Should NIOSH adopt the NIH-IREP model for lung cancer for use in the EEOICPA?

The National Cancer Institute revised the NIH-IREP lung cancer model in late 2003 in response to a report on analyses of the joint effects of radiation and cigarette smoking on lung cancer risk among the Japanese atomic bomb survivors (Pierce, Sharp et al. 2003).

The IREP model allows for interaction on the relative rate scale between radiation dose and cigarette smoking with an uncertainty distribution for an "adjustment factor" that accommodates an additive, multiplicative, or super-multiplicative interaction (Apostoaei and Trabalka 2004). Under the revised NIH-IREP lung model the distribution for this adjustment factor is more heavily weighted toward an additive interaction between radiation dose and cigarette smoking than under the NIOSH-IREP model. Consequently, the same inputs entered into NIH-IREP and NIOSH-IREP produce significantly different probabilities of causation for some exposure profiles. Apostoaei and Trabalka recently recommended that NIOSH adopt the NIH-IREP model for lung cancer (Apostoaei and Trabalka 2004).

Statistical and Biological Models for Interaction

NIOSH is concerned with appropriately characterizing the interaction on a relative rate scale between two time-varying continuous exposure variables (i.e., occupational radiation doses and cigarette smoking rates). In contrast to the statistical evaluation of product terms for two fixed binary exposure variables, an evaluation of the interaction between smoking history and occupational radiation exposure history may be relatively complex. Statistical evidence of a smoking-radiation dose interaction may depend upon model assumptions about the etiologically-relevant periods of exposure for each agent, assumptions about the importance of the temporal ordering of exposures, and assumptions about the shapes of the exposure-response patterns for single versus joint exposures. Misspecification of such assumptions may lead to incorrect conclusions about the nature of the interaction between exposures.

Multistage models of carcinogenesis provide a useful starting point for discussion of joint exposures in lung carcinogenesis. One consideration is the importance of the temporal pattern of exposures on the magnitude of the joint effects of exposure. For some carcinogens the temporal ordering of exposures and the time interval between exposures is an important determinant of the magnitude of their joint effects. If exposure to cigarette smoke leads to a change in the probability of an early stage event in a multistage process of carcinogenesis then accrual of cigarette smoke exposures late in life (and specifically after radiation exposure from the A-bomb) may have a relative small impact on lung cancer risk. In contrast, exposure to cigarette smoke early in life (and particularly prior to radiation exposure from the A-bomb) may have a relatively large impact on lung cancer risk.

Multistage models of carcinogenesis further suggest that the temporal pattern of exposures may impact the distribution of induction/latency periods for lung cancer (as well as the subsequent evolution of risk patterns over time). It is plausible that early

cigarette smoke exposure(s) may influence later susceptibility to radiation risk and that this association may differ in magnitude and temporality from that observed when radiation dose precedes cigarette smoking. One might postulate, for example, that radiation-induced lung cancer may tend to appear after shorter induction/latency periods for people who were smokers than non-smokers (Archer, Coons et al. 2004). Classical multistage models of carcinogenesis, and contemporary understanding of the molecular basis of lung cancer pathology suggest that the distribution of induction/latency periods for lung cancer may differ for those with single versus joint exposure to these agents (and that the distribution may vary in relation to the temporal order of exposure, and the time interval between exposures). Of course either exposure may influence more than one stage of a multistage disease process; however, regardless of whether an exposure influences one or more stages of this process, its relative influence on the change in the probability of each event may differ due to baseline rates for these events so that such a carcinogen's impact may primarily act at an early or late stage.

Joint effects of radiation and smoking among Japanese A-bomb survivors

The situation considered by Pierce, et al. is somewhat simpler than that of direct concern to NIOSH since in the case of the study of atomic bomb survivors radiation dose is considered as a fixed variable. Pierce et al. investigated lung cancer incidence using information for a subcohort of the Lifespan Study (LSS) of atomic bomb survivors that includes approximately 45,000 survivors for whom smoking history information was available and for whom cancer incidence was determined through 1994 (Pierce, Sharp et al. 2003).

