

Time-related Aspects of the Healthy Worker Survivor Effect

DAVID RICHARDSON, PHD, STEVE WING, PHD, KYLE STEENLAND, PHD,
AND WENDY MCKELVEY, PHD

PURPOSE: Health is important for continued employment and therefore continued accrual of occupational exposure; furthermore, steady employment can benefit health. Consequently, bias can occur in estimates of cumulative exposure–mortality associations. This has been called the healthy worker survivor effect (HWSE). The processes associated with the HWSE tend to lead to variation in mortality rates with time-since-termination of employment, most notably a peak in mortality shortly after termination of employment. We use simulations and an empirical example to demonstrate that time-since-termination can be a confounding factor in analyses of occupational-exposure–mortality associations.

METHODS: Simulation data were generated for 20,000 workers followed for 40 years under a model of no effect of employment duration (a proxy for cumulative exposure) on mortality. Proportional hazards regression methods were used to quantify exposure–mortality associations and evaluate methods to control for the HWSE. Results were derived after 100 iterations of the simulation. Relationships between employment duration and mortality were also investigated in a cohort of 122,247 male utility workers with adjustments for time since termination.

RESULTS: Simulation data show a peak in mortality rates in the first year after termination of employment which declined in magnitude with continued time since termination of employment; average employment duration also declined with time since termination of employment. This led to confounding of cumulative-exposure–mortality associations, with spurious evidence of a positive association between cumulative exposure and mortality in the post-termination period. Adjustment for time-since-termination eliminated this spurious association; in contrast, adjustment for a binary indicator of employment status led to positively-biased relative rate estimates. A similar pattern was observed in analyses of utility worker data. The log relative rate of all cancer mortality is -0.12 ± 0.03 per decade of employment without adjustment for time-since-termination, and -0.01 ± 0.03 with adjustment for time-since-termination of employment.

CONCLUSIONS: The HWSE can lead to temporal variation in mortality rates that is correlated with cumulative exposure. Under these conditions, adjusting for time-since-termination of employment may reduce bias in estimates of cumulative-exposure–mortality trends more effectively than the commonly-used method of adjusting for a binary indicator of employment status.

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INTRODUCTION

Occupational epidemiologists often examine associations between cumulative exposure to an occupational hazard and mortality. However, workers with higher mortality risks may

leave employment earlier than lower risk workers due to poor physical health or due to other characteristics that are associated with future mortality risk (e.g., heavy alcohol use). In contrast, healthy workers can remain employed and continue to accrue the health benefits of employment as well as higher cumulative exposure to occupational hazards. Previous studies have demonstrated that, in the absence of any true effect of occupational exposure on mortality, negative associations between cumulative exposure and mortality may be observed in occupational cohorts (1, 2). This has been termed the healthy worker survivor effect (HWSE) (3, 4). The HWSE is an important concern for those interested in worker protection because it may lead to masking or underestimation of adverse effects of occupational hazards when duration of employment is used as an exposure measure or when an exposure measure is highly correlated with employment duration.

As a consequence of the HWSE, mortality rates in industrial cohorts tend to be relatively low during the period of active employment compared with the post-termination

From the Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC (D.R., S.W.); National Institute for Occupational Health and Safety, Cincinnati, OH (K.S.); and Silent Spring Institute, Newton, MA (W.M.).

Address correspondence and reprint requests to: Dr. David Richardson, Department of Epidemiology, School of Public Health, CB # 8050, Bank of America Plaza, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-8050, USA. Tel.: (919) 966-2675; Fax: (919) 966-6650. E-mail: david_richardson@unc.edu

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period of follow-up (5–8). Furthermore, in the post-termination period, age-adjusted mortality rates tend to be highest shortly after termination of employment. An analysis of 10 occupational cohorts showed that standardized mortality ratios (SMRs) for all causes and all cancers were substantially below unity (0.3–0.5) during the period of active employment, regardless of length of employment (5). In the first year after termination of employment, in contrast, SMRs for all causes and all cancers were 2.4 and 4.2, respectively. Two years after termination, SMRs were near unity and remained at that level with continued follow-up (5). A similar pattern was reported by Delzell and Monson in analyses of a large cohort of rubber workers. The SMR for all cause mortality was 0.3 in the active period of employment, rose to 3.5 in the first year after termination, and then declined to unity with continued time-since-termination (7).

