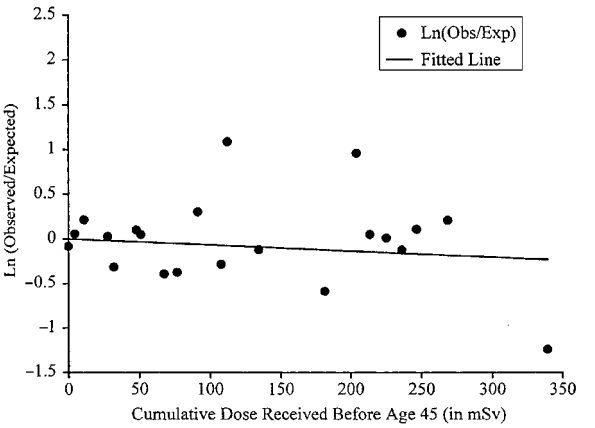

Figure 1 Ratio of observed to expected number of all-cancer deaths by level of cumulative dose received before age 45, and fitted line. Ten-year lag

–0.7% (SE = 1.2) change in cancer mortality per 10 mSv (Likelihood Ratio Test = 0.3, 1 d.f.). Adjusted for age at risk, birth cohort, employment status, paycode, internal radionuclide monitoring, paycode-birth cohort and employment status-age at risk interactions, and dose received after age 45.

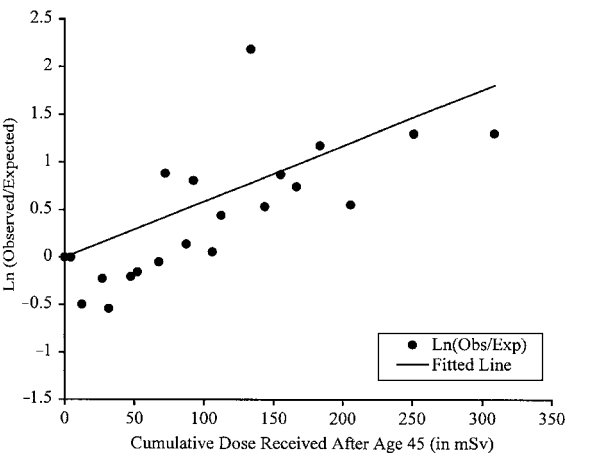

Figure 2 Ratio of observed to expected number of all-cancer deaths by level of cumulative dose received after age 45. Ten-year lag

5.9% (SE = 1.7) change in cancer mortality per 10 mSv (Likelihood Ratio Test = 9.8, 1 d.f.). Adjusted for age at risk, birth cohort, employment status, paycode, internal radionuclide monitoring, paycode-birth cohort and employment status-age at risk interactions, and dose received before age 45.

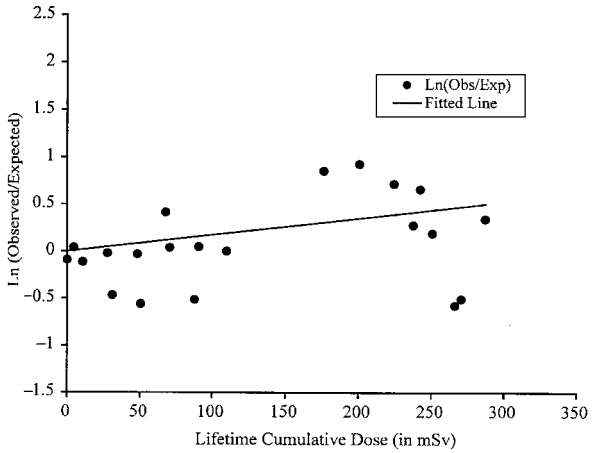

Figure 3 Ratio of observed to expected number of all-cancer deaths by level of lifetime cumulative dose. Ten-year lag

1.8% (SE = 0.9) change in cancer mortality per 10 mSv (Likelihood Ratio Test = 3.8, 1 d.f.). Adjusted for age at risk, birth cohort, employment status, paycode, internal radionuclide monitoring, paycode-birth cohort and employment status-age at risk interactions.

