Time-Factors in Exposure Effects among Uranium Workers

Final Report

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ABSTRACT

The Oak Ridge, Tennessee Y-12 plant has operated as a nuclear materials fabrication plant since the 1940s. Given the work environment, and prior findings that lung cancer mortality was elevated among white male Y-12 workers relative to US white males, we investigated whether lung cancer mortality was associated with occupational radiation exposures. We identified a cohort of 3864 workers hired between 1947 and 1974 who had been monitored for internal radiation exposure. Vital status was ascertained through 1990. Over the study period 111 lung cancer deaths were observed. Cumulative external radiation dose under a 5-year lag assumption was positively associated with lung cancer mortality (0.54% increase in lung cancer mortality per 10 mSv, se=0.16, likelihood ratio test [LRT]=5.84, 1 degree of freedom [df]); cumulative internal radiation dose exhibited a highly-imprecise negative association with lung cancer mortality. The positive association between external radiation dose and lung cancer mortality was primarily due to exposure occurring in the period 5-14 years after exposure (0.97% increase in lung cancer mortality rate per 10 mSv, se=0.28, LRT=6.35, 1 df). The association between external radiation dose and lung cancer mortality was negative for exposures occurring at ages <35 years and positive for exposures occurring at ages 35-50 years and 50+ years. Conclusions about the relationship between occupational radiation exposures and lung cancer in this population, however, are constrained by the uncertainties in external and internal radiation dose estimates, the lack of information about exposures to other lung carcinogens, and the limited statistical power of the study.

SIGNIFICANT FINDINGS

In a previous study that examined mortality among white male Y12 workers who were followed through 1979, Checkoway et al. reported that these workers had lower all-cause mortality rates than the general U.S. population, but had higher lung cancer mortality rates and higher rates of brain cancer and other lymphopoietic system cancer mortality. In those analyses, there was evidence of a positive association between external (but not internal) radiation dose and lung cancer mortality; and, when examining the joint effects of external and internal radiation exposures, lung cancer rate ratios were most elevated among workers who accrued 5+ rem of external and 5+ rem of internal dose.

With 11 additional years of follow-up, there remains evidence of a positive association between external radiation dose and lung cancer mortality in this cohort. When examining the joint effects of external and internal radiation exposures, lung cancer rate ratios are most elevated among workers who accrued 5+ rem of external and 5+ rem of internal dose. The radiation dose-lung cancer association is primarily due associations between radiation dose and lung cancer in the period 5-14 years after exposure; there was minimal evidence of association with doses accrued in the periods 15+ years after exposure. There was evidence of variation in radiation-lung cancer associations with age at exposure; doses accrued at older adult ages were positively associated with lung cancer.

TRANSLATION OF FINDINGS

These findings add to the occupational literature on risks of chronic exposure to low-level ionizing radiation. Methods for analyzing age at exposure will be useful for future studies. Further analyses of variation in radiation risks with time-since-exposure and age-at-exposure may be useful for informing implementation of the Energy Employees Occupational Illness Compensation Program Act [1,2].

SCIENTIFIC REPORT

A. Background

This project aimed to improve the methods used to evaluate the effects of latency, time-since-exposure, and age-at-exposure in studies of repeated or chronic occupational exposures. These methods may help to reduce exposure misclassification by better identifying the etiologically-relevant time period of exposure, and improve the understanding of variation between study subjects in susceptibility to the effects of an exposure by examining age-at-exposure. We applied these methods to analyses of radiation-lung cancer mortality associations among workers employed at the USDOE Y12 facility. We made use of previously collected vital status and cause of death information, and previously developed radiation dose estimates.

B. Specific Aims

This research project addressed the following specific aims:

1. Evaluation of lag assumptions. Radiation-mortality associations were calculated under a range of lag assumptions, with the best fitting lag period directly estimated.

2. Simultaneous evaluation of lag and time-since-exposure. Time-dependent exposure weighting functions were used to evaluate variation in exposure-disease associations with time-since-exposure. These methods allowed description of variation with time-since-exposure in associations between radiation and mortality in this cohort of uranium processing workers.

3. Investigation of age at exposure. We developed weighting functions to evaluate the effects of age-at-exposure, and estimated parameters for these weighting functions.

C. Methods

A cohort was assembled of all Y-12 workers hired after Union Carbide assumed management of the facility in 1947, who were employed at least 30 days between 5/4/1947 and 12/31/1974. When Union Carbide assumed management of the facility there was a major turnover of personnel and the production emphasis shifted from uranium enrichment to nuclear materials fabrication [3]. Therefore, as in prior studies, workers were excluded if there was an indication of employment at the Y-12 plant prior to 5/4/1947 or at any other US Department of Energy nuclear facility [4]. All workers in the study cohort were over 15 years of age at hire and less than 100 years old at end of follow-up.