In their analysis Pierce et al. further simplified their investigation of the interaction between cigarette smoking and radiation dose by treating cigarette smoking as a fixed (rather than time-dependent) variable. Subjects were treated as continuous smokers (at a fixed rate based upon the response to at least one survey about cigarette smoking) or never smokers. They do not consider age at start of smoking or its relation to age at time of bombing; they do not consider age at termination of smoking or its relation to age at onset of cancer; and, they do not consider the duration of smoking or cumulative pack-years.

Their cited reasons for this simplification included the analytical difficulties of utilizing information on each person's smoking history and the limitations of the available smoking history data. A fundamental question, however, is whether the investigators' simplified approach to treating the temporal aspects of joint exposures have led to spurious conclusions about the true nature of the joint effects of these agents. Mechanistic models and experimental evidence for some carcinogen pairs suggest that the temporal patterns of exposures and subsequent disease risk are fundamental considerations when trying to appropriately characterize the joint effects of the exposures. In such cases failing to consider the temporal aspects of the interaction may lead one to draw spurious conclusions about the nature of the interaction between these agents and the consistency of the interaction effect over time. In the case of cigarette smoking, prior epidemiological research has established that the temporal aspects of

smoking history are important considerations when evaluating smoking effects on lung cancer risk (Brown and Chu 1987; Doll, Peto et al. 2004). It is reasonable to postulate that the temporal aspects of smoking history may be as important or more important to analyses of the joint effects of smoking and radiation dose on lung cancer risk.

As Pierce et al. note, one reason for their simplified approach to constructing an exposure metric from individual smoking histories was the limitations in the available data. A number of authors have discussed limitations in the LSS study as they relate to analyses of radiation-cancer mortality associations. These include concerns about health-related selection processes, incomplete and inaccurate reporting on location at time of bombing (survivor), and other uncertainties about prompt and residual radiation exposure estimates (Shimizu, Kato et al. 1992; Stewart and Kneale 1998).

In addition to these considerations the study question investigated by Pierce et al. requires relatively complete and valid information on individual survivor's smoking histories. In order to fully characterize the nature of the interaction between smoking and radiation dose the study requires complete smoking histories that span the period prior to the nuclear attack until the end of follow-up for each survivor. The survey data used in this analysis, in contrast, provides snapshots in time of smoking histories for those who responded to mail questionnaires or clinic visits. Such information is highly incomplete (missing entirely for about 45% of survivors); for those with some information on smoking history, information analyzed on smoking rate pertains to the average smoking rate reported at one or more survey dates. No information in these analyses characterizes the potential variation in smoking rates over decades of life prior to the atomic bombing or, in fact, prior to first survey in the 1960s.

As in any epidemiological analysis based on self-reported information it is reasonable to question the reliability of this information. Such considerations are particularly important given the context of a research program initiated by an occupying military of a population of atomic bomb survivors. The authors state that about 2400 (i.e, roughly 5%) of those who responded to at least one mail or clinical survey provided incomplete or inconsistent information and had to be excluded from analyses. It is likely that other survivors provided information that was inaccurate but not logically inconsistent and therefore was included in these analyses.

Crucially, the analyses reported by Pierce et al. are constrained to provide information on the nature of the smoking-radiation dose interaction only for the period that begins approximately two decades after radiation exposure. Pierce et al. note that "there is something lost by the later-than-usual entry to follow-up" (Pierce, Sharp et al. 2003). Specifically what is lost is the ability to characterize the nature of radiation-induced lung cancer during the first roughly 19 years after exposure; further, while the joint effects of radiation and smoking exposure are of interest, these analyses do not evaluate their joint effects during this extended period (nearly two decades) after radiation exposure. This is another limitation that relates to the absence of complete smoking history information for A-bomb survivors. A person only enters follow-up on the date that smoking history information was first obtained. Consequently, while the pattern of lung cancer risk