Several hypotheses were investigated about potential time-related factors that might account for associations between cancer mortality and doses received at older ages. First, we considered whether associations between cancer mortality and doses received after age 45 persisted across different hire cohorts, since workers hired in the early period of ORNL's operation might have been subject to health-related selection or greater exposure misclassification. Table 4 shows that the association between lifetime cumulative dose and cancer mortality was tenfold larger among workers hired between 1943 and 1947 (3.4% per 10 mSv) than among workers hired later (0.3% per 10 mSv). However, the difference in association between hire cohorts appears largely to be due to the fact that workers tended to receive exposures at older ages in the early years of ORNL's operation. Associations between cancer mortality and doses received after age 45, adjusted for doses received at younger ages, were of similar magnitude for workers hired before (5.8% per 10 mSv), and after, 1948 (4.8% per 10 mSv). A likelihood ratio test indicated little heterogeneity in radiation-cancer associations between hire cohorts when considering doses received after age 45 (LRT = 0.1, 1 d.f.).

We also considered the possibility that the larger association of cancer mortality with doses received after age 45 than with doses received before age 45 was due to a shorter latency for doses received after age 45 than for doses received before age 45. Associations between doses received before age 45 and cancer mortality, adjusted for associations between dose received after age 45, were examined under varying lag assumptions (Table 5). There was little evidence of an association between dose received before age 45 and cancer mortality under 10-, 20-, or 30-year lag assumptions. It does not appear that differences in associations between doses received at older and younger ages are due to the necessity to consider longer lag assumptions for doses received at younger ages.

Table 4 Analyses of modification of dose-response associations by period of hire. Estimated per cent increase in all-cancer mortality per 10 mSv cumulative dose.[a] Ten-year lag

	Period of hire		Likelihood ratio test for common dose-response association between periods of hire (1 d.f.)
	Before 1948	After 1948	
Lifetime cumulative dose			
% increase	3.4	0.3	3.1
(SE)	(1.1)	(0.4)	
Doses received after age 45[b]			
% increase	5.8	4.8	0.1
(SE)	(2.2)	(2.9)	

[a] Adjusted for age at risk, birth cohort, employment status, paycode, internal radionuclide monitoring, interactions between paycode and birth cohort, and employment status and age at risk.

[b] Adjusted for cumulative dose received before age 45.

Table 5 Estimated per cent increase in all-cancer mortality per 10 mSv dose received before age 45 under 10-, 20-, and 30-year lag assumptions[a]

	Doses received before age 45		
	10-year lag	20-year lag	30-year lag
% increase	–0.67	0.59	0.40
(SE)	(1.18)	(1.25)	(2.37)

[a] Adjusted for age at risk, birth cohort, employment status, paycode, internal radionuclide monitoring, interactions between paycode and birth cohort, and employment status and age at risk, and cumulative dose received after age 45.

Table 6 Analyses of modification of dose-response associations by age at risk. Estimated per cent increase in all-cancer mortality per 10 mSv cumulative dose.[a] Ten-year lag

	Age at risk		Likelihood ratio test for common dose-response association between age at risk groups (1 d.f.)
	<70 years	⩾70 years	
Lifetime cumulative dose			
% increase	0.3	5.5	7.2
(SE)	(1.1)	(1.5)	
Doses received after age 45[b]			
% increase	4.6	8.4	1.1
(SE)	(2.8)	(2.4)	

[a] Adjusted for age at risk, birth cohort, employment status, paycode, internal radionuclide monitoring, interactions between paycode and birth cohort, and employment status and age at risk.

[b] Adjusted for cumulative dose received before age 45.

We next investigated whether associations persisted for younger as well as older ages at risk (Table 6). Lifetime cumulative dose showed little association with cancer deaths occurring before age 70 (0.3% per 10 mSv) but a substantial association with deaths after age 70 (5.5% per 10 mSv). A likelihood ratio test suggested substantial heterogeneity in dose-response relationships between the two periods of age at risk (LRT = 7.2, 1 d.f.).