Internal radiation doses

Internal exposure to ionizing radiation was primarily in the form of alpha radiation from uranium isotopes, with the primary route of exposure being inhalation of airborne uranium dust. Annual lung dose estimates for Y-12 workers were based on *in vivo* monitoring and urinalysis results. Routine urinalysis monitoring for internal exposure increased in coverage through the 1950s as departments with exposure potential were phased in to the urinalysis program (Figure 1). In 1961, *in vivo* monitoring became an additional part of the radiation monitoring program. Information about the degree of uranium enrichment was incorporated into the conversion of *in vivo* counting results to lung dose equivalents. Crawford-Brown et al. have report previously on the methods used to calculate these lung dose estimates [5]; these methods were based on metabolic and dosimetric models published by the International Commission on Radiological Protection (ICRP) in Publication 30 [6]. Typically, the calculations of lung burden assumed that the uranium compounds of primary concern were characterized as class W particles under the framework of ICRP 30, based upon evidence that the mean ratio of uranium excretion rate in urine divided by the lung uranium burden for the set of individuals in which both measurements were available on the same day was consistent with what one would calculate assuming continuous exposure to uranium with a clearance half-time just slightly larger than class W but not as long as class Y [7]. However, for some individuals, time series measurements of lung content were available that allowed direct estimation of their clearance half-times. In these cases, this direct estimate of clearance half-time, rather than the class W default, was used. While there have been significant developments in metabolic and dosimetric models since the release of Publication 30, with revised models detailed in ICRP Publication 78, lung dose estimates derived using these newer models were not available for our analyses [8].

Estimated values for lung dose from internal deposition were derived for unmonitored employment-years (58% of employment-years) by using available lung dose information belonging to the same individual for a neighboring year, or if this was not possible, by assigning an annual lung dose estimate based upon information about the worker's exposure potential given the department in which they were employed during the calendar year [5,9]. We refer to these as employment-years with imputed internal radiation dose values. As in previous analyses of radiation dose-cancer mortality associations among Y-12 workers [3], people who were never monitored for internal exposure were excluded from analyses of radiation dose-mortality associations. This exclusion was done in order to reduce bias due to exposure misclassification and because health-related screening or selection into employment may be related to whether or not a worker was included in the internal dosimetry program. Nonetheless, problems of misclassification of subjects with respect to internal dose level may be substantial because monitoring data were incomplete for many workers and, even with historical monitoring data, the internal dose estimation process resulted in lung dose estimates that have substantially uncertainty [5,10].

External radiation doses

Individual monitoring for external radiation exposure began in 1948 although external dose data were not available for most employment-years prior to 1961. In 1961 Y-12 adopted a policy of plant-wide monitoring for external radiation exposure; prior to that time, the policy at Y-12 was to monitor only those workers judged to have a reasonable potential for occupational radiation exposure. Monitoring was based on film badge dosimetry until the late 1970s when thermoluminescent dosimeters were used. There was low potential for occupational neutron

exposure; workers who were judged to have neutron exposure potential were monitored via neutron track, type A emulsion in a film dosimeter, and later by neutron TLDs [11,12].

For the period 1947-1960, external radiation dose estimates were derived for unmonitored employment-years by assigning a standard annual dose based upon the exposure potential of the employee's department [10]. For the period 1961-1985 estimates were derived for employment-years with missing annual external radiation dosimetry information using dose estimates for nearby time periods [9]. We refer to these as employment-years with imputed external radiation dose values.

Individual-level information about the geometry of irradiation and the photon energies for external exposures was not available for this study; such information is needed to derive estimates of lung dose from external radiation monitoring results [13]. We made the simplifying assumption that irradiation of the lung from external sources was the result of photons with energies in the range of 30-250 keV, with exposure occurring in an anterior-posterior geometry; under these assumptions, lung dose estimates for external exposure were derived by applying a lung dose conversion factor of 0.99 to the external penetrating radiation dose of record [11,14,15].

Computerized records of internal and external radiation lung dose estimates were constructed for each year of employment during the period 1947-1985 for each worker in this study. External dose estimates were expressed as equivalent doses and are reported in this paper in milliSievert, mSv (where 1 rem is equivalent to 10 mSv). Internal dose estimates were expressed in units of

rad. As in previous analyses of this cohort [3] a radiation weighting factor of 10.0 was assumed for alpha radiation in order to express internal dose estimates as equivalent doses.

Vital status and cause of death information

Vital status as of December 31, 1990, was determined by searches of the National Death Index, records of the Social Security Administration, the Health Care Financing Agency, the Tennessee Department of Motor Vehicles, a credit and pension benefits research group, as well as personnel and benefits and obituaries (Table 1). 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 eighth revision of the International Classification of Diseases adapted for the United States (ICDA-8).

Our analyses focused on relationships between radiation doses and lung cancer mortality, defined to include any death for which an ICDA-8 code of 162 appeared as an underlying or contributory cause. Information on smoking histories for these workers was not available. Therefore as an indirect method for evaluation of potential confounding of radiation dose-lung cancer mortality associations by cigarette smoking we examined associations between radiation dose and two other tobacco-related categories of cause of death: smoking-related cancers other than lung (any worker who had an underlying or contributory cause of death assigned ICDA-8 codes of 140-151, 155.0-155.1, 157, 160-161, 180, 188, 189.0-189.2 and did not have an underlying or contributory cause assigned to ICDA-8 code162) and non-malignant respiratory diseases (any worker who had an underlying cause of death assigned ICDA-8 codes 460-519).