In this article we suggest that temporal variation in mortality rates that occurs following termination of employment is an aspect of the HWSE that has been given insufficient attention during the development of methods to minimize bias associated with the HWSE. We hypothesize that variation in mortality rates with time-since-termination of employment can be correlated with cumulative exposure (since those who have been out of work longer may tend to have shorter employment duration than those who remain employed or were recently terminated) and that this can lead to bias in estimates of cumulative-exposure–mortality associations. This hypothesis is investigated using simulation and empirical data. While the HWSE may lead to bias in exposure–mortality analyses for most specific causes of death (7), we focus on a single outcome (all cancer mortality, a broad category of cause death often examined in occupational cohort studies) to simplify presentation of results. Simulation methods are used to explore conditions under which: 1) a peak in cancer mortality rates occurs in the risk period shortly after termination of employment; 2) this variation in cancer mortality rates with time-since-termination of employment is correlated with cumulative exposure; and, consequently, 3) a spurious association is observed in estimates of cumulative-exposure–cancer-mortality associations.

Previous authors have suggested that it is important to account for active employment (defined as the risk period prior to termination of employment at a study facility) vs. inactive employment (defined as the risk period subsequent to termination of employment at a study facility) in analyses of occupational-exposure–mortality associations, due to the tendency for workers with higher mortality risk to preferentially leave employment (1, 3, 5, 9, 10). We compare the adequacy of adjustment for a binary indicator of employment status to adjustment for time-since-termination as methods for reducing bias from the HWSE. We then apply these

methods to analyses of exposure–cancer-mortality associations in a large cohort of electrical utility workers.

MATERIALS AND METHODS

The Monte Carlo method uses simulated data to evaluate a research question under specified conditions. In this article, data are generated under the condition that occupational exposure has no effect on disease incidence; disease status is randomly assigned by sampling from a binary distribution. Using these data, we compare the adequacy of adjustment for a binary indicator of employment status to adjustment for time-since-termination as methods for reducing bias in analyses of occupational-exposure–disease trends. We then apply these methods to analyses of exposure–cancer-mortality associations using empirical occupational cohort data.

Simulation Method

We define the number of iterations of the Monte Carlo simulation as 100, and the size of each hypothetical study cohort as 20,000. Under this Monte Carlo scenario, simulation data are generated for 100 cohorts, each with 20,000 subjects. At the start of follow-up each subject is assigned an age-at-entry into the cohort and maximum length of employment by sampling from specified distributions (Table 1). The distributions of age-at-entry and length of employment are similar to those observed in a study of nuclear industry workers (11). The median age at entry is 25 years, while the 90th percentile for age-at-entry is 41 years. The median length of employment is 17 years. Subjects are followed for a maximum of 40 years. For each person-year of observation contributed by a study subject, disease status is determined by calculating the probability of disease under the model:

$$\text{Log}(h) = \delta_0 + \delta_1 \ln(\text{age}),$$

TABLE 1. Conditions for simulations

Parameter	Value
Number of iterations of the simulation	100
Number of workers in study cohort	20,000
Maximum length of follow-up, in years	40
Age at entry, in years	18 + 10(Exp(1))
Maximum length of employment, in years	25(Exp(1))
Baseline disease incidence rate (δ_0, δ_1) [†]	–6.0, 5.7
Rate of censoring due to death from causes other than the one under study, (η_0, η_1) [‡]	–5.1, 0.09
Time from onset of disease to death, in years	4(Exp(1))

[†] δ_0 and δ_1 are parameters of a Weibull model (centered at age 55 years) describing the annual incidence of disease.

[‡] η_0 and η_1 are parameters of a Gompertz model (centered at age 55 years) describing the rate of mortality due to causes other than the one under study. The exponential distribution (with mean of 1) is denoted Exp(1).

where h is the rate of disease, δ_0 and δ_1 are parameters for a Weibull model that defines the age-specific rate of disease, and age is a time-dependent indicator of attained age. Under this model, there is no true effect of cumulative exposure on disease incidence.

