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Methods for Investigating Age Differences in the Effects of Prolonged Exposures

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People experience physiological changes with age which may lead to changes in sensitivity to many kinds of exposure. In situations of prolonged, low level exposure, differences in the effects of exposures received at different ages may be difficult to evaluate, since study members receive low level exposures over a range of ages. Such investigations require examination of the effects of different age-patterns of exposure. Three approaches to investigating age-related variability in the effects of prolonged exposures are described: subcohort analyses; the use of smooth weighting functions; and, the evaluation of separate effects of cumulative exposures received at different age ranges. Each method can contribute to the overall evaluation of age-specific exposure effects. These methods are illustrated with occupational cohort data for employees of Oak Ridge National Laboratory. The methods presented in this paper should facilitate examination of the effects of aging on sensitivity to prolonged exposures. Am. J. Ind. Med. 33:123–130, 1998.

KEY WORDS: epidemiologic methods; occupational cohort; age at exposure; Oak Ridge National Laboratory; low-level exposure; dose response; ionizing radiation

INTRODUCTION

Epidemiologists often investigate the effects of repeated, or prolonged, low-level exposures. Examples of prolonged exposures include chemical, dust, repetitive motion, and radiation exposures at work, psychological stressors, environmental exposures, and dietary factors. A cumulative measure of exposure is commonly used in epidemiologic studies to evaluate the effects of long-term exposures. Since larger cumulative exposures are often associated with larger observed effects, a measure of cumulative exposure offers a way to simplify a potentially complicated exposure history [Checkoway et al., 1989; Checkoway and Rice, 1992].

A simple sum of time-specific exposures may be appropriate if separate exposures act independently and their effect is cumulative. However, for many types of exposure, the physiological changes that accompany aging might be expected to lead to changes in exposure effects (on either an absolute or a relative scale) [Curtis and Thomas, 1992; Jarvhom, 1992; Kirkwood, 1996]. As adults age, they experience declines in lung function [Knudson et al., 1983; Sherrill, Lebowitz et al., 1992], as well as reduced efficiency of the immune system [Narayanan, 1996; Pahlavani and Richardson, 1996], decreased physical and cellular repair processes [National Research Council and Committee on the Biological Effects of Ionizing Radiation (BEIR III), 1980; Charlton, 1996], and changes in cognitive function and reaction time [Fraser et al., 1996; Kluger et al., 1997]. Consequently, aging may be an important modifier of the effects of an exposure; and, researchers may be interested in whether the same magnitude of cumulative exposure is associated with different effects when received at different ages.

In order to investigate differences with age in the effects of a prolonged exposure, time-specific exposure estimates are needed. Outside of laboratory settings, individuals typically receive exposures at different ages, and for differ-

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ent durations of time. In the best of situations, exposure data might provide time-specific, quantitative exposure estimates for each person in a study, more commonly however, estimates are based on the length of time a person is exposed (e.g., duration of employment in a job, or residence in an area), or the length of exposure time-weighted by an estimate of exposure rate (e.g., working-level-months of an occupational exposure, or pack-years of cigarette smoking).

Regardless of the refinement of exposure measurements however, when there is variation among study members in exposure levels, and in the ages at which exposures were received, analyses may investigate differences with age in exposure effects. Such analyses may not only elucidate etiologic processes, but also may increase the ability to detect exposure-response associations. If sensitivity to the effects of an exposure varies with age, then exposure misclassification can be reduced by identifying differences in the etiological relevance of periods of exposure. This paper discusses methods for the examination of variation with age in the effects of prolonged exposures, and illustrates these methods with data from follow-up of workers employed at Oak Ridge National Laboratory (ORNL) [Richardson, 1997].

METHODS

Methods in this paper are discussed in terms of analyses of grouped cohort data in which tables of person-time and events are examined; analyses based on risk sets (for example, proportional hazards methods) could be discussed in similar terms, and the same types of methods could be applied. Analyses of cohort data may examine the association between death or disease rates and exposure. Using lifetable methods, these analyses can be conducted by tabulating person-time and events by strata of exposure [Wood, et al., 1997]. When categorizing person-time and events by cumulative exposure, the level of exposure at which person-time and events are allocated may change over time, reflecting the progressive accumulation of exposure. Such a tabulation of person-time and events by cumulative exposure, however, typically obscures information about the ages at which exposures occurred.