Statistical methods

Analyses were conducted using a nested case control approach. Risk sets were formed by incidence density matching of cases (lung cancer deaths) to non-cases on attained age.[16] For each case, a risk set was formed that included all workers who were alive and eligible to be in the study at the attained age of the index case. A selection date was defined for each subject. For a case this was the date of death; and, for controls in a risk set this was the date at which the subject attained the age of the index case. Controls were also matched to cases on year of birth (in eight 5-year groups from <1905 to 1935+), sex, race (defined as Black versus other), socioeconomic status (based upon the worker's pay schedule at hire, and defined in the following categories: hourly; weekly; and monthly), length of employment as of the selection date (<365 days versus 365+ days), and employment status on the selection date (defined as active, terminated within the last two years, or terminated two or more years prior, cross-classified by age at termination <62, and 62+ years). The first four factors were included in regression analyses in order to provide control for potential confounding by these socio-demographic characteristics. Length of employment was included in regression analyses in order to control for previously reported findings of elevated mortality rates among short-term workers (i.e., those employed for less than one year) [17]. Employment status was included in regression analyses in order to minimize potential bias due to the healthy worker survivor effect [18].

Conditional logistic regression was used to evaluate associations between case status and radiation exposure history; regression analyses were conducted via SAS PHREG [19]. All employment and exposure history information was truncated as of the subject's selection date. A stratified logistic regression model was used. Assuming the study data are divided into K strata

indexed by k=1…K, this model takes the form $\text{logit}(R_k(x))=\alpha_k+x\beta$, where $\text{logit}(R_k(x))$ is the log odds of mortality in stratum k at cumulative radiation dose level x and α_k is the stratum-specific log odds of mortality when x=0. Since we are analyzing density-sampled case-control data, the estimated coefficient $\hat{\beta}$ from the logistic model fitting is interpretable as an estimate of the change in the log rate ratio per unit increase in x, and the results are discussed as such. As in prior analyses of these data, estimates of rate ratios were calculated with a referent category defined as <10 mSv of internal and/or external radiation dose [3]. Analyses were also conducted in which cumulative dose level was treated as a continuous variable; in the latter analyses parameter estimates for the radiation dose effect have been multiplied by 100 to yield an estimate of the log percentage change in mortality rate 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 chi-square distribution with one degree of freedom (df); larger values indicate a better fit of the regression model to the observed data.

The approach of time-window analysis was used to investigate variation in radiation exposure effects with time-since-exposure (i.e., to investigate the effects of exposures accrued at specified time intervals preceding the date of case occurrence or the selection date for controls). Separate regression parameters were included for cumulative doses accrued within the following exposure time windows: 5-14 years, 15-24 years, and 25+ years prior. Using a similar approach we investigated age-at-exposure; in these analyses time windows were defined for exposures accrued at ages <35, 35-49, and 50+ years. Boundaries for time-windows were defined a priori in ranges that were broad enough to allow accrual of doses at low annual dose rates. Since vital status follow-up was through 1990, while dosimetry data were only available through 1985, all

analyses concern a minimum of a five year exposure lag assumption (i.e., exposures accrued in the five years preceding the date of case occurrence, or the selection date for controls, were excluded from all analyses).

Modeling temporal variation in radiation risk

The focus of these analyses was on temporal patterns of variation in radiation-lung cancer mortality associations. Let's say that y_j denotes the case status of individual j in a risk set that is matched on attained age A. The radiation exposure history for each worker was recorded as a radiation dose estimate for each calendar year of observation. We assigned an age-at-exposure, a, to each calendar year based on the worker's age at the midpoint of the calendar year. Therefore, the array $x_j(a)$ indexes the radiation dose accrued by individual j at age, a. The summation of these doses up to attained age A, $\sum_{a=1}^{A} x_j(a)$, is the total cumulative dose accrued by individual j.

We began by investigating whether the relative effect of exposure varied with time-since-exposure. An exposure weighting function, $w(t)$, was used to express this variation, with the time-scale, t, defined as the difference between a worker's attained age, A, and their age when an increment of exposure occurred, a.

A piecewise constant model (i.e., a model for time-window analysis) was used in order to provide simple description of the pattern of variation in radiation exposure effects with time-since-exposure. A separate regression parameter was included for the cumulative dose accrued

within each of the following exposure time windows: 5-<15 years, 15-<25 years, and 25+ years prior to the age at which risk was being estimated. Specifically, we applied a piecewise-constant model of the form

$$\text{logit Pr}(y_j=1|z_j, x_j(a)) = \beta_0 + \beta_1 \sum_{a=1}^{A} I[t<15]x_j(a) + \beta_2 \sum_{a=1}^{A} I[15<=t<25]x_j(a) + \beta_3 \sum_{a=1}^{A} I[t>=25]x_j(a),$$

where I["logical expression"] which equals 1 if "logical expression" is true and 0 if it is false. Parameter estimates β_1- β_3 describe the change in the log of the relative risk per 10 mSv dose, for cumulative radiation doses accrued in time windows defined by <15, 15-<25, and 25+ years since exposure, respectively.

The value $[100(\hat{\beta}_1)]$ provides an estimate of the (log) percent change in mortality risk per 10 mSv dose in the first time window under an exponential relative risk model. At low doses, this value approximates the estimate of excess relative risk per Sv (ERR/Sv) that would be derived under an additive relative risk model [20]. One advantage of using an exponential relative risk model is that parameter estimates are not constrained (as they are when using an additive relative risk model), thereby reducing problems with model convergence and estimation of confidence intervals.

A SAS program was written in order to calculate the cumulative effective dose for each study member at specified values for the parameter(s) defining $w(t)$ [21]. Conditional logistic regression models were fit to these data using SAS PHREG in order to estimate the association between cumulative effective dose and cancer mortality [19].