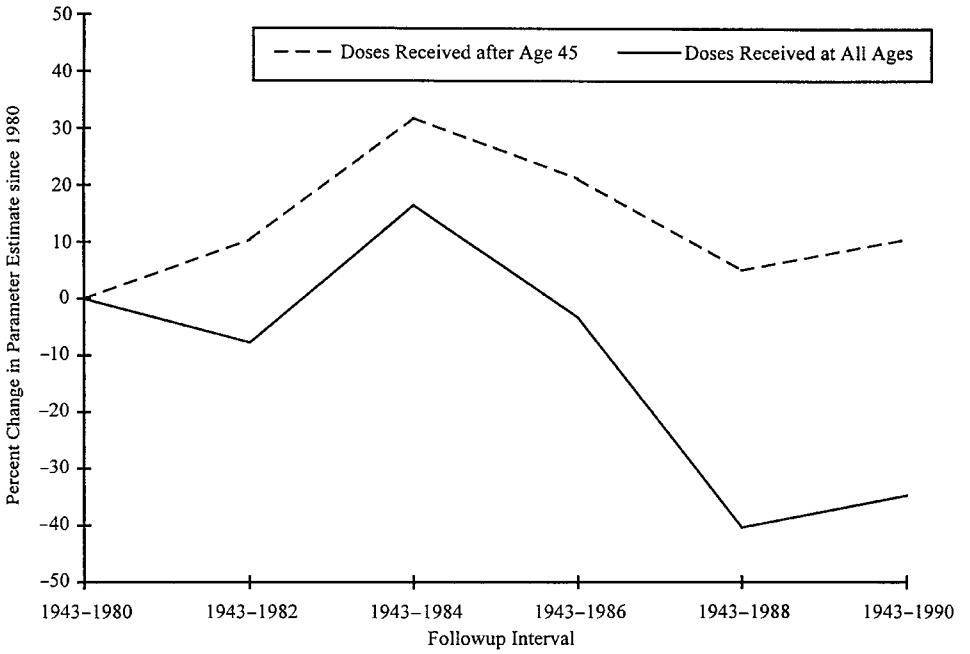

Figure 4 Relative change in estimated dose-response relationship for follow-up ending 1980–1990 for doses received at all ages, and doses received after age 45 adjusted for doses received before age 45

However, doses received after age 45 exhibited much less heterogeneity in dose-response relationships with age at risk (LRT = 1.1, 1 d.f.). Doses received after age 45 were positively associated with cancer deaths before age 70 (4.6% per 10 mSv, SE = 2.8), and after age 70 (8.4% per 10 mSv, SE = 2.4).

Finally, we considered whether associations between cancer mortality and radiation doses received after age 45 persisted over different periods of follow-up of the ORNL cohort. Figure 4 shows the per cent change in these dose-response estimates with follow-up. The vertical axis indicates the per cent change in the dose-response estimate relative to the estimate derived for the period 1943–1980; the horizontal axis shows the period of follow-up over which the dose-response associations were calculated. With inclusion of the most recent years of follow-up, the dose-response association between all-cancer mortality and lifetime cumulative radiation dose under a 10-year lag assumption declined from 2.7% per 10 mSv for follow-up through 1980 to 1.8% per 10 mSv for follow-up through 1990 (Figure 4). In contrast, doses received after age 45 showed relatively more stable associations with cancer mortality over the period of follow-up, changing from 5.6% per 10 mSv (SE = 1.4) for follow-up through 1980 to 5.9% per 10 mSv (SE = 1.7) for follow-up through 1990. This suggests that the instability of the parameter estimate for doses received at all ages reflected, in part, the changing distribution of ages at which exposures occurred.

