Division of
Biostatistics

Department of
Preventive Medicine

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Dear Dr. Elliott,

Thank you for the opportunity to comment on the development of the Energy Employees Occupational Illness Compensation Act of 2000. As you probably are aware, my colleague at USC, Duncan Thomas, and I served on a recent National Academy of Sciences Committee that reviewed a draft report of the NCI-CDC Working Group to revise the 1985 Radioepidemiological Tables. Our committee’s report was recently released and is available from National Academy Press. I would like to comment upon several aspects of that endeavor which may be relevant to the EEOICA. In particular our report discusses a number of issues related to the construction of “probabilities of causation” (PC) from epidemiological data and their use in the compensation arena.

First of all one should acknowledge that the concept of the probability of causation is somewhat slippery. This was recognized by an earlier NAS review of the original 1985 Tables, which suggested the use of a different name for the concept, i.e. “assigned share” or AS. This choice of name reflected, in part, the fact that unlike a true probability, the usual definition of PC = (RR-1)/RR, may be negative (if an exposure is actually beneficial). There is a more important aspect of the failure of the PC to behave like a probability, however. That is that PCs do not in general “average out” the way ordinary probabilities do. That is if there is a population of exposed individuals each one of who are unique in terms of their baseline disease rates and in their susceptibility to exposure then the average of the individual PCs of persons with disease, will not generally be equal to (RR-1)/RR as estimated from an epidemiological study. Specifically if each individual has a different background probability of disease it is possible to construct examples in which the personal probability of causation for everyone with disease is arbitrarily close to one, but the estimate obtained from an epidemiological study can be arbitrarily close to zero. In fact, a number of statistical articles (Robins and Greenland, 1989, 1991, Greenland 1999) have gone into a great deal of detail concerning this failure of the PC to average over groups of heterogeneous
individuals, and take this as a rationale for abandoning its use in compensation and in the settling of litigation. Further these articles make the generic statement that no epidemiological study can address the variation in individual disease risk and thus even the most extreme models for heterogeneity in baseline risk cannot be invalidated by epidemiological data. I point out this issue to alert you to the fact that the use of probability of causation for compensation and litigation purposes is the subject of heated current debate in some quarters.

As a committee, then, we were faced with a basic question about whether the AS estimated from epidemiological data actually has any usefulness at all. Our general approach towards this critique of the PC was to point out that the extreme failures of the PC (to average over individuals) posed by Robins and Greenland are in fact very extreme in their assumptions about the variability of individual baseline disease risk and to also take issue with their view that no epidemiological study can inform us about variability of individual risk. We specifically pointed out that comparisons of the correlation in disease outcome between monozygotic and dizygotic twins and between dizygotic twins and other siblings can be used to estimate frailty models with both general “genetic” and “shared environment” components, i.e. to estimate the heterogeneity of individual disease risk due to genes and any environmental factors for which exposures are more similar for twins than they are for other siblings. Duncan Thomas performed an interesting simulation as part of preparations for a debate with Sander Greenland on this topic that was part of the ASA 2000 radiation and health conference and is also summarized in our report. Based upon a model for individual variation in risk of total mortality estimated based upon Danish twins data, a model which admitted considerable heterogeneity in individual risk, Thomas showed that the correlations between true individual probability of causation and population estimates (the AS) were quite high leading to our conclusion that “the AS approach still has some validity, at least for the relative ranking of claimants”.

There was some discussion in our report of the limitations of the PC (even if it can be estimated) for the purposes of compensation. In particular we take a very dim view of the idea that compensation schemes should be based upon a hard and fast calculation whether for an individual his or her estimated PC is greater than or less than 1/2. Our objections to this are partly based on unhappiness with such an inherent discontinuity in compensation; partly because of the fact that PC’s will always be uncertain, and partly due to a recognition that compensation should consider degree of suffering (for example, expected years of life lost) as well as the probability that the illness is cause by the exposure. Compensation on the basis of an individual PC > 1/2 may be required based on tort law, when cases are under litigation, however once it has been agreed that a class of individuals are entitled to some compensation the value of this specific threshold is voided.

The 1985 Radioepidemiological tables only included cancer sites for which the Working Group of that time deemed to be clearly related to radiation exposure (p<0.05 in the A-bomb or other relevant data). The 2000 Working Group chose to include many more cancer sites than just those that had definitively been shown to be radiogenic by this criterion. Our committee recognized the logic of including additional sites based on the perception that broad classes of similar tumors are likely to be similarly radiogenic even if some of them are so rare in the Japanese population that increased hazards couldn’t be clearly demonstrated in the A-bomb survivors’ data for that site when analyzed separately. In fact we provided a “meta-analysis” of a very broad class of tumors (consisting of all solid tumors which are not “hormonally related”) and showed that there is relatively little evidence in the A-bomb survivors data of differences in excess relative risk between sites based upon published A-bomb survivor risk estimates (Thompson et al).
While our committee supported in principle the idea of expanding the list of tumors for which AS calculations were provided there was one important concern that we felt had not been addressed in the Working Group report: specifically, how to properly incorporate sampling variability into the uncertainty calculations when dealing with rare tumors. In particular our concern was related to our understanding of how the compensation program established by the VA now works. In this scheme (as I understand it), based upon an individual’s estimated exposure, an upper confidence limit (at the $\alpha=0.01$ level) for the AS is calculated – in this calculation a variety of uncertainty factors are considered – and a case is moved forward for compensation on the basis of whether this upper limit is $> 1/2$. The problem with including the rarer tumors in this setting is that the mere fact that the tumor is rare means that estimates of the excess risk (and hence AS) are highly uncertain, with this in turn implying that confidence limits may reach to very high levels even for very small doses in certain instances. We suggested the use of pooled analyses (and proposed a specific random effects-based approach) for the calculation of confidence intervals so as to minimize the “rewarding of ignorance” in the calculation of the upper confidence limits for the AS calculation in the case of rare diseases. Whether and how to deal with compensation for diseases where no significant dose response is seen when analyzed separately; but also for which little evidence exists that the dose response differs from that of other broadly similar diseases, is a delicate one, and probably should be considered anew by NIOSH.

I hope that these general comments are useful to you.

Sincerely,

Daniel O. Stram
Associate Professor

References:


