Letters to the Editor

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A Firefighter With a Transtibial Amputation?

To the Editor: A 34-year-old man applied to be a firefighter in a New Jersey city in 2006. He successfully completed all aspects of the preemployment firefighter physical performance test, designed to reflect the essential elements of the job, including climbing 12 flights of stairs, carrying 75 pounds up a flight of stairs, and pulling a hose. He ranked 103 of 165 applicants and was offered the job conditional upon successful completion of a preplacement medical evaluation.

Medical examination revealed a left transtibial amputation due to spinal meningitis and resultant gangrene of the left lower leg at age 5. His residual limb had 4 to 5 inches of tibial bony length, with moderate soft tissue coverage. He used a permanent carbon graphite prosthesis, which incorporated a gel liner and pin suspension. He reported a 30-year history of successfully using a prosthesis up to 24 hours per day without difficulty, including as a high performance athlete, eg, football, track, and training for the Paralympics. His prosthesis was waterproof and accommodated any needed personal protective equipment, including boots. On physical examination, he ambulated well, left knee range of motion was full with extension to 0 degrees and flexion to 120 degrees, muscle strength was 5 of 5 throughout, and sensation was intact to light touch and pinprick throughout the residual limb. All other medical findings and ancillary tests were normal, including spirometry and an electrocardiogram stress test, in which he exercised 12 minutes into a Bruce protocol stage 4.

The examining physician's opinion was that the applicant was not medically fit to train as a firefighter since he did not meet the requirements of the National Fire Protection Association (NFPA), 1582 standard, chapter 6, section 6.14.1 (5), which lists a "lower extremity amputation above the foot" as a category A exclusion, ie, that the candidate shall not be certified as meeting the medical requirements of the job.[1] The city did not appoint him, and he appealed to the State Department of Personnel Merit System Board, which requested the State Medical Examiners Panel, of which we (LDB, GB and PF) are the members, to make recommendations.[2]

We thoroughly reviewed the submitted medical data and his individual circumstances. Of note, the NFPA standard had not been formally adopted for this position. We acknowledged that he had an impairment, but concluded, with a reasonable degree of medical certainty, that he had no significant functional limitation that would either interfere with his ability to perform the essential functions of the job of firefighter or cause a direct threat to himself or others. Although the prosthesis could possibly malfunction or detach during work, we considered it unlikely given his long-term experience with it. Thus, we recommended that he be considered physically capable to undergo the physical training for the job. The Merit System Board affirmed this recommendation and ordered that he be allowed to train as a firefighter.

As noted by the American Medical Association, an impairment is "a loss, loss of use, or derangement of any body part, organ system, or organ function," while a disability is "an alteration of an individual's capacity to meet personal, social, or occupational demands because of an impairment."[3] Having an impairment does not necessarily mean that someone is disabled from performing certain tasks, including those related to work. Information obtained from the University of North Carolina Occupational Environmental Medicine List-serve and the military indicated that other persons with lower extremity amputations successfully work as firefighters and serve on active combat duty in the armed services.[4] This applicant seemed capable of meeting the occupational demands.

Persons with lower extremity amputations should be evaluated on an individual basis for the job of a firefighter, rather than prima facie excluding all such persons, since the individual's fitness contributes to determining the ability to safely do the job.[5,6] Considering the advances in prosthetic devices and their use by persons with amputations, the NFPA should classify lower extremity amputation as a category B conditional exclusion (section 6.14.2) rather than as a category A absolute exclusion.

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Re: Exposure to Beryllium and Occurrence of Lung Cancer: A Reexamination of Findings From a Nested Case-Control Study

To the Editor: We read with interest the recent reanalysis conducted by Levy and colleagues[1] of a case-control study by Sanderson and colleagues.[2] The authors' interpretation of their reanalysis is that it casts doubt on the purported association between beryllium and lung cancer, observed in the original analyses.[2]

We believe the reanalysis by Levy and colleagues contains several methodological problems that call into question this reinterpretation of the original study. Our concern centers around three main points in their reanalysis: 1) their rejection of log-transformation of the exposure variable; 2) the assertion that the older average age at death of controls (compared with cases) is problematic in incidence-density sampled cohorts; and 3) the validity of their analysis matching controls to within 3 years of the date of death or last observation. We also offer an alternative explanation for their observation that cases were hired 4 years younger, on average, than were controls.