Discussion

We examined the association between occupational exposure to external penetrating ionizing radiation and cancer mortality among workers at ORNL, and variation in this association depending on the ages at which doses were accrued. Using methods similar to those typically used to investigate latency, we evaluated the hypothesis that doses received at younger ages were aetiologically less relevant to cancer mortality than doses received at older ages.[16,38] When examining doses received at older ages, radiation-cancer associations increased in magnitude, improved in fit, and were more consistent between periods of hire, age at risk, and follow-up, compared to associations for doses received at all ages.

We previously reported a 3.4% increase in all-cancer mortality per 10 mSv cumulative dose under a 10-year lag assumption, based on follow-up of workers through 1984.[6] With additional follow-up, the magnitude of the association between lifetime cumulative dose and cancer mortality has diminished; however, this may reflect the changing distribution of ages at which exposures were accrued by these workers (Figure 4). Our previous analyses did not consider age at exposure.

Radiation doses at ORNL were previously reported to be strongly associated with cancer deaths occurring at older ages, but not with cancer deaths occurring at younger ages.[8,37] Gilbert *et al.* suggested this might reflect a pattern of bias in which cigarette smoking, or some other confounding factor, was associated with higher radiation doses among workers born in earlier historical periods.[37] Patterns of association with age at risk and age at exposure are difficult to untangle. However, in our analyses, when doses received after age 45 were considered, there was less evidence of heterogeneity in associations between radiation dose and cancer deaths before and after age 70 than for doses received at all ages (Table 6). If smoking or other occupational exposures were to explain the findings for age at

exposure reported here, they would have to be associated with doses received at older ages, but not with doses received at younger ages, and this pattern of bias would have to persist between early and later periods of hire (Table 4).

This report focused on all-cancer mortality because ionizing radiation can cause cancer at most sites, external radiation exposures were to the whole body, and numbers of site-specific cancers were insufficient for investigation of other time-related factors. Additionally, results for all-cancer can be compared to findings from numerous previous studies of this cohort.[4–10] Increased numbers of cancer deaths over a broad range of doses will occur as this cohort ages, and larger numbers of deaths will permit more detailed investigation of variation in radiosensitivity for different types of cancer according to age at exposure. We have reported elsewhere, for a larger cohort of ORNL workers including women and men who were employed at other DOE facilities, that age at exposure patterns are similar for lung cancers and cancers other than lung.[20,21]

Analyses in this paper examine white male workers at ORNL who had relatively complete annual external dosimetry records.[22,23] Attention has been given to potential problems of external radiation dosimetry at ORNL, particularly in the early years of operation.[22–24,39] While limitations of the available radiation dosimetry data are an important consideration, analyses in this paper address these concerns, in part, by examining radiation-cancer associations separately for workers hired in earlier, and later periods of ORNL's operation (Table 4). We report positive associations between all-cancer mortality and radiation doses received after age 45 for workers hired in both historical periods. A recent analysis of workers at ORNL and the Oak Ridge Y-12 plant showed that adjustment of pre-1960 doses for one component of potential measurement error had little effect on dose-response estimates for ORNL workers.[9]

Our analyses presented a simple statistical evaluation of the differences with age at exposure in radiation-cancer associations. The fit of a model for the association between cancer mortality and cumulative dose received at all ages was compared to the fit of a model which allowed the effect of radiation to depend on whether doses were received before or after age 45. A large improvement in the fit of the model describing the radiation-cancer association was observed (LRT = 7.9, 1 d.f.). These findings support Stewart and Kneale's conclusion that sensitivity to the carcinogenic effects of low-level radiation increases at older adult ages of exposure.[40]

Such findings, however, are at odds with conclusions drawn from the Life Span Study (LSS) of atomic bomb survivors. National and international committees have concluded that after childhood the relative effect of radiation is either uniform or declines with age at exposure.[1,41] Some researchers have cautioned against uncritical evaluation of findings from the LSS for understanding the effects of low-level radiation; LSS data may suffer substantial exposure misclassification, as well as selection bias, which could affect understanding of patterns of risk with age at exposure.[42–46]