Subcohort Analyses

One way to examine differences with age in the effects of exposures is to distinguish between individuals whose exposure histories began at different ages. In an occupational setting, age at first exposure often is considered as the age at hire; in other settings, age at first exposure may reflect an environmental release, or the start of a habit such as cigarette smoking.

Such an approach is of limited use, however, when exposures are accrued over a prolonged period of time. If exposure rates vary over time (or if exposures are of the same rate, but of varying duration), age at first exposure provides only limited information about the distribution of exposures by age. One can identify groups presumed to have no exposure before a specified age, but it is not possible to compare the effects of exposures received only at older ages to the effects of exposures received only at younger ages, since people first exposed at younger ages will often continue to receive exposure at older ages.

An alternative is to define subcohorts by using information about the age at first exposure and the age at last exposure. With this method, the effects of cumulative exposure among study members who only received exposures during one specified range of age can be compared to the effects of cumulative exposure among study members who only received exposures during a different range of age. However, limiting analyses to people who only received exposures at particular ages severely reduces the statistical power of a study by excluding those exposed both at older and younger ages, which may constitute a large proportion of the study population.

Exposure Weighting

A cohort does not have to be restricted to examine the effects of age at exposure. If exposures received at a specific range of age are hypothesized to be most relevant to the onset of disease, this hypothesis can be empirically evaluated.

In studies of low level chemical and radiation exposures, researchers often discount exposures which were received during a period immediately preceding detection of a disease in order to investigate latency assumptions [Rothman, 1981]. Using an analogous approach, a researcher can investigate age-effects. For example, if exposures received at younger ages are hypothesized to be etiologically irrelevant (or less relevant) to subsequent disease, then the change in fit of an exposure-response association can be evaluated after excluding exposures received at younger ages [Salvan et al., 1995]. Similar to an evaluation of latency, by using this method, different assumptions about age-effects can be evaluated.

When lagging exposures, it is common to entirely disregard exposures received immediately prior to detection of disease. This can be described mathematically as weighting exposures received during the lag period by zero, while weighting other exposures by unity [Hornung and Meinhardt, 1987]. An investigation of age-effects can be conducted similarly; for each time interval for which exposure data are available, a subject's age is calculated at the midpoint of the period, and this age is used to derive a weight for that period of exposure.

The following equation describes a weighting function in which exposures received before a critical age 'c' are

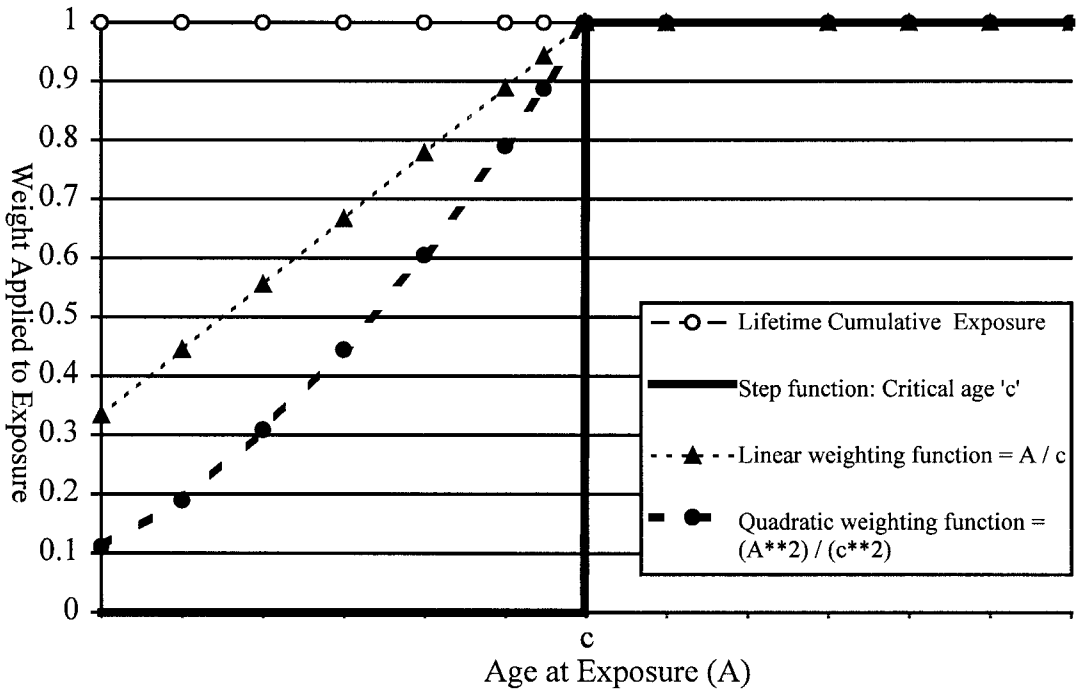

FIGURE 1. Functions to weight annual exposures by age at exposure.

disregarded, while exposures received after that age are weighted by unity (Equation 1) (Fig. 1). The cumulative exposure at any age is the sum of the weighted exposures received up to that age.

