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Cox Model Setup: Garshick et al. Respond

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(Article begins on next page)

Cox Model Setup May Lead to Erroneous Conclusions

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I read with interest the extensive study on lung cancer and elemental carbon exposure in trucking industry workers (Garshick et al. 2012). I believe that the Cox model setup the authors used generated potentially distorted results.

Garshick et al. (2012) used proportional hazard regression to estimate associations between lung cancer mortality and elemental carbon (EC). They adjusted for age and lung cancer secular trends by generating risk sets using attained age in 1-year increments as the timeline; they also included an ordinal variable for calendar year (1985–2000) in all models. It follows that the models were adjusted for year of birth (because year of birth = calendar year – attained age in years).

In addition, Garshick et al. (2012) noted that

> To meet the assumptions of proportional hazards, we assigned separate baseline hazards based on decade of hire (< 1960, 1960–1969, 1970–1979, ≥ 1980) and age in 1985 (40 to < 50, 50 to < 60, 60 to < 70, ≥ 70 years). For example, the baseline hazard for a person 40 years of age in 1985 (born in 1945) who began work in 1975 was the same as that for all workers in their 40s in 1985 who were also hired in the 1970s . . . .

As the authors correctly concluded, this stratification of baseline hazards adjusts for decade of birth.

Because Garshick et al. (2012) used both approaches together in one analytical setup, they adjusted twice for year of birth within the same model (although with different coarseness). Thus, the results may be distorted (e.g., probable overadjustment, potential collinearity).

Furthermore, the authors

> conducted sensitivity analyses with and without total years of employment as a time-dependent covariate (modeled as either continuous or in quartiles) to assess its effect as a potential confounder.

Adjusting cumulative exposure by duration of employment time-dependently reduces cumulative exposure to an estimate of long-term average concentration. However, models that directly estimate the effect of average exposure appear to be preferable (also reported on by the authors). An adjustment of cumulative exposure by total duration of employment should not be confused with an approach adjusting for the healthy worker survivor bias (Rothman et al. 2008). Thus, the sensitivity analyses Garshick et al. (2012) used to adjust cumulative exposures by duration of employment did not produce the correct effect estimates for cumulative exposure.

In summary, the Cox analyses appear to be misspecified and results cannot be interpreted in a straightforward way.

P.M. is a member of the research committee and scientific advisory group of the European Research Group on Environment and Health in the Transport Sector (EUGT) and received research grants from the EUGT for a project on the effectivity of low-emission zones. He is the head of the Institute of Occupational Epidemiology and Risk Assessment at Evonik Industries, which produces specialty chemicals that are also sold to the automobile industry.

Peter Morfeld
Institute for Occupational Epidemiology
and Risk Assessment
Evonik Industries
Essen, Germany
E-mail: peter.morfeld@evonik.com

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Cox Model Setup: Garshick et al. Respond

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We appreciate the interest in our article (Garshick et al. 2012). In his letter, Morfeld suggests that the analytic approach used for Cox proportional hazard regression modeling included two similar adjustments for year of birth. We disagree with this comment.

In the analysis, risk sets were generated using attained age as the timeline. An ordinal variable for calendar year was included as a covariate; thus, we do agree that our approach adjusted for exact year of birth.

We also stratified the analysis on decade of hire (four groups) and age in 1985 (four groups). We stratified on decade of hire to adjust for different unmeasured work practices and vehicle characteristics. We stratified on age in 1985 because the age at which persons enter the study is a determinant of lung cancer risk; participants had to be healthy enough to remain employed to enter the cohort in 1985. Two of the survival curves for decade of hire overlap unless they are jointly stratified by age in 1985, indicating that joint stratification is important to maintain the proportional hazards assumption. This approach allows us to maintain the assumption of proportional hazards and to finely adjust for lung cancer secular trends and attained age but does not adjust twice for year of birth within the same model.

Our analytic approach also included sensitivity analyses with and without total years of employment as a time-dependent covariate to assess its effect as a potential confounder. Morfeld suggests that adjusting cumulative exposure by duration of employment time reduces cumulative exposure to an estimate of long-term average concentration. We agree that if exposure in our workers was relatively constant, cumulative exposure would be the simple product of duration and average exposure. However, exposure varies considerably over time and between and within jobs. Therefore, it is not surprising that the results for duration and average exposure are not similar to those for the cumulative exposure.

In his letter, Morfeld states that "an adjustment of cumulative exposure by total duration of employment should not be confused with an approach adjusting for the healthy worker survivor bias." However, our assessment (Garshick et al. 2012) identified years of employment as a negative confounder because it was positively associated with cumulative exposure and negatively associated with lung cancer risk. Failure to account for this would result in the underestimation of lung cancer risk. Adjustment for total duration of employment strengthened effects with cumulative exposure and may be considered an assessment of the effects of cumulative exposure at varying durations of employment.