In these analyses, we wish to simulate data similar to those observed in occupational cohort analyses of all cancer mortality; values for δ_0 and δ_1 are specified such that simulations approximate the age-specific cancer mortality rates in a large cohort of US workers. Since we specify values for δ_0 and δ_1 , and determine age for each person-year, we can calculate h , which is used to assign the subject's disease status (0 or 1) in each year by sampling from the binomial distribution (1, h). Workers with incident disease terminate employment in the first year that disease occurs. A worker with incident disease is assigned a time from onset of disease to death by sampling from an exponential distribution (Table 1). Regardless of disease status, follow-up of each subject may be censored as a result of death due to a cause other than the one under investigation (i.e., cancer). For each person-year, the age-specific probability of censoring due to death from a cause other than the one under investigation is determined under the model:

$$\text{Log}(c) = \eta_0 + \eta_1(\text{age}),$$

where c is the rate for competing causes of death, and η_0 and η_1 are parameters for a Gompertz model that defines the age-specific rate of mortality due to causes other than the one under investigation.

Therefore, each worker is employed until: their maximum duration of employment, their date of incident disease, their date of death due to competing cause, or 40 years (whichever was shortest). In these analyses, death due to cancer occurs within the study period if a worker's date of incident disease plus their time from morbidity to mortality is less than 40 years and occurs prior to the date of a competing cause of death. On average, 6% of the subjects in each cohort ($n = 1182$) were classified as deceased due to cancer at the end of follow-up.

The HWSE is primarily a concern in exposure-mortality analyses in settings where the exposure of interest is highly correlated with duration of employment. In regression analyses of these simulation data, duration of employment and cumulative exposure were considered identical; this is similar to many occupational studies that lack individual time-specific exposure estimates. Proportional hazards regression was used to evaluate cumulative-exposure-mortality associations (12). Attained age was the primary time scale for these proportional hazards models, thereby achieving exact control for confounding by attained age. Results are presented for three models: in the first model, the only parameter is a linear term for cumulative exposure; in the second model, cumulative-

exposure-mortality associations are adjusted for a binary indicator of employment status (active vs. inactive employment); in the third model, cumulative-exposure-mortality associations are adjusted for a polytomous indicator of time since termination of employment (active vs. < 1, 1-< 2, 2-< 3, 3-< 4, 4-< 5, 5-< 6, 6-< 7, 7-< 8, 8-< 9, 9-< 10, ≥ 10 years since termination). Since there is no true effect of cumulative exposure on disease incidence in these simulation data, evidence of such an association is indicative of bias.

Each simulation was repeated 100 times, and the resulting parameter estimates describing the exposure-mortality association were averaged (box plots showing the distribution of estimates of association are shown at <http://www.unc.edu/~davidr/hwse>).

Analyses of Empirical Data

For analyses of empirical data, we examined a cohort of 122,247 male workers who were hired on January 1, 1950 or later and had been employed full-time for at least 6 months between January 1, 1950 and December 31, 1986 by the following five electric utility companies: Carolina Power and Light Co., Virginia Electric Power Co., PECO Energy Co. (formerly Philadelphia Electric Co.), Tennessee Valley Authority, and Pacific Gas and Electric Co. Vital status follow-up was conducted through December 31, 1988 (13). In these analyses, duration of employment and cumulative exposure were considered identical.

Proportional hazards regression was used to evaluate associations between cumulative exposure and all cancer mortality (12). Attained age was the primary time scale for these proportional hazards models, thereby achieving exact control for confounding by attained age. Birth cohorts were defined by 10-year categories of year of birth (< 1900, 1900-1909, 1910-1919...1940-1949, 1950+). Results are presented for three models: in the first model, parameters are included for birth cohort and cumulative exposure; in the second model, cumulative-exposure-mortality associations are adjusted for birth cohort and a binary indicator of employment status (active vs. inactive employment); in the third model, cumulative-exposure-mortality associations are adjusted for birth cohort and a polytomous indicator of time since termination of employment (active vs. < 1, 1-< 2, 2-< 3, 3-< 4, 4-< 5, 5-< 6, 6-< 7, 7-< 8, 8-< 9, 9-< 10, ≥ 10 years since termination). Beta coefficients from proportional hazards regression models are reported as the log relative rate (LogRR) of cancer mortality per decade of cumulative exposure. Information about the precision of point estimates is given in terms of the standard error (se) of the regression coefficient. Hazard ratios may be obtained by exponentiation of β coefficients, and 95%