Regarding the first issue, Levy et al imply that a log transform of the independent variable in the regression analysis was conducted in the original study to improve its normality. We concur that normality of the independent variable is irrelevant. However, as described by Breslow and Day (pp. 227–238),[3] a log transform is commonly employed to improve model fit for exposure data expressed as a dose rate: "Postulating a log-linear relation of the form $\log RR(x) = \alpha + \beta \log(x)$ means that risk itself is proportional to a power of dose, x^{β}, a relationship known to occur frequently from both human and animal studies." The categorical results in the original analyses[2] suggest a power model provides a more appropriate fit, which was confirmed by the analyses of exposure expressed as a continuous variable. Thus, the results shown in Table 2 of the reanalysis[1] are consistent with those in the original analysis.[2] The observation by Levy et al[1] that the regression coefficients for the untransformed beryllium variables are close to zero, while those for the log-transformed variables are positive, is consistent with the categorical results in Table 3 of the original analyses,[2] which showed an elevated lung cancer rate ratio in the second-lowest exposure category and then slight increases or attenuation in rate thereafter. These categorical analyses (with their implication for choice of appropriate exposure transformation) are not mentioned in the reanalysis by Levy et al.[1]

Many other studies of occupational carcinogens have found that log-transforming exposure variables improves fit over untransformed data, and a number of hypotheses have been advanced to explain this observation.[4] To facilitate using a log transform for those with zero exposure, a small value must be added to each person's exposure. In Breslow and Day's example,[3] a value of one is added to each g/d estimate of tobacco and alcohol consumption. Levy et al criticize the choice of small value used in the original analysis. However, our own recent reanalysis of the original study found the association of the log of 10-year-lagged average and maximum beryllium exposure to be relatively insensitive to the choice of small value added (ie, comparing 0.01 with half the minimum non-zero exposure value within the study group) (Schubauer-Berigan MK, Deddens JA, Steenland K, Sanderson WT, Petersen MR. Adjustment for temporal confounders in a reanalysis of a case-control study of beryllium and lung cancer. *Occ Environ Med*. Submitted).

Our second major criticism of the reanalysis by Levy et al[1] is its suggestion that risk set sampling methodology introduced a bias in the study because it requires the control to have been under observation at the time of case occurrence. This requirement of a density-sampled nested case-control study leads to its approximation of a Cox proportional hazards model (CPHM).[5] As is common in studies of cancer, age is the most important time-related factor in lung cancer risk; therefore, age was selected as the time scale in the original analysis.[2] Thus, all workers hired at an age younger than the case's age at death and who lived to an older age than the case are within that case's risk set. Conditional logistic regression analysis based on exposures truncated at the case's death age for the entire matched set has been shown to provide unbiased estimates relative to an age-based CPHM.[6] This necessarily results in the trivial observation that cases have younger ages at death than do matched controls.

Our third major criticism of the reanalysis by Levy et al[1] concerns their analyses restricted to controls whose age at death or date last observed is within 3 years of that of the matching case. This matching technique violates the assumptions that are required in order for the analysis to estimate a CPHM. Information about the control that occurs after the

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time (age at death) of the case may not be used to select controls without introducing a potential bias. Furthermore, while it may be appropriate to match on calendar time (or, equivalently, date of birth) when using age-based density sampling for selecting controls if birth cohort is an important potential confounder, this is not what Levy et al have achieved. Consider a case who dies at age 65 in 1975 (born in 1910). The corresponding age-based risk set would consist of any worker hired before age 65 who was still alive at age 65. If one matches also on calendar year within 3 years, then the risk set would be restricted to workers who reached age 65 between 1972 and 1978 (ie, were born between 1907 and 1913). Many of these workers in the risk set could have lived to ages well beyond this time. However, the risk set obtained by the suggested matching methodology of Levy et al would include only workers who died between age 65 and 68 or who reached that age alive on December 31, 1992 when follow-up ended. It is difficult to see how such a matching technique could lead to an unbiased result. We contend, therefore, that the analyses in Tables 3 and 4[1] are of little value.

Of some interest is the observation by Levy et al[1] that the average age at hire for cases was approximately 4 years younger than that of controls. In our reanalysis (Schubauer-Berigan MK, Deddens JA, Steenland K, Sanderson WT, Petersen MR. Adjustment for temporal confounders in a reanalysis of a case-control study of beryllium and lung cancer. *Occ Environ Med*. Submitted), we attribute this finding to the fact that hire age is highly correlated with year of birth (Pearson's $r = -0.91$), for which the original analysis did not control.[2] Birth year is a potentially important confounder of the beryllium-lung cancer association because background lung cancer risk due to smoking was expected to be lower for workers born before 1900 (25% of the case-control group) than for workers born later. This is associated with beryllium exposure because workers hired during the WWII era were more likely to be older than those hired during other periods (many were born before 1900). These older workers tended to die of other diseases during the 10- and (especially) 20-year latency period and thus had minimal or zero lagged exposure. By adjusting for birth year, we found that cumulative beryllium exposure was not associated with lung cancer risk at any lag. However, the significant positive association of lung cancer with both average and maximum beryllium exposure remained after this adjustment (Schubauer-Berigan MK, Deddens JA, Steenland K, Sanderson WT, Petersen MR. Adjustment for temporal confounders in a reanalysis of a case-control study of beryllium and lung cancer. *Occ Environ Med*. Submitted). It is not appropriate to simultaneously adjust for age at hire because of its high correlation with birth year, and the lack of an a priori rationale for hire age as a source of confounding.

Other, more minor, errors in the reanalysis by Levy et al[1] include the incorrect flagging of some *P* values in Table 1. According to the original analysis,[2] the *P* value for the trend of the log of 20-year-lagged employment duration with lung cancer mortality was below 0.05, and the values for the log of 20-year-lagged average and maximum exposure were below 0.01. Thus, not "some" (as reported by Levy et al[1]) but nearly all exposure metrics were significantly elevated in the original lagged analysis. Sanderson et al[2] demonstrated an increase in beryllium-associated lung cancer risk when lagging exposures by 10 years. The fact that exposure-related lung cancer risk did not increase further when the exposure was lagged by 20 years should not be construed as evidence against an etiologic association, as implied by Levy et al.[1]

Finally, we note that, in contrast to their implication that the designation by the International Agency for Research on Cancer (IARC) of beryllium as a group 1 carcinogen relied upon the case-control study by Sanderson et al,[2] IARC's designation predates that study by 8 years.

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Authors' Response

To the Editor: The major points made by Schubauer-Berigan et al on our reanalysis[1] of the Sanderson et al nested case-control data[2] reflect their non-acceptance of an artifact that we found can occur under certain patterns of employment when incidence density sampling is used to match controls to cases and then exposure is lagged for purposes of investigat-

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ing the effect of disease latency. Because their arguments ignore our findings of this artifact, we reiterate it below before addressing their specific comments.

The above-mentioned artifact does not occur when exposure lagging is not used, and the theoretical foundations on which incidence density sampling is based[3,4] do not address what happens when it is combined with exposure lagging. This artifact can be explained without going into detail by noting that when exposure lagging is not used, there is a truncation of exposure measurement for both control and matching case at one point, namely the age at censor (ie, age at death or at last ascertainment if alive) of the case, which by algorithm is always less than or equal to that of the control.

When incidence density sampling is combined with exposure lagging, a second truncation occurs and all exposure for both case and control occurring after the lag cutoff (defined as the age at censor of the case minus the assumed disease latency) is truncated. It is this second truncation that can produce the artifact that, under certain employment patterns, a control having the same exposure as the matching case has a greater chance than the case of having some or all of his or her exposure truncated. The statistical basis for this artifact is shown in the appendix of this response. Its existence was demonstrated in our recent article[1] and further supported by findings from a simulation study (Deubner DC, Roth HD, Levy PS. Empirical evaluation of complex epidemiologic study designs. Submitted to *J Occup Environ Med*) (under review). This being said, we now address the three issues that Schubauer-Berigan et al raise.

1. Issues Relating to Our Critique of the Logarithmic Transformation. Our argument (stated on pages 99 and 100 of our article[1]) is based on the fact that the log transformation of values close to or equal to 0.1 (the surrogate for zero used in the Sanderson et al paper[2]) transforms them much further away from the central value of the log transformed distribution than the untransformed values are from the central value of the original distribution, thus giving them more impact in the subsequent conditional logistic regression distribution than the original values would have in the analysis using the untransformed exposure variable. We also stated that this would not be a problem if the artifact discussed in the first paragraph of this response did not result in controls having a greater likelihood than cases of having some or all of their exposure truncated owing to this artifact. Their response does not address this artifact and so their critique is based on their ignoring the issues that we raised in our article and reiterated in this paragraph. The material that we present in the Appendix further reinforces what we stated in our article.

With respect to their discussion of whether the exposure-response distribution is best specified by the untransformed or log transformed distribution, it is difficult for us to see how the patterns shown in their discussion of Table 3, in Sanderson et al,[2] relating to conditional logistic regression with quantiles of exposure as the covariate implies a power relationship between exposure and response (nor was this or any other explanation given for the use of the log transform in the original article[2] other than that the original distribution is skewed and not normally distributed, which is not a requirement for using logistic regression). Also, the findings in the lagged analyses presented in Table 3 of Sanderson et al[2] are moot since they are subject to this same artifact mentioned heretofore.

2. Our "Assertion" that the Older Average Age of Death of Controls Compared with Cases is Problematic in Incidence-density Sampled Cohorts. We nowhere state in our reanalysis that there is a global problem with the use of incidence-density sampling (aka *risk-set sampling*) or with the use of age as the time variable. We would not be so presumptuous as to negate a methodology that has been used for many years in numerous epidemiological studies and is based on a sound theoretical framework. As we stated above, however, we could find nothing in the methodological literature specifically addressing its use with exposure lagging. The fact is that simply confining exposure measurement to that which occurred before the latency cutoff point does not negate the methodological issues that we discussed first in our paper and now in this response to the Schubauer-Berigan et al criticisms of our recent paper. Given this artifact, the nearly 9-year mean difference between cases and controls with respect to age at censor is far from trivial.