A piecewise constant model was also developed to investigate age at exposure effects; in these analyses time windows were defined by ages <35, 35-<50, and 50+ years. In these analyses the timescale, t, for the exposure weighting function was age-at-exposure (i.e., the age when an increment of exposure occurred, a).

D. Results

Table 1 reports the distribution of workers with respect to vital status, and the numbers of deaths due to lung cancer, smoking-related cancers other than lung, and non-malignant respiratory disease. Nearly a quarter of the cohort has been followed until death, and the percentage of workers lost to follow-up is extremely low (<1%).

Figure 1 shows the percentage of workers monitored for external and internal radiation exposure by calendar year; note that the study period extended through 1990 while dosimetry data were only available through 1985. Prior to 1961, the majority of Y-12 workers were not monitored for external radiation exposure; in more recent years, however, external monitoring data were available for nearly all workers in this cohort. Internal monitoring of the work force was incomplete in all years of study. Less than half of the employed workers at Y12 had internal monitoring data available for the years prior to 1958 and after 1965.

Table 2 reports estimates of lung cancer mortality rate ratios for categories of cumulative external and internal lung dose under a 5 year exposure lag assumption. When examining categories of cumulative external lung dose, the estimated rate ratio was less than unity for the

exposure category defined by 10-49.9 mSv, and greater than unity for the exposure category defined by 50+ mSv cumulative dose when compared to the referent group (defined by the category of <10 mSv external dose). When considering cumulative internal radiation dose, rate ratio estimates were greater than unity for categories defined by 10-<50, 50-99.9, and 100+ mSv cumulative dose when compared to the referent group (defined by the category of <10 mSv internal dose). For neither external nor internal radiation dose was there evidence of a montonic trend in lung cancer mortality rates across cumulative dose categories. As shown in Table 2, the distribution of lung cancer deaths was highly skewed towards the lowest categories of cumulative external radiation dose; only seven lung cancer deaths were observed among workers who accrued 50+ mSv cumulative external dose (assuming a five year exposure lag assumption).

Table 3 presents the results of analyses examining the joint effects of external and internal exposures. Compared to the referent group (defined by the category of <10 mSv external and internal dose), rate ratio estimates were greater than unity for each group defined by higher cumulative levels of internal and/or external dose. The rate ratio estimate for the category defined by 50+ mSv external dose and 50+ mSv internal dose was 2.23 (based on 7 lung cancer deaths).

Table 4 reports dose-response trend estimates that were obtained by fitting a regression model with continuous terms for cumulative external radiation dose and cumulative internal radiation dose. In analyses of lung cancer mortality, a positive dose-response trend was observed for cumulative external radiation dose. The dose response coefficient for cumulative internal radiation dose is negative but contributes little to the fit of the regression model (LRT=0.85, 1

d.f.). As suggested by the analyses of rate ratios in categories of cumulative dose (Table 2), the overall trend in lung cancer mortality with cumulative external dose is largely due to a small number of excess lung cancer deaths among those who accumulated 50+ mSv external dose.

In analyses of mortality due to smoking-related cancers other than lung, negative associations were observed with cumulative external and cumulative internal radiation doses. Similarly, for analyses of non-malignant respiratory disease mortality, negative associations were observed with cumulative external and cumulative internal radiation dose; however, these dose terms contributed very little to model fit. Table 4 also reports the mean and maximum cumulative external and cumulative internal lung radiation doses. The mean cumulative external lung dose was approximately four-fold lower than mean cumulative internal dose; however, the maximum cumulative external dose (5.9 Sv) was substantially higher than the maximum cumulative internal lung dose (3.0 Sv).

Table 5 reports trend analyses conducted using the exposure time-window method for evaluation of variation in exposure effects with time-since-exposure. The overall association between external radiation dose and lung cancer mortality was primarily due to an association with doses accrued in the period 5-14 prior. External doses occurring 15-24 years since exposure were negatively associated with lung cancer mortality while doses accrued in the period 25+ years since exposure were positively associated with lung cancer. Internal radiation doses accrued in all three exposure time windows were negatively associated with lung cancer mortality. Time-window-specific estimates of association were highly imprecise in all analyses of mortality due to smoking-related cancers other than lung and mortality due to non-malignant respiratory

disease. The last row of Table 5 reports the percentage of employment-years for which there are imputed external and internal radiation doses. For estimates of cumulative exposures accrued 5-14 and 15-24 years ago, external radiation dose values were imputed for 10% of employment-years; in contrast, estimates of cumulative external dose accrued 25+ years ago are based primarily on imputed dosimetry information. Information on internal exposure was highly incomplete (over 50% of employment-years had imputed doses) in all risk periods.

Time-window analyses were also used to explore variation in the radiation dose-lung cancer risk association with age-at-exposure (Table 6). External radiation doses accrued at ages <35 years were negatively associated with lung cancer mortality, while doses accrued at ages 35-49 years and 50+ years were positively associated with lung cancer mortality; associations between internal dose and lung cancer mortality were negative and highly imprecise for all three time-windows defined by age at exposure. External radiation doses accrued in each age window were negatively associated with mortality due to smoking-related cancers other than lung. When examining non-malignant respiratory disease, doses accrued at ages <35 years of age exhibited a positive association; associations were negative for doses accrued at ages 35-49 and 50+ years.