confidence intervals for hazard ratios may be calculated as $\exp(\text{LogRR} \pm 1.96 \cdot \text{se})$.

RESULTS

Simulation Analyses

Conforming to expectations from the literature on the HWSE, a spurious negative association is observed between cumulative exposure and simulated cancer mortality data (log relative rate per decade cumulative exposure = -0.06 , $\text{se} = 0.03$). This negative cumulative-exposure-cancer-mortality association can be understood as a result of the fact that cancer mortality rates tend to be relatively low in the active period of employment, and workers who are actively employed tend to accrue higher cumulative exposures than comparable terminated workers.

As shown in Figure 1, simulated cancer mortality rates are highest shortly after termination of employment and diminish thereafter. Figure 2 shows the person-time weighted average cumulative exposure in categories of time-since-termination. The highest average cumulative exposures are observed in the active period (when mortality rates are relatively low). Those who have been out of work longer tend to have lower cumulative exposure (i.e., shorter employment duration). In the post-termination period of follow-up, the simulation provides an example of conditions under which a peak in cancer mortality rates shortly after termination of employment (Figure 1) is correlated with relatively high cumulative exposure levels (Figure 2).

In the inactive period of employment status, a spurious positive association between cumulative exposure and cancer mortality is observed (log relative rate per decade cumulative exposure = 0.34 , $\text{se} = 0.03$). In contrast, in the period of active employment status, there is minimal evidence of a cumulative-exposure-mortality association (log relative rate per decade cumulative exposure = 0.03 , $\text{se} = 0.13$). Table 2 shows that adjustment for employment

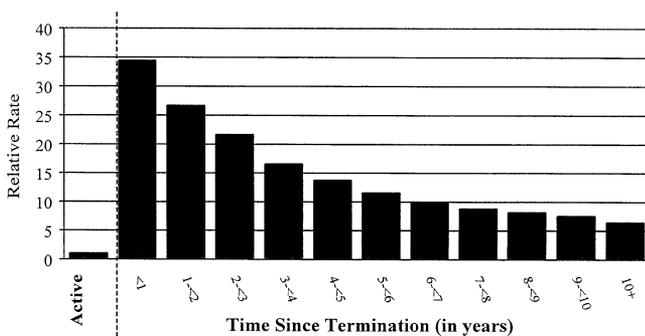


FIGURE 1. Simulation analyses. Relative cancer mortality rate by time since termination of employment (active employment status is the referent).

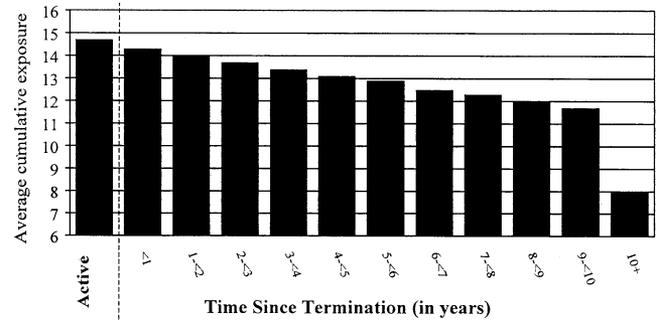


FIGURE 2. Simulation data. Person-time weighted average cumulative exposure by time since termination.

status using a binary indicator variable fails to eliminate this spurious association; a positive estimate of association between cumulative exposure and cancer mortality is observed in analyses that control for a binary indicator of employment status (log relative rate per decade cumulative exposure = 0.33 , $\text{se} = 0.03$).