during the years (and decades) immediately after radiation exposure is potentially very important to the characterization of the joint effects of smoking and radiation dose, this period of observation is not captured by these analyses. As Pierce et al. note, information on smoking was obtained in several mail surveys and clinical interviews between 1964 and 1992. Therefore people do not enter follow-up until 1964 or later and consequently (in contrast to most analyses of LSS data) lung cancer risk during the first 19 years after exposure to ionizing radiation is not incorporated into the analysis of the joint effects of smoking and radiation. Many females did not enter follow-up until approximately 25 years after radiation exposure (when the first mail survey that included females was conducted) which is important since two-thirds of the study subjects in this analysis are female. Evaluation of the joint effects of smoking and radiation on lung cancer risk is therefore constrained by the inability to evaluate, for example, a prompt peak in lung cancer risk following ionizing radiation exposure among smokers. If the joint effects of radiation and smoking exposures on lung cancer risk were relatively largest in these early years after radiation exposure, and diminished with protracted time since exposure, then the analysis by Pierce would mischaracterize their joint effects due to the limitation of only examining later periods of follow-up.

The requirement that persons be alive and cancer-free at the time of the smoking surveys also has implications for evaluations of variation in ERR/Sv with age-at-exposure. As illustrated in Figure 3 of the paper by Pierce et al.(2003) a relatively small number of A-bomb survivors who were aged 50 or older at time of bombing were eligible for inclusion in this analysis; and a substantial proportion of these survivors would be classified in the lowest (i.e. referent) radiation dose category (Pierce, Sharp et al. 2003). Figure 3 does not show the number of lung cancer cases among those aged 50+ at time of bombing but presumably a very small number of lung cancer cases were available for analyses of radiation dose-lung cancer associations among those exposed to radiation (above the referent level) at older adult ages. Prior analyses of the full LSS cohort found that the ERR/Sv for lung cancer was larger for those exposed at older adult ages (e.g., age 50+) than at younger adult ages (Pierce, Shimizu et al. 1996). Pierce et al., in contrast, note that in these analyses there is no statistically significant age-at-exposure effect for lung cancer when allowing the ERR/Sv to decrease with attained age (Pierce, Sharp et al. 2003). This conclusion, however, needs to be tempered by the fact that their recent analysis has very little ability to evaluate radiation effects on lung cancer risk among those survivors exposed to radiation at older adult ages since only a very small number of survivors (and in particular lung cancer cases) were observed among survivors who were exposed at older adult ages. Furthermore, conclusions drawn from these analyses of radiation effects are limited to the period of follow-up that commences roughly 19 years after exposure to radiation. Therefore these analyses may have excluded the period of risk of greatest relevance for radiation-induced lung cancer among survivors exposed at older adult ages. If, as is plausible, the induction/latency period for radiation-induced lung cancer among people exposed as older adults tends to be shorter than 19 years then this analysis would fail to capture a period of primary concern for radiation-induced lung cancer among adults exposed at older ages.

Summary

The epidemiological literature provides a very limited scientific basis for characterizing the joint effects of cigarette smoke and external exposure to ionizing radiation on lung cancer risk. The paper by Pierce et al. (2003) addresses an important question; however, interpretation of the findings of their analyses is constrained by the limitations outlined above. Crucially, their analyses only provide information on cases ascertained approximately two decades after the bombing and significant questions about the temporal aspects of the interaction between smoking and radiation are not addressed.