E. Discussion

There is evidence of a positive association between cumulative external radiation dose and lung cancer mortality; and, in analyses of the joint effects of internal and external radiation doses in relation to lung cancer mortality, the highest mortality risk was observed for workers who accrued 50+ mSv cumulative external dose and 50+ mSv cumulative internal dose. The analyses of the joint effects of external and internal dose, however, result in highly-imprecise risk

estimates. The results derived from these analyses of updated cohort data for the Y-12 cohort are consistent with those findings reported previously by Checkoway et al (1988). In their prior analysis of this cohort, Checkoway et al. noted that the trend in lung cancer mortality rates with cumulative internal radiation dose under a 0-year lag was not monotonically increasing, although estimated rate ratios were elevated for the dose groups 10-49.9 mSv, 50-99.9 mSv and 100+ mSv relative the referent group (<10 mSv). Similarly, with updated follow-up we noted the lack of a monotonic trend in estimated lung cancer rates with cumulative internal dose under a five-year lag but did observe elevated rate ratio estimates for all exposure groups >=10 mSv internal dose.

The absence of evidence of a positive dose-response trend in analyses of internal lung dose and lung cancer mortality (in contrast to evidence of a positive trend with external lung dose) is notable given the greater magnitude of internal than external dose estimates. In part this discrepancy may be a consequence of relatively greater measurement error in the estimation of internal lung doses than external lung doses. Derivation of internal lung dose estimates from historical bioassay, *in vivo*, and air monitoring results involved numerous assumptions about the exposures and their relevant biokinetics. Furthermore, a large proportion of employment-years have imputed internal lung dose values (as opposed to lung dose estimates derived from historical measurements); and, some workers had exposures to radionuclides other than uranium (including transuranic elements and fission products in recycled uranium at the Y-12 facility) that may increase the error in our lung dose estimates [7,22]. Of course, the external dose estimates for Y-12 workers also suffer substantial uncertainty, particularly for external exposures in the period prior to 1961 when coverage of the work force by the external monitoring program was much less complete [11]. Another possible explanation of a lack of positive dose response for

internal radiation and lung cancer, including negative estimates, is selection of healthier workers into jobs with higher potential for internal uranium deposition. At Department of Energy's Hanford nuclear weapons plant, workers received additional medical tests prior to being placed in special hazard jobs. A similar employer- or self-selection process could contribute to our observations.

A primary focus of these analyses was on temporal variation in lung cancer mortality risk following radiation exposures at the Y-12 facility. Previous research suggests that the effects of ionizing radiation exposure on lung cancer risk may vary with time-since-exposure [23,24 Hauptmann, 2001 #3908]. Our time-window analyses of the association between cumulative external dose and lung cancer mortality suggest that the association between external radiation dose and lung cancer mortality peaks and subsequently diminishes with the continued time-since-exposure, however, the ability to detect associations with doses greater than 25 years in the past is compromised by the lack of individual external dosimetry records for 76% of this cohort. The temporal patterns in external radiation dose-lung cancer mortality associations with time-since-exposure observed in this study are similar to observations drawn from other epidemiological studies [24,25].

We also investigated variation in radiation dose-lung cancer mortality associations with age-at-exposure. Age at exposure has been noted as a potentially-important effect modifying factor in several previous studies of uranium workers. A case control study of lung cancer among uranium processing workers at four facilities (Y-12, TEC, Mallinckrodt, and Fernald) reported little evidence of association with either internal or external radiation dose estimates. The authors

of that study reported that there was a suggestion of association among workers hired at older ages [26]. A cohort study of workers at the Fernald uranium processing plant reported evidence of excess lung cancer mortality among workers with the highest accrued internal radiation doses, after adjustment for external doses, and in analyses of the joint effects of internal and external dose [27]. The author reported that the strongest associations were among workers exposed externally after age 40 years. We found that the effects of radiation dose on lung cancer mortality were primarily due to associations with doses occurring at ages 35-49 years.

The magnitudes of the effect estimates in these analyses of lung cancer mortality among Y-12 workers are small enough that the observed associations could, in principle, be due to confounding by cigarette smoking. We attempted to address concerns about smoking as a potential confounder indirectly in these analyses by examining associations between radiation dose and mortality from smoking-related cancers other than lung and non-malignant respiratory disease. We recognized that the work environment at Y-12 involves dust exposures that could lead to non-malignant respiratory disease, and therefore were cautious in our interpretation of findings for non-malignant respiratory disease since evidence of a positive association could be indicative of either confounding by smoking or occupational dusts. However, we found no evidence of a positive association between cumulative external or internal dose and mortality from smoking-related cancers other than lung (Table 4-6). Similarly, mortality from non-malignant respiratory disease was negatively associated with radiation doses in most analyses; the only positive association of note was for external radiation dose at ages 15-34 years, an exposure time-window in which doses were negatively associated with lung cancer mortality. Rather than leading to spurious evidence of positive associations between occupational radiation

exposure and lung cancer mortality, these findings suggest that cigarette smoking may be a weak negative confounder of associations between radiation exposure and lung cancer mortality in this cohort. Employment at Y-12 also involved potential occupational exposures to carbon dust, solvents, lubricants, nitric acid, hydrogen peroxide and fluoride, and chlorinating agents [10]. Unlike radiological exposures, individual exposure estimates for these non-radiological occupational exposures are not available. It is possible, therefore, that the observed association between estimates of external radiation exposure and lung cancer mortality is confounded by non-radiological occupational exposure effects.