If this correlation between post-termination variation in cancer mortality rates and cumulative exposure is responsible for a positive bias in estimates of the cumulative-exposure-cancer mortality association after adjustment for employment status, then this bias should be eliminated by controlling for variation in mortality rates with time-since-termination of employment (using a series of indicator variables). There is little evidence of association between cancer mortality and cumulative exposure in the model that includes adjustment for time-since-termination (log relative rate per decade cumulative exposure = 0.02 , $\text{se} = 0.04$).

Empirical Data: Electrical Utility Workers Study

Figure 3 shows age- and birth-cohort-adjusted all cancer mortality rates with time-since-termination of employment in a cohort of 122,247 electrical utility workers. Cancer mortality rates are relatively low in the active period of

TABLE 2. Simulated data for 20,000 workers 40 years follow-up. There is no true effect of cumulative exposure on cancer mortality in these simulated data. Proportional hazards regression estimates of association between cumulative exposure and cancer mortality

Adjustment for	Estimated cumulative-exposure-mortality association		
	Model I: Age	Model II: Model I plus employment status	Model III: Model I plus time-since-termination
LogRR	-0.06	0.33	0.02
standard error	0.03	0.03	0.04

Estimates were derived after 100 repetitions of each simulation. Attained age was the time-scale for these proportional hazards models and was therefore exactly controlled for in analyses. Cumulative exposure and duration of employment were considered identical in these analyses. LogRR indicates log relative rate per decade of cumulative exposure.

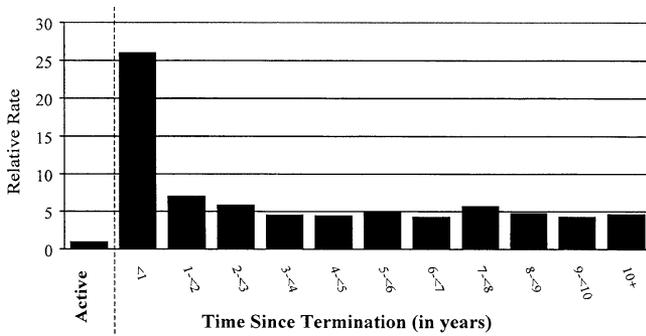


FIGURE 3. All cancer mortality among electrical utility workers. Relative cancer mortality rate by time since termination (active employment status is the referent).

employment, and peak shortly after termination of employment. Figure 4 shows the person-time weighted average cumulative exposure in categories of time-since-termination. In the post-termination period, the highest cumulative exposure levels are observed immediately after termination of employment. Although the unconfounded association between cancer mortality and cumulative exposure in this cohort is unknown, the variation in adjusted cancer mortality rates (and cumulative exposure levels) with time-since-termination of employment is similar to patterns observed in the simulation analyses (the peak in cancer mortality rates in the first year after termination of employment, however, is more dramatic in this empirical example than in the simulation analyses) suggesting that similar patterns of bias might arise.

Table 3 presents estimates of trends of associations between all cancer mortality rates and cumulative exposure. Cumulative exposure is negatively associated with cancer mortality (log relative rate per decade cumulative exposure = -0.12, se = 0.03). In the inactive period of employment status, a positive association between cumulative exposure and cancer mortality is observed (log relative rate per decade cumulative exposure = 0.45, se = 0.03). In the period of active employment status, there is minimal

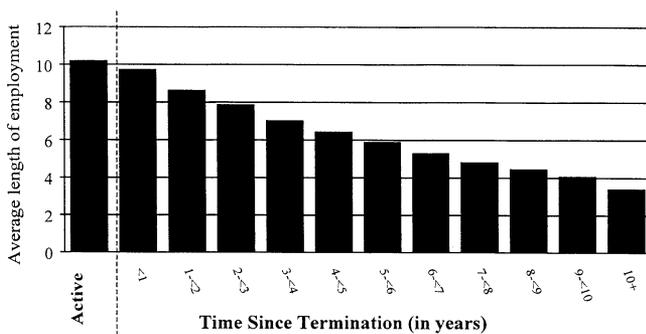


FIGURE 4. Electrical utility workers data. Person-time weighted average cumulative exposure by time since termination.