Step function for discounting exposures received at younger ages:

$$\text{Weight} = 0 \quad \text{if age} < c;$$
$$\text{Weight} = 1 \quad \text{if age} >= c \tag{1}$$

Under an exposure-weighting scheme, those exposures hypothesized to be etiologically relevant are weighted most heavily [Checkoway et al., 1990]. If entirely discounting exposures seems biologically less plausible than gradually discounting exposures, other weighting functions could be investigated. Examples of other weighting functions are shown in Equations 2–4, and in Figures 1 and 2. Weights are based on the individual's age at exposure A; again, different critical ages of exposure, c, might be considered.

Linear weighting function:

$$\text{Weight} = A/c; \quad \text{bounded by 0, 1.} \tag{2}$$

Quadratic weighting function:

$$\text{Weight} = A^2/c^2; \quad \text{bounded by 0, 1.} \tag{3}$$

Sigmoid weighting function:

$$\text{Weight} = (A/c)^k/[(A/c)^k + (A/c)] \tag{4}$$

Equation 4 is a sigmoid function, under which the parameter k affects the shape of the hypothesized weighting function. With increasing values of k, the sigmoid curve approaches the step weighting function described by Equation 1 (Fig. 2).

Evaluating the Separate Effects of Age-Specific Exposures

When using an exposure-weighting function, exposures hypothesized to be etiologically irrelevant do not have to be excluded from an analysis. Instead, these exposures can be counted separately, and their association with the outcome can be evaluated by including an additional term in the model describing exposure effects. To conduct analyses that examine the separate effect of exposures received at separate ranges of age, person-time and events must be cross-classified by the level of cumulative exposure accrued at different ages. In terms of the weighting functions discussed above, cumulative exposure received at older ages would be the time-dependent sum of exposures weighted using one of the equations above; and, cumulative exposure received at younger ages would be the time-dependent sum of the exposures weighted by the complement of the weight derived from the equation (the complement would be 1 − Weight). Person-time and events would be cross-classified, at each interval of follow-up, according to the levels of weighted cumulative exposures. In an evaluation of the separate effects of cumulative exposures received at two different age ranges, the trend in disease rates with increasing exposure received at one age period can be examined,