3. Criticism that Our Analysis is Restricted to Controls Whose Age at Censor is Within 3 Years of That of the Matching Case. Schubauer-Berigan et al assert that our restriction of controls to those whose age at censor is within 3 years of that of the matching case violates assumptions for using conditional logistic regression when incidence density sampling is employed and of its cohort study analog, Cox proportional hazard regression. There is, to our knowledge, nothing stated in the literature that one can't perform analysis on subgroups of the risk set on which the controls are selected so long as the findings are extrapolated to the appropriate target population. In this instance, our subgroup is those controls that are more closely matched (ie, within 3 years of the age at censor) with the matching case. Our rationale for doing this is, again, that it helps reduces the effects of the artifact in lagged analysis caused by the broad matching on age at censor used in the original nested case-control study.[2] The criticisms point out that our analysis in Table 4 did not control for certain covariates that are confounders. This is true but it

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is also true of the conditional logistic regression performed in Sanderson et al[2] and we wanted our own analysis to be univariate similar to that in the Sanderson et al paper[2] so that they can be directly compared.

The criticisms point out *year of birth* as a confounder and we have found *age at hire* as a confounder. Both of these are confounders in the epidemiological sense because they are associated with both exposure and with case/control status. Schubauer-Berigan et al state that they have submitted a manuscript showing that when *year of birth* is controlled for, average and maximum exposure remain associated with lung cancer (we assume that this analysis is based on all cases and controls since they criticize our subgroup analysis).

In response to the above criticisms, we performed analysis restricting, as before, controls to those whose age at censor is within 3 years of that of the matching case and including *year of birth* as a covariate. We obtained for *maximum exposure* an exposure-lung cancer odds ratio equal to 1.11 (95% CI = 0.95–1.29) and for *average exposure* an odds ratio equal to 1.14 (95% CI = 0.97–1.34). These are only slightly higher than the respective odds ratios equal to 1.06 (95% CI = 0.92–1.22) and 1.11 (95% CI = 0.95–1.31) shown in Table 4 of our article. In all instances, these odds ratios overlap unity and they remain much lower than the odds ratios of 1.20 shown in Sanderson et al.[2]

We disagree with the statement made by Schubauer-Berigan et al that "It is not appropriate to simultaneously adjust for age at hire because of its high correlation with birth year, and the lack of an a priori rationale for hire age as a source of confounding." Since age at hire is the age at which workers first are exposed to beryllium, there is indeed an a priori rationale for testing whether it is a possible confounder. However, the point is moot since we made no attempt to control for both simultaneously in any of our analyses.

4. "Minor" Errors. Schubauer-Berigan et al state we have incorrectly flagged the index study *P* values in our Table 1. This is correct and is unfortunate, because part of our purpose was to initiate a conversation on the methods in the nested case-control study[2] and how the artifact creates case-control differences when exposure is lagged. Incorrectly flagging these *P* values suggests the artifact is less strong than it is. Schubauer-Berigan et al point out that the 1993 IARC decision did not rely on the index study. We agree with this. It relied on another NIOSH study, by Ward et al[5] published in 1992.

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Appendix

Notation: A = age at censor of case; A' = age at censor of control; L = assumed disease latency time; $A - L$ = latency cutoff point; a_e = age when first employed for case; a_e' = age when first employed for control; a_t = age at termination of employment for case; a_t' = age at termination of employment for control; $D = a_t - a_e$ = duration of employment for case; $D' = a_t' - a_e'$ = duration of employment for control.

For the cases, some exposure will be truncated if $a_t > A - L$, and analogously for the controls, some exposure will lag if $a_t' > A - L$. From these two relations, the following probability statements follow:

$$\begin{aligned} &P\{\text{some exposure truncated}|\text{case}\} \\ &\quad = P\{a_t > A - L\} \\ &\quad = P\{a_t - a_e > A - a_e - L\} \\ &\quad = P\{D > (A - L) - a_e\} \end{aligned} \tag{1}$$

For the controls,

$$\begin{aligned} &P\{\text{some tenure truncated}|\text{control}\} \\ &\quad = P\{a_t' > A - L\} \\ &\quad = P\{a_t' - a_e' > A - a_e' - L\} \\ &\quad = P\{D' > (A - L) - a_e'\} \end{aligned} \tag{2}$$

From relations (1) and, (2) if $a_e' > a_e$, a control employed for the same duration as the matching case has a higher probability of having at least some exposure truncated than the matching case.

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