Because lung cancer risk decreased with total employment duration, we can treat duration as a surrogate of time-varying health status. As we noted in our article (Garshick et al. 2012), "this was likely due to bias caused by left truncation in a cohort composed of prevalent hires combined with a healthy worker survivor effect." We were not surprised to note this relationship because of the structure of the cohort. As shown previously by Applebaum et al. (2011), left truncation results in downward bias with exposure duration. In our article (Garshick et al. 2012), we extensively discussed a healthy worker survivor effect and left truncation and also cited studies where these effects have been observed. We also cited examples where adjustment for work duration was used as a method to address bias due to a healthy worker survivor effect.

As Morfeld noted in his letter, adjustment for the healthy worker survivor effect is complex. We do not claim that adjustment using employment duration completely adjusts for a healthy worker survivor effect, but our results provided evidence that it is present in this cohort and should be addressed.

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Eric Garshick
Pulmonary and Critical Care
Medicine Section
VA Boston Healthcare System
Harvard Medical School
Boston, Massachusetts
E-mail: Eric.Garshick@va.gov

Francine Laden
Jaime E. Hart
Channing Division of Network Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Mary E. Davis
Department of Urban and Environmental
Policy and Planning
Tufts University
Medford, Massachusetts

Ellen A. Eisen
Environmental Health Sciences Division
School of Public Health
University of California, Berkeley
Berkeley, California

Thomas J. Smith
Exposure, Epidemiology and Risk Program
Department of Environmental Health
Harvard School of Public Health
Boston, Massachusetts

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DNA Damage after Continuous Irradiation: Findings in Mice Compared with Human Epidemiologic Data

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Olipitz et al. (2012) suggested that their study of biomarkers in several hundred mice exposed to 10.5 cGy of ionizing radiation for 5 weeks casts into doubt radiation standards and concerns about protracted exposure after accidental releases of radioactivity. Yet, the authors failed to discuss the many human studies that have appeared in recent years showing excess cancers after protracted exposure (e.g., Cardis et al. 2005; Krestinina et al. 2007; Muirhead et al. 2009). The most likely explanation for the contradiction is that the biomarkers they examined are not predictive of cancer incidence 10–50 years after exposure, a possibility they did not mention. Before a cellular biomarker can be trusted to predict cancer risk, it first must be linked to epidemiologic data, something that Olipitz et al. have not done.

If Olipitz et al. (2012) interpreted their biomarker results correctly, then recent studies on humans must have been wrong. For example, in a study of 400,000 nuclear workers, Cardis et al. (2005) reported excess cancer from protracted exposure at a rate per Gray higher than that found in studies of one-time exposures in atomic bomb (A-bomb) survivors. In a study of 175,000 radiation workers receiving protracted exposures in the United Kingdom, Muirhead et al. (2009) observed excess cancer at the same rate as found in A-bomb survivors. Krestinina et al. (2007) found excess cancer in 17,000 members of the civilian population who received protracted exposure from emissions from the Soviet weapons complex—also at a higher rate than found in the A-bomb cohort. In addition, Chernobyl thyroid exposures meet the protracted test because > 90% of the dose came from iodine-131, which has an 8-day half-life (Gavrilin et al. 2004). It would have been helpful if Olipitz et al. (2012) had explicitly mentioned these epidemiologic contradictions to their data interpretation, thus allowing the reader to judge whether or not their mouse data should influence worker and public radiation standards for protracted exposures.

In the past, cellular radiation studies have conflicted with human epidemiologic data. Thus, the study by Olipitz et al. (2012) is not a test of the linear nonthreshold theory (LNT). The authors started with a dose almost universally accepted to cause a (small) risk of cancer if given all at once.

Perhaps Olipitz et al. (2012) would argue that the dose categories covered in the epidemiology studies cited above do not really include protracted exposures to 10.5-cGy doses, but only to doses no lower than 20 or 30 cGy. However, Olipitz et al. claimed to see "nothing" after 5 weeks, so the implication is that they would also see nothing after 10–15 weeks. If they thought otherwise, it would have been appropriate to say so. In addition, epidemiologic studies in regions with high natural background are not definitive. In one such study, Nair et al. (2009) concluded that their study in India, together with cancer mortality studies in China, could only set limits, suggesting that "it is unlikely that estimates of risk at low doses are substantially greater than currently believed."

One of the biggest paradoxes in the debate on low-level radiation—whether about immediate or protracted exposure—is that an individual risk can be a minor concern, while the societal risk (the total delayed cancers in an exposed population) can be of major concern. Attempts to calm public overreaction should not ignore the human epidemiologic data. Further discussion of these controversies and their policy implications have been published previously (Beyea 2012).

The manuscript is solely the work of the author. It has not been reviewed by anyone connected to litigation, nor has the author received funds for its preparation.

The author, founder of Consulting in the Public Interest, advises plaintiff law firms on litigation involving off-site, low-level radiation exposure from the Hanford weapons complex.

Jan Beyea
Consulting in the Public Interest
Lambertville, New Jersey
E-mail: jbeyea@cipi.com

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DNA Damage after Continuous Irradiation: Yanch and Engelward Respond

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We thank Beyea for his comments and would like to respond, in particular, regarding the works he cites in his letter. First, the results of our study are, in fact, consistent with the findings of many human epidemiologic studies. The latest National Research Council (NRC)