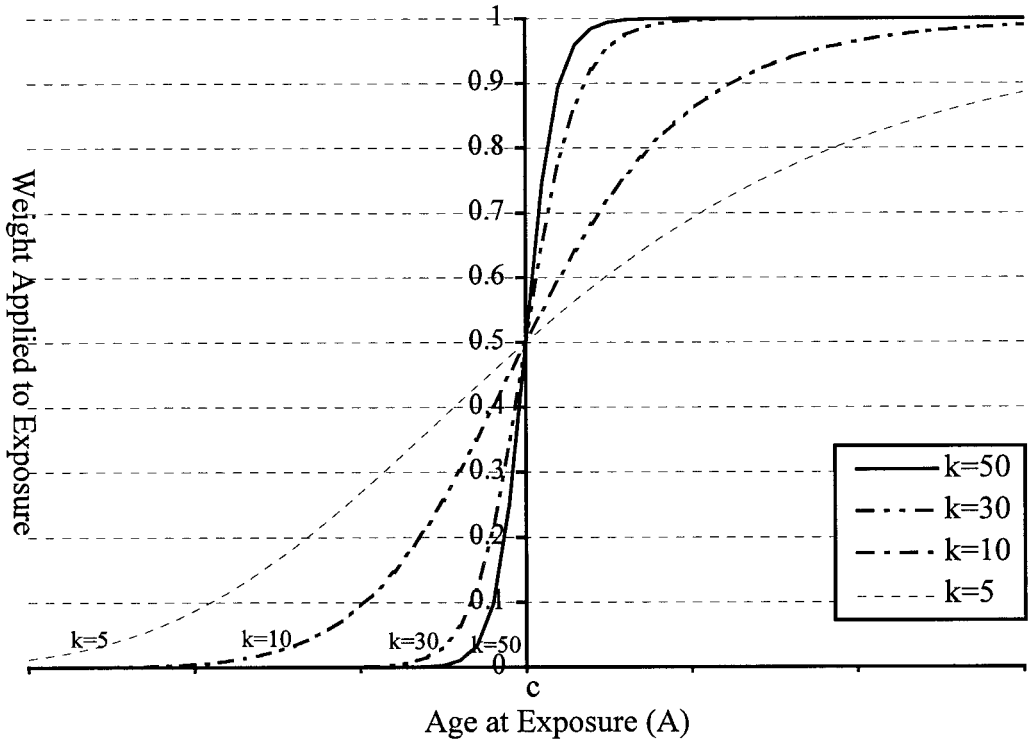

FIGURE 2. Sigmoid function to weight annual exposures by age at exposure.

after adjusting for exposures received in the other age period.

Tests of Heterogeneity in Effect With Age at Exposure

In regression analyses of grouped data, it is often desirable to associate quantitative values with exposure categories. This allows estimation of the percent change in death or disease rates per unit exposure. One method for assigning values to exposure categories is to calculate the person-time weighted mean cumulative exposure for each cell of the lifetable [National Research Council and Committee on the Biological Effects of Ionizing Radiation (BEIR IV), 1988]. As tables become increasingly stratified, cell-specific mean exposures reflect smaller intervals of person-time. One advantage of this method is that regression estimates are less influenced by decisions about the number of exposure categories and their boundaries.

Another advantage of using cell-specific mean values is that these values can be summed to derive the total cumulative exposure. This allows a test of differences in the effects of cumulative exposures received at different age intervals using nested regression models. For example, the separate effects of cumulative exposures accrued before some critical age, referred to as 'dose-young', and cumulative exposures accrued after that critical age, referred to as 'dose-old', may be examined. The regression model

$$\ln(\text{rate}) = ZB_z + B_{young}(\text{dose-young}) + B_{old}(\text{dose-old})$$

could be compared to the nested model, with one less parameter, which describes the association between disease rates and total cumulative exposures,

$$\ln(\text{rate}) = ZB_z + B_{young+old}(\text{dose-young} + \text{dose-old})$$

The first model includes a vector of covariates as included in all models (Z) and their associated parameter estimates (B_z), as well as separate parameter estimates (B_{young} and B_{old}) for cumulative exposure received before and after some specified age. The second model includes the same covariates, and a single parameter estimate ($B_{young+old}$) for the sum of the age-specific cumulative exposures. The difference in the residual deviances between the models represents the improvement in fit of a regression model after including an additional term to describe the separate effects of exposures received in separate age periods (interpretable using a chi-square test with one degree of freedom).

This approach does not have to be limited to two age categories. Person-time and events can be cross-classified by categories of cumulative exposure received at several different age ranges (e.g., cross-classifying person-time and events by the levels of cumulative exposure received at ages 15–25, 25–35, 35–45, 45–55, 55+). Typically, if exposure rates are low, the cumulative exposure accrued within a

small age range may be too low to allow meaningful exposure-response analyses. However, by summing the cell-specific mean exposures received in different age categories, tests of heterogeneity can be used to compare different categorizations of age-specific cumulative exposures. For example, one could examine a model that partitions cumulative exposure at age 35. The cumulative exposure accrued before age 35 would be the sum of the cell-specific mean exposures received at ages 15–25 and 25–35; and the cumulative exposure accrued after age 35 would be the sum of the cell-specific mean exposures received at ages 35–45, 45–55 and 55+. Using the same data, the magnitude and fit of the dose-response association for cumulative exposures partitioned at age 45 could be compared to a model in which cumulative exposure was partitioned at age 35. The cumulative exposure received before age 45 would be the sum of the cell-specific mean exposures received at ages 15–25, 25–35, and 35–45; and, the cumulative exposure received after age 45 would be the sum of the cell-specific mean exposures received at ages 45–55 and 55+.

Examination of Lag Assumptions and Time Windows

In studies of low-level chemical and radiation exposures, effects may be presumed to appear only after some minimal latency period. Extending the methods described above, lag assumptions and time windows may be evaluated simultaneously with the effects of age-specific exposures. Again, person-time and events are allocated by level of time-specific accrued exposure. To examine lag assumptions or time windows, however, person-time and events are cross-classified by age-specific exposures, and by periods of time-since-exposure.

Since cell-specific mean values may be summed together, multiple narrow categories of age at exposure and time windows of exposure might be used, and the evaluation of age effects and time windows is done by comparing nested regression models. Person-time and events may be cross-classified by the level of cumulative dose accrued in each period of age at exposure and time since exposure; total (lifetime) cumulative exposure would be the sum of the cell-specific mean exposures received in these periods. The goodness of fit of regression models partitioning cumulative exposure by age, or age and lag periods, can be examined by different summations of these cell-specific mean exposures.

Example: Workers Employed at ORNL: The cohort used to illustrate these analyses includes white males hired from 1943 and 1972 who worked at least 30 days at ORNL and who had not worked at another Department of Energy (DOE) facility prior to 1978 [Wing, 1993; Richardson, 1997]. Vital status was ascertained through 1990 primarily by using Social Security Administration records and the National Death Index; death certificates were retrieved, and underlying causes of death, and cancer contributory causes, were coded to the eighth revision of the International Classification of Diseases adapted for the United States (ICDA8) [Watkins et al., 1993]. All cancer mortality was defined as any death for which an ICDA8 code of 140–209 appeared as an underlying or contributory cause. Exposure to external penetrating radiation was measured using individual dosimeters [Parrish, 1982; Watkins et al., 1993; Kerr, 1994; Wing et al., 1994]. Poisson regression analyses controlled for age at risk, year of birth, paycode, employment status, and monitoring for internal radionuclide contamination [Frome, 1983; Preston et al., 1993]. Radiation doses were lagged 10 years in all analyses.

TABLE I. Percentage Increase in All Cancer Mortality per 10 mSv Dose Among ORNL Workers Who Received No Exposure at Ages 45 and Above and Among Workers Who Received No Exposure Before Age 45

	Workers who received doses only at ages less than 45 years	Workers who received doses only at ages greater than 45 years
No. of cancer deaths	329	188
No. of workers	6,316	2,657
% increase per 10 mSv[a]	3.02	8.55
(SE)	(3.08)	(4.20)
Change in deviance (1 df)	0.85	3.38

[a]Adjusted for age, birth cohort, employment status, paycode, internal radionuclide monitoring, and the interactions between paycode and birthcohort, and employment status and age; 10-year lag assumption.

RESULTS

One way to assess differences in the effects of exposures received at different ages is to consider subcohorts. Table I presents an analysis in which age at first exposure and age at last exposure were used to define subcohorts. The association between cumulative exposure to low level external radiation and all cancer mortality was examined separately among those who received no exposure after age 45 and among those who received no exposure before age 45; therefore, both groups include, among the unexposed, 2193 workers who had no recorded external radiation exposure. Associations between radiation and cancer mortality were of larger magnitude for workers only exposed after age 45. Of the 8,307 workers in the study cohort, 1,527 workers (18.4%) were excluded because they received external radiation dose at ages above and below 45 years.

Table II presents an example of cross-classifying person-time and events by cumulative dose received at two ranges of age. Separate dose categories are used to allocate person-time and events according to the level of cumulative

TABLE II. Estimated Rate Ratios (RR) and Number of Cancer Deaths Among ORNL Workers by Age-Specific Cumulative Doses*

	Age ≥45 0 mSv RR (deaths)	Age ≥45 0–60 mSv RR (deaths)	Age ≥45 60–120 mSv RR (deaths)	Age ≥45 ≥120 mSv RR (deaths)
Age <45	1	1.01	0.99	5.56
0 mSv	(136)	(221)	(5)	(4)
Age <45	1.21	1.18	1.90	4.32
0–60 mSv	(65)	(92)	(8)	(6)
Age <45	1.20	1.16	4.82	—
60–120 mSv	(5)	(5)	(2)	(0)
Age <45	1.13	1.15	1.36	3.2
≥120 mSv	(4)	(5)	(2)	(4)

*Adjusted for age, birth cohort, employment status, paycode, internal radionuclide monitoring, and the interactions between paycode and birthcohort, and employment status and age; 10-year lag assumption.

dose received after age 45 and the level of cumulative dose received before age 45. In this table, columns represent the categories for exposures received after age 45, and rows represent the categories for exposures received before age 45. The pattern of radiation risk moving down a column is the dose-response pattern for exposures received before age 45 for workers, all of whom were in the same category of exposure received after age 45. Relative risks tended to be larger for the highest categories of exposure received after age 45, while there was little evidence of association between relative risk and exposure received before age 45. Cumulative dose received after age 45 was associated with a 5.46% increase in all cancer mortality per 10 mSv (change in deviance 9.85, 1 df); cumulative dose received before age 45 was associated with a 0.69% increase in all cancer morality per 10 mSv dose (change in deviance 0.39, 1 df). Subsequent adjustment for cumulative exposure received before age 45 had little effect on the association between cancer mortality and cumulative exposure received after age 45 [Richardson, 1997].

Both the subcohort analysis and the cross-classification of doses above and below a critical age suggest that effects of exposure differ for doses received at older age. Both approaches, however, correspond to a model in which the exposure effect is assumed to change abruptly at age 45. We next evaluated several smooth weighting functions that describe the change in the exposure-disease association with increasing age at exposure. Table III presents the results of applying different exposure weighting functions. The linear and quadratic functions did not fit the data as well as the step function evaluated previously. The fit of the sigmoid weighting function improved as the weights approached a step function. For the steepest function (when the parameter $k = 100$), a 6.49% increase in all cancer mortality per 10 mSv external radiation dose was estimated; the goodness of fit of the dose-response model to the observed data is indicated by the change in deviance (13.09, 1 df). These examples serve to illustrate some approaches to evaluating changes with age in sensitivity to a low-level exposure; a more extensive evaluation of these effects among ORNL workers is presented elsewhere [Richardson, 1997].

DISCUSSION

For some types of exposure (e.g., radiation), cumulative exposure may reflect a probabilistic situation, in which incremental periods of low level exposure are associated with a small incremental increase in the likelihood of the exposure leading to an event; and, with increasing cumulative exposure, the likelihood of an event increases. For other types of exposure (e.g., a repetitive motion or a low level chemical exposure), cumulative exposure may reflect the accumulation of damage or bioaccumulation of an agent. In all of these cases, however, identification of a particular instance of exposure which initiated the disease may be illogical and impossible.

The methods we present may allow a researcher, nonetheless, to investigate whether the effects associated with low-level exposures change with the age at which exposures occurred. The progressive decline in the vitality of the human body with adult age is widely recognized. With older age, susceptibility to most causes of death and disease may change. Furthermore, for some diseases, such as cancer, development is likely to be mediated by many exposures during an individual's life [Trosko, 1996]. At older ages, a person may be more likely to have received previous exposures which initiate carcinogenic processes [Cookfair, 1982]. The belief that cancer development is a multistage process is supported by the evidence of long latency periods between exposures and subsequent cancer, the effects of age on cancer incidence, and evidence that different exposures may act as initiators or promoters of cancer [Pearce, 1988]. Theoretical models of such multistage processes suggest that the effect of an exposure depends on the age at which exposure occurs [Thomas, 1990]. Under a multistage model of cancer, in order for cancer to occur a cell must pass through several sequential changes [Brown and Chu, 1987]. A carcinogen may act as an initiator, at an early stage of carcinogenesis, and/or act as a promoter, at a later stage in the development of cancer [Crump et al., 1987]. Since the age at which an exposure occurs is related to the probability of a cell having undergone the necessary transitions preceding the stage upon which the exposure acts, age may modify an exposure's effect [Chu, 1987]. Since the process of aging may be mediated by life experience of different exposures and experiences, discussions of aging bring to the fore the complexities of human social and historical processes in which any investigation of exposure–disease association is situated [Charlton, 1996].

TABLE III. Estimated Percentage Increase in Cancer Mortality per 10 mSv Dose Weighted by Age at Exposure Among ORNL Workers

	Equation 2 age/45	Equation 3 age^2/2025	Equation 4 exponent k = 10	Equation 4 exponent k = 30	Equation 4 exponent k = 50	Equation 4 exponent k = 100
% increase[a]	2.28	2.51	5.65	6.01	6.29	6.49
standard error	0.97	1.07	1.72	1.64	1.59	1.60
Change in deviance with dose term	4.95	4.92	8.79	10.79	12.39	13.09

[a]Adjusted for age, birth cohort, employment status, paycode, internal radionuclide monitoring, and the interactions between paycode and birthcohort, and employment status and age; 10-year lag assumption.

By partitioning cumulative exposures, a researcher can separately assess the effects of exposures received at older ages and exposures received at younger ages. The comparisons we discussed were with reference to estimates of the effect of lifetime (total) cumulative exposure; a model for lifetime cumulative exposure presumes that the effect of exposure is uniform at all ages. A model that allows effects to vary with age allows a simple statistical test of heterogeneity of the effects of exposures received at different ages.

The accrual of exposure over time leads to correlation of cumulative dose with the passage of time. Consequently, historical, social, and biological changes over time create a subtext to the record of cumulative exposure in the study population; and their separate effects may be difficult to disentangle. These methods allow investigation of those processes related to aging.

The methods presented in this paper may also be extended to examine latency assumptions and time-windows of exposure. Simple evaluations of latency are easily accommodated; lagging the cumulative dose received in a specified age range is done in the same fashion as lagging total cumulative dose. Time window analyses allow investigation of the etiologic relevance of exposures to cancer risks in different periods of follow-up after the exposure. As described under Methods, person-time and events may be simultaneously stratified by age at exposure and time windows of exposure; this allows evaluation of different time windows and the effects of age at exposure as a series of nested models in one table of person-time. When examining situations of low level exposures, doses accrued in periods stratified by age at exposure and time-windows may allow accrual of only low level cumulative exposures. However, the use of cell-specific means allows the summation of small time-windows. In this way, person-time and events can be tabulated within small windows of exposure, and these can be combined in different groups in order to investigate hypotheses about latency and time-since-exposure as different models evaluated within the same table of person-time.

These methods were developed to study the effects of low-level exposure to radiation among workers at a Department of Energy facility. Data from the nuclear industry provide a rich source of information for developing and applying these methods, since individual records are available on time-specific quantitative measures of exposure for a large number of workers [Wilkinson, 1991; Geiger et al., 1992; International Agency for Research on Cancer, 1994]. While detailed quantitative exposure data are often not available in occupational settings, the process of aging remains a powerful effect that may modify sensitivity to exposures. Consequently, even with less precise measures of exposure, investigation of age-related differences in exposure effects may prove valuable.

Stewart and Kneale have stressed the importance of analyses that examine the effects of age at exposure in occupational studies of low-level ionizing radiation [Kneale and Stewart, 1995; Stewart and Kneale, 1996]. The results of analyses of cohort data for workers employed at ORNL support their contention, demonstrating substantial increases in radiation-cancer associations for doses received at older ages [Richardson and Wing, 1997]. Aging undoubtedly reflects a complicated biological and social process which, while experienced differently among individuals, appears to have the general characteristic of senescence of most bodily systems. However, there is clearly substantial variability within a population in the course of aging processes, and potential variability of these effects on exposure-disease associations. Consequently crude boundaries (e.g., a step function) used to distinguish the ranges of age at which exposures occurred may be sufficient analytically to investigate changes in sensitivity to an exposure with age. These methods should allow further investigation of such effects in a wide range of study populations and for many types of exposure.

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REFERENCES

Brown CC, Chu KC (1987): Use of multistage models to infer stage affected by carcinogenic exposure: example of lung cancer and cigarette smoking. J Chron Dis 40(suppl 2):171S–179S.

Charlton BG (1996): Senescence, cancer and ''endogenous parasites'': A salutogenic hypothesis. J R Col Phys Lond 30:10–2.

Checkoway H, Rice CH (1992): Time-weighted averages, peaks, and other indices of exposure in occupational epidemiology. Am J Ind Med 21:25–33.

Checkoway H, Pearce NE, Crawford-Brown DJ. (1989): ''Research Methods in Occupational Epidemiology.'' New York: Oxford University Press.

Checkoway H, Pearce N, Hickey JL, Dement JM (1990): Latency analysis in occupational epidemiology. Arch Environ Health 45:95–100.

Chu KC (1987): A nonmathematical view of mathematical models for cancer. J Chron Dis 40(suppl 2):163S–170S.

Cookfair DL (1982): A case control study of lung cancer among workers at a uranium processing plant. (Dissertation) Department of Epidemiology. Chapel Hill, NC: University of North Carolina at Chapel Hill.

Crump KS, Allen BC (1987): Time-related factors in quantitative risk assessment. J Chron Dis 40(suppl 2):101S–111S.

Curtis SB, Thomas DC (1992): Dose-time-response models for radiation carcinogenesis. Adv Radiat Biol 16:45–75.

Fraser GE, Singh PN, Bennett H (1996): Variables associated with cognitive function in elderly California Seventh-day Adventists. Am J Epidemiol 143(12):1181–90.

Frome EL (1983): The analysis of rates using Poisson regression models. Biometrics 39:665–674.

Geiger HJ, Rush D, Michaels D. (1992): ''Dead Reckoning: A Critical Review of the Department of Energy's Epidemiologic Research.'' Washington, DC: Physicians for Social Responsibility.