Evidence of temporal patterns in cancer risk following exposure to a carcinogen provide a potentially useful starting point for drawing inferences about the stage(s) upon which the carcinogen acted [28]. Peto et al., for example, used this approach for interpretation of results of analyses of mesothelioma mortality in asbestos workers, concluding that mesothelioma arises from a multistage process with asbestos affecting an early stage [29]. Similarly, Kaldor, Peto et al. interpreted dose-time-response patterns for respiratory cancer among South Wales nickel refinery workers in relationship to patterns predicted by multistage models [30]. The observed temporal patterns in radiation effects in this cohort of uranium workers (i.e., evidence of diminishing exposure effects with protracted time-since-exposure and relatively greater effects of exposures occurring at older ages) are consistent with exposure to a carcinogenic agent that acts at a late stage in a multistage process of carcinogenesis. However, further exploration of temporal patterns (or direct fitting of multistage models) is not reasonable given the substantial limitations of these data, which include poor historical records with which to derive internal and external dose estimates, the relatively small size of this radiation-monitored cohort, the reliance

upon information on cause of death as a proxy for cancer incidence, and the lack of information about exposures to non-radiological lung carcinogens.

Although it is common in the discussion of findings from studies of nuclear workers to focus the interpretation of results on quantitative risk assessments, drawing comparisons to estimates of the change in cancer risk per unit radiation dose derived from other populations, we have opted not to focus on that approach to interpretation of these data. Given the limitations of these data, this study provides a weak basis for quantitative risk estimation. Rather than conducting these analyses for such purposes, our analyses were motivated by an interest in evaluating whether prior epidemiological findings of excess lung cancer mortality (and suggestive associations with occupational exposure to ionizing radiation) were observed in analyses that applied contemporary analytical methods to updated study data. The study findings provide suggestive evidence of an association between lung cancer mortality and estimates of cumulative occupational exposure to external radiation at the Y-12 facility; further, the temporal trends in association are consistent with patterns observed in several other radiation-exposed worker cohorts.

Developments for Research Methods

A substantial effort in this project entailed development and validation of survival analysis methods that may be used to estimate model parameters describing latency and age at exposure effects. We developed an approach to estimate parameters for complex exposure weighting models (Appendix Table 1) that involves a computationally-intensive iterative search. It is possible to conduct such a search using Poisson regression methods. However, this is extremely

laborious since a separate tabulation of person-time and events must be tabulated for each iteration of the search algorithm. Therefore, a nested case control study design (with controls selected via incidence density sampling) was utilized. The nested case control approach afforded computational efficiency firstly by reducing the data structure (i.e., by sampling controls for each case), and secondly by eliminating the need to construct a separate data structure for each iteration of the search. Unlike in Poisson regression, the analytical data structure for the case control design allows one to recalculate weighted cumulative dose estimates under varying assumptions about the weight function.

As in previous analyses of the Y12 cohort data, we initially utilized Poisson regression methods. When we switched to a nested case control study design, we compared some simple regression model results obtained using Poisson regression methods to results obtained via logistic regression analyses of nested case control data. We found that results differed substantially. We first speculated that this was due to sampling error; however, as we increased the ratio of controls per case we found that the difference in results increased further. This led to the realization that the incidence density sampling program that we were using (a program described by Pearce, 1990) was incorrect and produced biased results. We therefore developed and published a correct algorithm for incidence density sampling (Richardson, 2004). We demonstrated that this algorithm produced results that were converged to those obtained via Cox proportional hazards regression methods.

Using this incidence density sampling method, however, we still found some difference in results obtained via case control and Poisson regression analyses. Exploration of the reason for this bias

led us to identify a routine source of bias in Poisson regression analyses. Categorization of a continuous variables (e.g., cumulative radiation dose) and assignment of scores to categories introduces exposure measurement error (Richardson and Loomis, 2004). We found that the case control approach is not only computationally-efficient, but also not subject to bias resulting from decisions about exposure category cutpoints and score assignment that are inherent in traditional Poisson regression methods.

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MATERIALS AVAILABLE FOR OTHER INVESTIGATORS

The Y12 cohort data are available to investigators via the Comprehensive Epidemiologic Data Resource [31,32].

Table 1. Number of workers, vital status as of December 31, 1990, and number of deaths due to specified causes.

Vital status	**Number (%)**
Alive	2965 (76.7)
Unknown	19 (0.5)
Dead	880 (22.8)
Lung cancer	111
Smoking-related cancers except lung	50
Non-malignant respiratory disease	50
Total	3864

Table 2. Rate ratio estimates* for lung cancer mortality according to categories of cumulative external and internal radiation dose under a 5 year lag assumption.

	Lung cancer deaths	Rate Ratio	(95% CI)
External dose (mSv)			
< 10	53	Referent†	
10 – 49.9	51	0.92	(0.58, 1.46)
50+	7	1.33	(0.56, 3.18)
Internal dose (mSv)			
< 10	13	Referent†	
10 – 49.9	38	1.52	(0.74, 3.13)
50- 99.9	20	1.20	(0.54, 2.67)
100+	40	1.40	(0.65, 3.01)

* Rate ratio estimates are adjusted for age, birth cohort, sex, race, socioeconomic status, length of employment, employment status; in addition, estimated rate ratios for categories of external dose are adjusted for categories of internal dose, and estimated rate ratios for categories of internal dose are adjusted for categories of external dose.