One can speculate about characteristics of interactions between smoking and radiation on lung cancer risk by drawing upon evidence from analyses that have investigated smoking and radiation effects by fitting multistage models of carcinogenesis to epidemiological data. Although ionizing radiation has the general ability to produce mutational events, loss of certain functional capabilities at an early stage may increase the likelihood of radiation-induced later stage events. The pattern of increased risk of radiation-induced cancer with age at exposure (above age 20), and evidence of a linear dose response, has been the basis for positing that ionizing radiation exhibits primarily late-stage effects, although the large effect of childhood irradiation may also indicate an effect on an early stage of the carcinogenic process (Doll 1978; Schottenfeld and Fraumeni 1996; Peto 2001). The patterns of lung cancer risk observed among smokers have been the basis for drawing inferences about the stage(s) of carcinogenesis affected by cigarette smoking. It has been posited that smoking affects an early stage of the carcinogenic process as well as a late stage (Brown and Chu 1987). To the extent that these exposures influence different stages of a multistage process of carcinogenesis the magnitude of their joint effects (and the distribution of induction/latency periods for induced cases) may depend upon their temporal ordering.

Studies of underground uranium miners provide evidence about the joint effects of smoking and radiation exposure, although the mechanisms of interaction may differ for radon inhalation versus external radiation exposures. Recent analyses of lung cancer among American underground uranium miners by Archer et al. investigate differences in estimated latency periods by age at start of exposure and smoking status; the findings suggest that latency periods were typically longer for smokers than non-smokers and longer for those exposed at young ages when compared to those exposed at older ages (Archer, Coons et al. 2004). In contrast, Langholz et al found no significant evidence of differences in latency periods by smoking status in analyses of radon exposure and lung cancer mortality among Colorado Plateau uranium miners, but did find that radon effects peaked and declined much faster for those exposed at older ages than for those exposed at younger ages (Langholz, Thomas et al. 1999). Studies of radon exposure in the home and cigarette smoking have also examined the joint effects of these exposures; in a recent collaborative analysis, a model in which the combined effects of radon and smoking was additive was rejected (Darby, Hill et al. 2005).

The assertion by Apostoaei et al. that the lung cancer model based on the analyses by Pierce et al. (2003) represents the current state of knowledge about radiation-induced lung cancer overstates the significance of that analysis of A-bomb survivor data. Rarely

if ever does a single research paper establish the state of literature. The analyses by Pierce et al (2003) examine cancer incidence in a subcohort of approximately 44,000 A-bomb survivors who were alive and cancer free at the time of a smoking survey and provided responses that were logically-consistent. While interesting, the findings reported by Pierce et al. (2003) provide a weak basis for a meaningful scientific understanding of the joint effects of radiation and smoking on lung cancer risk. Neither those findings nor the other findings in the epidemiological literature provide compelling support for the conclusion that the smoking-radiation interaction is likely additive on the relative rate scale, as described by the current NIH-IREP model. Unfortunately, neither is there is there compelling evidence to support the NIOSH-IREP model. Rather, the nature of this interaction remains poorly characterized and the epidemiological literature provides an extremely limited scientific basis for this aspect of compensation decisions. A decision about how to model this interaction therefore becomes primarily a policy decision about how to make a compensation determination in the face of scientific uncertainty. The revisions to the NIH-IREP model with respect to age-dependency of lung cancer risk models in response to the analyses by Pierce et al. (2003) are questionable given the fact that analyses reported by Pierce et al. (2003) encompass relatively few A-bomb survivors who were exposed at older adult ages and include follow-up only for the period that commences roughly 19 years after exposure, therefore failing to characterize risk patterns during a potentially important risk period after radiation exposure.

Conclusion

The current epidemiological literature provides an inadequate basis for determining whether the current NIOSH-IREP or NIH-IREP model provides a more appropriate characterization of the joint effects of smoking and radiation dose on lung cancer risk. One alternative suggested by NIOSH is to run both models and use the result that provides the higher probability of causation. One might expect that appropriate specifications of uncertainty distributions around the parameters that differ for the two IREP models could produce similar results, however, the approach suggested by NIOSH would offer one method for accounting in a claimant-friendly manner for the substantial uncertainty about the smoking-radiation dose interaction.

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