Hornung RW, Meinhardt TJ (1987): Quantitative risk assessment of lung cancer in U.S. uranium miners. Health Phys 52:417–430.

International Agency for Research on Cancer (1994): Direct estimates of cancer mortality due to low doses of ionising radiation: an international study. IARC Study Group on Cancer Risk among Nuclear Industry Workers. Lancet 344:1039–1043.

Jarvhom B (1992): Dose-response in epidemiology—Age and time aspects. Am J Ind Med 21:101–106.

Kerr GD (1994): Missing dose from mortality studies of radiation effects among workers at Oak Ridge National Laboratory. Health Phys 66:206–208.

Kirkwood TB (1996): Human senescence. Bioessays 18:1009–1016.

Kluger A, Gianutsos JG, et al. (1997): Patterns of motor impairement in normal aging, mild cognitive decline, and early Alzheimer's disease. J Gerontol Ser B 52:28–39.

Kneale GW, Stewart AM (1995): Factors affecting recognition of cancer risks of nuclear workers. Occup Environ Med 52:515–523.

Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. (1983): Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 127:725–734.

Narayanan S (1996): Laboratory markers as an index of aging. Ann Clin Lab Sci 26:50–59.

National Research Council and Committee on the Biological Effects of Ionizing Radiation (BEIR III) (1980): ''The Effects on Populations of Exposure to Low Levels of Ionizing Radiation.'' Washington, DC: National Academy Press.

National Research Council and Committee on the Biological Effects of Ionizing Radiation (BEIR IV) (1988): ''Health Risks of Radon and Other Internally Deposited Alpha-Emitters.'' Washington, DC: National Academy Press.

Pahlavani MA, Richardson A (1996): The effect of age on the expression of interleukin-2. Mech Aging Dev 89:125–154.

Parrish B (1982): Evaluation of external personnel monitoring devices and data for Oak Ridge National Laboratory epidemiological study. (Master's Thesis) Environmental Sciences and Engineering. Chapel Hill, NC, University of North Carolina at Chapel Hill, 202.

Pearce N (1988): Multistage modelling of lung cancer mortality in asbestos textile workers. Int J Epidemiol 17:747–752.

Preston DL, Lubin JH, Pierce DA, McConney ME (1993): ''Epicure: User's Guide.'' Seattle, WA: Hirosoft International Corporation.

Richardson DB (1997): Time-related factors in radiation-cancer associations among workers at Oak Ridge National Laboratory. Department of Epidemiology. Chapel Hill, N.C., University of North Carolina at Chapel Hill.

Rothman KJ (1981): Induction and latent periods. Am J Epidemiol 114:253–259.

Salvan A, Stayner L, Steenland K, Smith R. (1995): Selecting an exposure lag period. Epidemiology 6:387–390.

Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B (1992): Continuous longitudinal regression equations for pulmonary function measures. Eur Respir J 5:452–462.

Stewart AM, Kneale GW (1996): Relations between age at occupational exposure to ionising radiation and cancer risk. Occup Environ Med 53:225–230.

Thomas DC (1990): A model for dose rate and duration of exposure effects in radiation carcinogenesis. Environ Health Perspect 87:163–171.

Trosko JE (1996): Role of low-level ionizing radiation in multi-step carcinogenic process. Health Phys 70:812–823.

Watkins JP, Reagan JL, Cragle DA, Frome EL, West CM, Crawford-Brown D, Tankersley WG (1993): ''Collection, Validation, and Treatment of Data for the Oak Ridge Nuclear Facilities Mortality Study.'' Oak Ridge, TN, ORISE.

Wilkinson GS (1991): Epidemiologic studies of nuclear and radiation workers: an overview of what is known about health risks posed by the nuclear industry. Occup Med 6:715–724.

Wing S (1993): A review of recent findings on radiation and mortality at Oak Ridge National Laboratory. In Lengfelder E, Wendhauser H (eds): ''Neue Bewertung des Strahlenrisikos'' Munich: Medizin Verlag, pp 217–228.

Wing S, West CM, Wood JL, Tankersley W (1994): Recording of external radiation exposures at Oak Ridge National Laboratory: Implications for epidemiological studies. J Exposure Anal Environ Epidemiol 4:83–93.

Wood JW, Richardson DB, Wing S (1997): A simple program to create exact person-time data in cohort analyses. Int J Epidemiol 26:395–399.