† Referent Category.

Table 3. Rate ratio estimates (RR)* for lung cancer mortality according to joint cumulative external and internal lung dose estimates. Exposure assignment is lagged 5 years.

	Radiation dose to lung from internal depositions (mSv)		
Radiation dose to lung from external exposures (mSv)	<10 RR (95% CI) number of deaths	10 – <50 RR (95% CI) number of deaths	>= 50 RR (95% CI) number of deaths
<10	Referent[†] 10	1.80 (0.78, 4.16) 27	1.26 (0.51, 3.16) 16
10 – <50	1.39 (0.35, 5.51) 3	1.31 (0.49, 3.52) 11	1.36 (0.58, 3.21) 37
>= 50	-- (--)§ 0	-- (--)§ 0	2.23 (0.74, 6.73) 7

* Rate ratio estimates are adjusted for age, birth cohort, sex, race, socioeconomic status, length of employment, and employment status.

[†] Referent Category.

§ Confidence intervals were not computed because the observed number of lung cancer deaths is equal to zero.

Table 4. Estimated percent increase in mortality per 10 mSv radiation dose for three causes of death. Cumulative external and internal radiation dose under a 5-year exposure lag assumption.

	External Radiation	Internal Radiation
Lung Cancer		
Percent Increase per 10 mSv dose (std error)	0.55 (0.17)	-0.77 (0.90)
LRT, 1 df	5.84	0.85
Smoking-related cancers other than lung		
Percent Increase per 10 mSv dose (std error)	-8.68 (12.55)	-0.89 (1.66)
LRT, 1 df	0.32	0.64
Non-malignant respiratory disease		
Percent Increase per 10 mSv dose (std error)	-0.27 (2.65)	-0.85 (1.44)
LRT, 1 df	0.01	0.42
Mean cumulative dose (mSv)	10.1	44.7
Max cumulative dose (mSv)	5863.2	3058.0
Employment-years with imputed dose (%)	23%	58%

Note: estimates were adjusted for age, birth cohort, sex, race, socioeconomic status, length of employment, and employment status; in addition, estimated dose-response trends for external dose are adjusted for internal dose, and estimated dose-response trends for internal dose are adjusted for external dose.

Table 5. Estimated percent increase in mortality per 10 mSv radiation dose for three causes of death. Cumulative external and internal doses accrued 5-14, 15-24, and 25+ years prior to the date of case occurrence or control selection.

	External Radiation			Internal Radiation		
	Time Since Exposure (in years)			Time Since Exposure (in years)		
	5 - 14	15-24	25+	5 - 14	15-24	25+
Lung Cancer						
Percent Increase per 10 mSv dose	0.97	-0.21	0.55	-0.08	-0.19	-3.09
(std error)	(0.28)	(1.09)	(0.27)	(1.82)	(1.52)	(2.69)
LRT, 1 df	6.35	0.05	2.32	0.00	0.07	0.02
Smoking-related cancers other than lung						
Percent Increase per 10 mSv dose	-0.36	-32.01	-0.27	-3.44	4.74	-4.99
(std error)	(8.90)	(26.82)	(4.80)	(4.15)	(3.54)	(3.70)
LRT, 1 df	0.00	1.70	0.00	0.05	0.65	2.19
Non-malignant respiratory disease						
Percent Increase per 10 mSv dose	14.56	-19.22	0.07	-3.65	-1.61	0.21
(std error)	(32.26)	(27.17)	(1.78)	(5.03)	(3.78)	(0.97)
LRT, 1 df	0.18	0.59	0.00	0.58	0.19	0.04
Employment-years with imputed dose	10%	10%	76%	61%	52%	56%