TABLE 3. Electrical utility workers cohort. Proportional hazards regression estimates of association between cumulative exposure and cancer mortality

Adjusted for	Estimated cumulative-exposure–mortality association		
	Model I: Age and birth cohort	Model II: Model I plus employment status	Model III: Model I plus time-since-termination
LogRR	-0.12	0.43	-0.01
standard error	0.03	0.03	0.03

Attained age was the time-scale for these proportional hazards models and was therefore exactly controlled for in analyses. Cumulative exposure and duration of employment were considered identical in these analyses. LogRR indicates log relative rate per decade of cumulative exposure.

evidence of a cumulative-exposure–mortality association (log relative rate per decade cumulative exposure = 0.05, se = 0.03). After adjustment for a binary indicator of employment status a strong positive association is observed for all cancers (log relative rate per decade cumulative exposure = 0.43, se = 0.03). Adjustment for variation in mortality rates with time-since-termination of employment substantially reduces evidence of association between cumulative exposure and all cancer mortality (log relative rate per decade cumulative exposure = -0.01, se = 0.03).

DISCUSSION

This article shows that a peak in cancer mortality rates may occur in the risk period shortly after termination of employment, that this peak in mortality risk may be correlated with duration of employment, and that this association may bias estimates of cumulative-exposure–cancer-mortality associations. Adjustment for a binary indicator of employment status will control for differences in mortality rates between active and inactive periods of follow-up; however, it will not control for variation in rates with time-since-termination of employment. Using simulated data in which there is no association between employment duration and mortality we show that adjustment for employment status may lead to a spurious positive association, whereas adjustment for time-since-termination of employment effectively eliminates bias from the HWSE. We then compared the impacts of adjustment for employment status and time-since-termination on the relationship between duration of employment and cancer mortality in a cohort of utility workers. As in the simulated data, there is a negative association between employment duration and cancer mortality and a strong positive relationship when employment status is included as a covariate. Adjustment for time-since-termination produces a measure of association that is close to the null.

We used simulation analyses to illustrate that spurious evidence of a cumulative occupational-exposure-mortality association may occur under study conditions that we believe are comparable to those encountered in certain research settings. Although the simulation is based on a model in which occurrence of physical disease among workers leads to termination of employment and subsequent mortality, the disease onset time could be an indicator of any behavioral, social, or material process that is associated with both leaving work and subsequent mortality. Under the conditions of these simulations cancer mortality rates and average cumulative exposure varied with time since termination of employment. This led to confounding of analyses of cumulative-exposure-cancer-mortality associations that was reduced by adjustment for time-since-termination of employment. The observation that cumulative-exposure-mortality associations tend to be negatively biased in analyses that adjust only for attained age, while suffering minimal bias in analyses that further adjust for time-since-termination of employment was consistently observed when varying assumptions of the simulation model over a wide range of values (results shown at <http://www.unc.edu/~davidr/hwse>).

Our simulation analyses address the situation of a study of an inception cohort with relatively short survival time following onset of disease under investigation. It should be stressed that these conditions do not conform to those of every occupational cohort study. If the study cohort is not an inception cohort (i.e., if some workers start employment prior to the start of follow-up) then workers may enter follow-up with accrued cumulative exposures; in such situations there may be less correlation between cumulative exposure and time-since-termination of employment. We focused on examples in which the average time between onset of disease and mortality was 4 years, a choice that leads to simulated data in which there is a peak in mortality in the period shortly after termination of employment (Figure 1). If the average time from the onset of disease to mortality is much longer than we assumed (e.g., 20 years, as assumed in previous analyses by Steenland et al.), health-related termination of employment will not lead to a significant peak in mortality rates shortly after termination of employment. Under such conditions, mortality rates vary minimally with time-since-termination of employment and consequently adjustment for a binary indicator of employment status will lead to estimates of exposure-mortality associations that are comparable to estimates derived after adjusting for time-since-termination of employment. Also it should be noted that we presented analyses in which there was no lagging of exposure assignment. An exposure lag will not influence the temporal variation in mortality rates that occurs as a result of the HWSE but may influence the distribution of cumulative exposure with respect to time-since-termination of employment. Since variation in mortality rates with

time-since-termination may still be correlated with occupational exposure, analyses of cumulative-exposure-mortality associations that lag exposure assignment may still be affected by this source of bias. Therefore, we emphasize that our objective in presenting these simulation analyses was to show that certain study conditions exist under which this type of bias in occupational-exposure-mortality associations can arise.

We focused on the example of mortality due to all cancers, a broad category of cause of death that is routinely examined in occupational studies. The importance of controlling for time-since-termination is likely to depend upon the cause of death under investigation. Previous authors have shown that mortality rates for several other categories of cause of death also peak in the period shortly after termination of employment. For example, Steenland et al. reported that ischemic heart disease mortality rates follow a similar pattern to all cancer mortality, with SMRs reaching a peak (SMR = 2.0) in the first year post-termination (5). Similarly, Delzell and Monson have reported that SMRs for deaths due to circulatory disease, malignant neoplasms, external causes, and all residual causes of death were relatively low in the active period of employment (0.2-0.5), and at their peak in the first year post-termination (SMRs = 3.1, 5.6, 2.4, and 3.1, respectively) (7). The greatest variation in mortality rates with time-since-termination might be expected in analyses of diseases for which there is a period of serious morbidity (that will lead to termination of employment), and for which mortality occurs within a few years after disease incidence.

The effect of selection out of work by unhealthy employees may be more pronounced among those at pre-retirement ages than among those leaving employment at normal retirement age. Delzell and Monson examined variation in mortality rates with age-at-termination of employment and time-since-termination of employment in a cohort of rubber workers. They reported a deficit in all cause mortality (SMR = 0.70) in the first year after termination of employment among those who terminated at ages 65+, and an excess in mortality (SMR = 5.0) in the first year among those who terminated at ages <65 years (7). In a study based on a large sample of the Finnish population, Vinni and Hakama reported an excess of mortality compared with the general population among those who terminated employment at less than 65 years of age, while no excess was observed among those who terminated employment at ages 65+ (14). The role of age at termination of employment could be evaluated using similar methods to those presented in this article.

In these analyses, we focused on the situation in which the occupational exposure does not influence disease incidence. If occupational exposure leads to termination of employment because the exposure causes morbidity that occurs on-the-job, and is subsequently associated with the cause of

death under investigation, termination of employment is an intermediate step in the exposure–mortality association. Robins has suggested that adjustment for termination of employment may be inadequate to control for bias in situations where it is an intermediate variable, and has proposed an alternative approach to analyses of occupational data based on the G-estimation method (3, 15). The G-estimation method provides an important alternative to traditional analytical methods in occupational epidemiology; however, traditional Poisson and proportional hazards regression methods continue to be widely used in occupational epidemiology. It has been noted that under the conditions routinely encountered in occupational health research, confounding due to the HWSE may be relatively strong while the role of employment status as an intermediate variable may be relatively weak (1, 2). The role of employment status as a direct intermediate variable is likely to be particularly weak in settings where exposure influences chronic diseases that tend to occur at post-retirement ages and have long induction and latency (as distinct from morbidity) periods. When there is little or no association between occupational exposure and employment termination the methods discussed in this article will be appropriate.

The HWSE is a routine concern in analyses of occupational cohort data. Actively-employed workers who are seriously ill tend to terminate employment, and voluntary (or involuntary) termination of employment may adversely impact health. Regardless of occupational exposure effects, therefore, mortality rates may tend to vary with time-since-termination of employment. Since those who have been out of work for a longer period of time tend to have shorter employment duration (and lower cumulative doses) than those who remain employed, cumulative exposures tend to be inversely related to time-since-termination of employment. If not accounted for, health-related termination of employment may lead to bias in analyses of cumulative-exposure–mortality associations due to correlation between time-related patterns of variation in mortality rates and cumulative exposure. Using simulation methods, we have shown that in the absence of a true exposure effect, a spurious

cumulative-exposure–mortality association may be observed; under these conditions, adjusting for time-since-termination of employment may reduce bias in estimates of exposure–mortality trends more effectively than adjustment for a binary indicator of employment status.

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