Lung cancer: interaction of radiation exposure with smoking. What to do in IREP?

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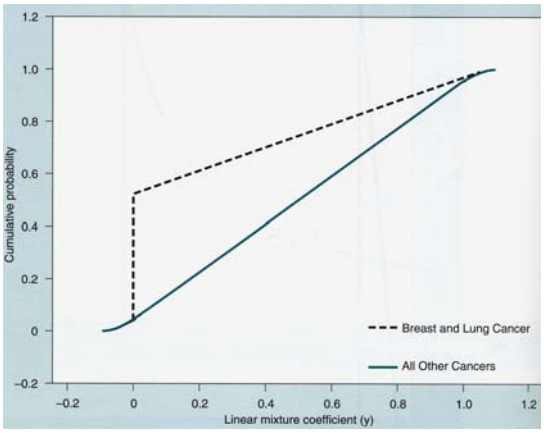
The issue here is how to estimate age-specific values of lung cancer ERR at a given dose for the US population, in the presence of large differences in baseline rates caused by smoking status. The NCI approach, documented in the 2003 NCI-CDC report on revision of the NIH Radioepidemiological Tables (Land *et al*. 2003), differs from the NIOSH-IREP approach in the balance that is chosen between the additive and multiplicative models.

Both codes use a linear combination of an additive and a multiplicative model:

$$(ERR)_{US} = y \times (ERR)_{mult} + (1-y) \times (ERR)_{add} ,$$

where the variable y varies between -0.1 and 1.1. Here, $(ERR)_{mult}$ is the site-, sex-, and age-specific excess relative risk obtained from the A-Bomb data, and $(ERR)_{add}$ is the same value, adjusted for the corresponding ratio between baseline rates in the two countries. y=0 corresponds to the additive model, y = 1 to the multiplicative model.



The NCI approach is to sample from a probability distribution for y that is shown here. The solid line indicates that any value of y (from 0 to 1) is equally likely, while the dashed line, adopted for lung cancer, indicates that a 50% chance is given to pure additivity (y=0) and 50% weighting is distributed equally among any other value of y between 0 and 1. (There is also a small probability assigned to values of y less than 0 and greater than 1). The NCI approach was based on the results of Pierce et al (2003) in a recent analysis of A-bomb survivors.

By contrast, the NIOSH model uses an interaction term based primarily on radon (alpha particle exposure) data, sampling from a probability distribution of *y* values that is weighted towards the multiplicative.

For the endpoint of lung cancer, studies looking at the interaction between smoking and (high) radiotherapy doses have concluded that the interaction are reasonably well described by a multiplicative model (Neugut et al. 1994, van Leeuwen et al. 1995, Gilbert et al. 2003). Studies looking at the interaction between radon (alpha particle) exposure and smoking have either found either a multiplicative interaction (Samet et al. 1991, Pershagen et al. 1994, Morrison et al. 1998, Melloni et al. 2000) or an interaction which is intermediate but closer to multiplicative (Hornung et al. 1995, NRC 1999). One study (Tokarskaya et al. 2002) has suggested that the balance between additive and multiplicative models depends on the smoking level (higher smoking levels make the interaction more multiplicative, lower smoking levels make the interaction more additive). There is one recent report for A-bomb survivors of a purely additive interaction (Pierce et al. 2003). Specifically, Pierce et al (2003) found that, among A-bomb survivors with both radiation dose estimates and smoking history data, lung cancer risk was consistent with an additive model for interaction model between radiation and tobacco smoking, but inconsistent with a purely multiplicative model.

There is little *in-vitro* or mechanistic research to help guide us, though one study from Hei and colleagues showed an additive interaction between cigarette smoke condensate and gamma ray exposures (Piao and Hei 1993).

It is clear that the nature of the interaction between tobacco and radiation exposure is not known. Although the analysis from Pierce at al (2003) is solid, there are many uncertainties, in large part due to the limited quantification available of smoking patterns in the A-bomb survivors. Apart from this uncertainty, we do not know whether the interaction patterns found there (in a Japanese population with a mean date of birth approximately 1910) can be used for a US population with any more confidence than the radiotherapy patterns (Neugut et al. 1994, van Leeuwen et al. 1995, Gilbert et al. 2003) where the mean date of birth is more recent, the population is Western, the smoking data are rather more complete, but the radiation doses are higher.

In summary, this Reviewer suggests that the overall weight of evidence suggests that the interaction is indeed intermediate between additive and multiplicative, and we really cannot say more than that.

On a practical level, therefore, it does not seem reasonable to use, for the primary IREP model, the NCI model which weights the balance much more towards additive. This Reviewer suggests that, at the present time, a model in which all values of *y* between zero and 1 are equally likely represents the most reasonable approach for probability of causation estimates. It would certainly be reasonable to include, within 95% confidence limits, a model which is 50% additive (y=0) and the rest of the probability distributed equally between y=0 and y=1 (the current NCI-IREP model), as well as a model which is 50% multiplicative (y=1) and the rest of the probability distributed equally between y=0 and y=1. It is suggested that the "tails" below 0 and above 1 be removed.

Thus the suggestion is that the "extreme" IREP models are not purely additive or purely multiplicative, but somewhat intermediate. It is suggested that risk estimates from all three model be included in IREP outputs, with appropriate annotations for each.

A problem with the IREP lung model(s) as they stand is the lack of documentation as to exactly what is done. A user of IREP, either the NCI or the NIOSH version, really would have no idea what or which model is being used, a quite unfortunate state of affairs. This really needs to be rectified.

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