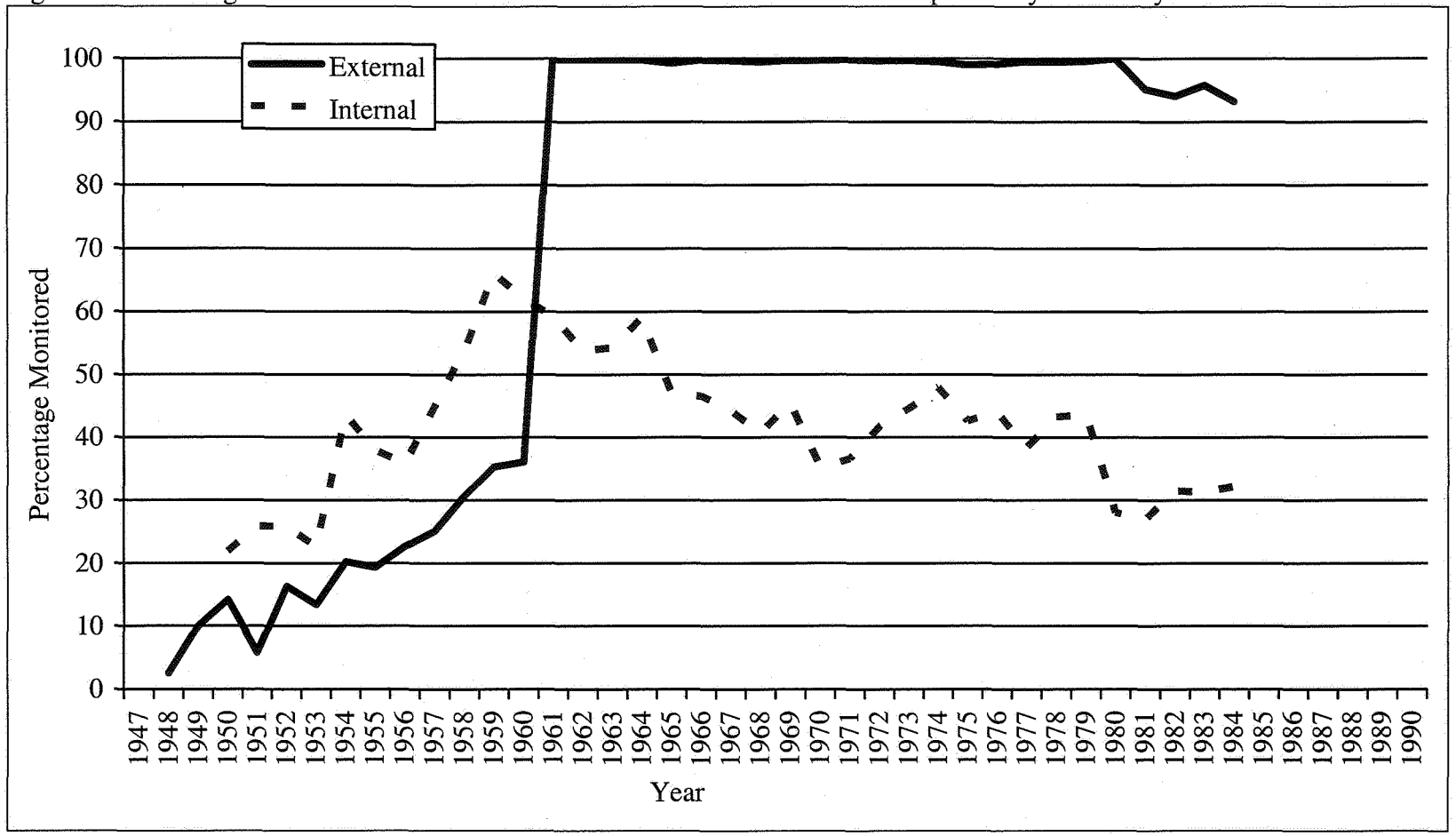
Note: estimates were adjusted for age, birth cohort, sex, race, socioeconomic status, length of employment, and employment status; in addition, the estimated dose-response trend for a time-window-specific dose is adjusted for the other 5 time-window-specific doses.

Table 6. Estimated percent increase in mortality per 10 mSv radiation dose for three causes of death. Cumulative external and internal dose under a 5-year exposure lag assumption in three time-windows defined by age-at-exposure.

	External Radiation			Internal Radiation		
	Age at Exposure (in years)			Age at Exposure (in years)		
	15-34	35-49	50+	15-34	35-49	50+
Lung Cancer						
Percent Increase per 10 mSv dose	-53.80	0.90	14.48	-0.42	-1.24	-0.97
(std error)	(33.13)	(0.21)	(13.48)	(1.72)	(1.63)	(2.25)
LRT, 1 df	5.79	9.28	0.27	0.70	0.17	0.58
Smoking-related cancers other than lung						
Percent Increase per 10 mSv dose	-4.54	-9.25	-20.02	-6.16	1.02	-0.62
(std error)	(23.55)	(20.07)	(35.36)	(4.89)	(2.71)	(4.19)
LRT, 1 df	0.05	0.32	0.37	1.96	0.14	0.02
Non-malignant respiratory disease						
Percent Increase per 10 mSv dose	74.18	-0.46	-11.43	0.07	-2.05	-1.73
(std error)	(27.08)	(3.75)	(23.57)	(1.14)	(2.90)	(3.27)
LRT, 1 df	4.54	0.32	0.37	1.96	0.14	0.02
Employment-years with imputed dose	34%	20%	12%	55%	57%	63%

Effect estimates are adjusted for attained age, birth cohort, sex, race, socioeconomic status, length of employment, and employment status via stratification.

Figure 1. Percentage of workers monitored for external and internal radiation exposure by calendar year.



Appendix Table A1. Alternative exposure weighting functions

Name	Parameters	Weighting Function
Step Function	η	$w(t) = I[t >= \eta]$
Sigmoid Function	σ_1, σ_2	$w(t) = \frac{\left(\frac{t}{\sigma_2}\right)^{\sigma_1}}{\left(\frac{t}{\sigma_2}\right)^{\sigma_1} + \left(\frac{t}{\sigma_2}\right)}$
Bilinear Function	ϕ_1, ϕ_2	$w(t) = \left[\left(\frac{t}{\phi_1} I[t <= \phi_1]\right) + \left(\frac{\phi_2 - t}{\phi_2 - \phi_1} I[\phi_1 < t <= \phi_2]\right)\right]$

The function I["logical expression"] equals 1 if "logical expression" is true and 0 if it is false.

The value t is the time-scale over which weights vary. For analyses of age at exposure $t=a$ and denotes the age at the midpoint of each calendar year of exposure. For analyses of time since exposure $t=A-a$ and denotes the difference between the attained age and the age at the midpoint of each calendar year of exposure.