In contrast, a case-control study of lung cancer at four uranium processing facilities reported excess lung cancer associated with low-level external radiation dose only among workers first exposed after age 45.[47] Among Hanford workers, stronger associations between radiation and cancer mortality have been reported for doses received at older ages at exposure.[48] Also, a cohort study of nuclear workers at the Santa Susana Field Laboratory reported that associations between low-level external radiation and mortality due to all-cancer, lung cancer, and solid tumours at radiosensitive sites were strongest when examining doses received after age 50.[49]

A pooled analysis of radiation-cancer associations among workers at seven nuclear facilities, however, reported no association between radiation and all-cancer mortality, and little difference in effect with age at exposure.[50] While pooled analyses may examine large numbers of workers, such analyses combine data that are heterogeneous in quality and completeness, from facilities involved in a variety of processes. As Cardis *et al.* reported, dose-response associations in their pooled analysis exhibited substantial variation between cohorts.[50] Kneale and Stewart reported that radiation-cancer associations increased with age at exposure at each of the facilities they examined, although heterogeneity in associations suggested pooling data would be inappropriate.[10] Similarly, pooling of data for ORNL and the Y-12 facility also appeared to be a problem due to poorer measurement of exposures at Y-12 than at ORNL prior to 1960.[9]

Some studies of people medically treated by irradiation have suggested greater sensitivity to radiation for exposures received at older adult ages. Studies of ankylosing spondylitis patients report that the relative risk of leukaemia following radiation therapy was largest for those patients first treated at ages over 45 years; 'for deaths certified as due to acute myeloid leukaemia the relative risk increased with increasing age at exposure.'[51] Studies of people treated by irradiation for metropathia haemorrhagica have reported that standardized mortality ratios for leukaemia and cancers of pelvic sites were larger for patients first treated by irradiation at older ages.[52] Inskip *et al*. also noted that among women treated for uterine bleeding standardized mortality ratios for leukaemia were higher among women treated after age 50 than for women treated at younger ages.[53] Although women were not included in these ORNL analyses, it may be noted that studies of the association between low-level radiation and breast cancer, in contrast, have reported that associations decreased with older age at exposure.[54]

Occupational exposures at ORNL other than radiation should receive attention; however, in previous analyses neither examination of job titles, which were used as an indicator of occupational exposures other than radiation, nor evaluation of potential exposure to beryllium, lead, and mercury, substantially changed estimates of the association between radiation and cancer mortality.[7] We adjusted estimates of radiation-cancer associations for potential internal exposure to radionuclides; this had little effect on our findings. While data from internal exposure monitoring provide only a poor indicator of exposure to radionuclides, internal contamination was expected to be uncommon at ORNL. With the exception of age at risk, the demographic and employment factors included in these regression models exerted little influence on estimated associations between external radiation and cancer mortality.

These findings raise important considerations for protection of workers and the public from radiation exposures. Associations between cancer mortality and radiation doses received after age 45 reported in this study are more than an order of magnitude larger than estimates derived from the Life Span Study of atomic bomb survivors. Although findings from this

occupational cohort study, like findings from all epidemiological studies, may suffer various biases, studies of this ORNL cohort deserve particular attention because of the high levels of individual radiation exposure monitoring and the relatively complete long-term follow-up. Evidence of variation in sensitivity to the carcinogenic effects of radiation exposure may be particularly important for future investigations. A common observation in occupational studies is that workers become more vulnerable to the harm caused by injury and occupational exposures as exposures are received at older adult ages. Sensitivity to the carcinogenic effects of ionizing radiation might be expected to follow this pattern; as we age, the ability of the body to correctly repair cellular damage declines, the immune system becomes less efficient, and the body accumulates exposures which may influence carcinogenic processes.[12–15,40] Since ionizing radiation is a widespread occupational, environmental, and medical exposure, a better understanding of the risks associated with low-level exposure, and a better understanding of the potential variation within populations in vulnerability to radiation, is important to evaluations of the use of technologies that lead to increased radiation exposure.

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