Age specific interactions between smoking and radon among United States uranium miners

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Abstract

United States uranium miners who smoked have death rates from lung cancer that are intermediate between the rates predicted by the additive and multiplicative models (on a ratio scale) across all age groups. Age specific patterns of interaction have not been thoroughly examined, and most analyses have been internal ones in which there was no truly non-exposed group. Here age specific death rates of lung cancer among ever smoking uranium miners have been examined for conformity with the additive and multiplicative models. The multiplicative model fits well for the youngest and oldest categories, but poorly for the middle age ranges. In the middle age range, predicted rates under the multiplicative model were quite high, surpassing the corresponding United States death rates for all causes combined. If the multiplicative model is assumed to hold across all ages, one hypothesis that might explain the observed age specific patterns is that the full expression on the multiplicative model might not be seen at certain ages due to a limited pool of miners susceptible to lung cancer. These data, however, have several limitations such as small numbers of deaths from lung cancer among never smokers, the use of qualitative rather than quantitative smoking and radon exposure data, and ignorance of the underlying biological mechanisms of interaction.

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Interactions between two strong risk factors are often found to have effects on cause specific mortality that are intermediate between additive and multiplicative models on a ratio scale.¹ The additive model is defined as $RR_{12} = RR_1 + RR_2 - 1$ (or alternatively $R_{12} = R_1 + R_2 - R_0$), and multiplicative is defined as $RR_{12} = RR_1 \times RR_2$ (or alternatively $R_{12} = R_1 \times R_2 / R_0$), where the RRs refer to rate ratios and the Rs refer to rates; and RRs are calculated by dividing the rates for those exposed to factor 1 or 2 by the baseline rate (R_0) for those exposed to neither factor.

Prior analyses by Hornung and Meinhardt of the data for United States uranium miners who smoke, have shown that death rates from lung cancer for this cohort are somewhere

between additive and multiplicative, with a tendency to move away from multiplicative toward additive as follow up time increases.² No data were presented on the age specific patterns of interaction between cigarette smoking and exposure to radon.

Here I have reanalysed these data to examine age specific interactions. The Hornung and Meinhardt analyses relied on relative risk regression analyses with an internal referent group, in which all subjects were uranium miners with some exposure to radon daughters.² I have used a somewhat different approach, relying on lifetable analyses using never smoking United States veterans as a referent group to derive age specific expected death rates from lung cancer for smoking miners under additive and multiplicative models.³ The age specific expected rates were then compared with age specific observed rates.

The motivation for this examination of age specific patterns of interaction was to determine at which ages the multiplicative model failed to hold. Under the assumption that the multiplicative model is correct (that is, it reflects the true underlying biological processes), one possible explanation (among many) for the less than multiplicative phenomenon is that a full multiplicative effect of two strong risk factors might increase cause specific mortality so greatly (for example: to a level greater than the expected rates for all causes) that it could not be fully expressed, due to a limited population of susceptible persons at risk from the specific cause. If this hypothesis were true, one might expect the data to fail to conform to a multiplicative model especially for age groups for which the multiplicative model predicted the highest excesses of lung cancer. Examination of the age specific data for United States uranium miners enables further investigation of this hypothesis.

Materials and methods

Death rates of lung cancer for United States veterans never smokers, and ever smokers of cigarettes were obtained from the 1950s to the early 1980s from Aaron Blair at the National Cancer Institute (personal communication). These men were virtually all white. Age specific rate ratios for ever smokers v never smokers were then calculated (RR_1).

Data for white United States uranium miners exposed to radon were available from a cohort of miners assembled by the National

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Table 1 Rates of lung cancer ($\times 10^5$)

Age	Death rate (R_0) of never smokers (US vets) (n = 55 049)	Death rate (R_1) of ever smokers (US vets) (no radon) (n = 142 518)	Death rate (R_2) of radon exposed (never-smoking miners) (n = 516)	Death rate (R_{12}) of radon and smoking (smoking miners) (n = 3052)
30-50	5.7 (4)	26.3 (51)	45.0 (3)	164.1 (50)
50-59	10.0 (12)	90.5 (370)	218.9 (5)	722.9 (114)
60-69	21.3 (83)	190.7 (1766)	286.1 (4)	1012.0 (85)
70 +	46.6 (226)	370.3 (3336)	286.5 (2)	1703.6 (50)

US vets = United States veterans.

Institute for Occupational Safety and Health (NIOSH), for both never smoking and ever smoking miners.⁴ Smoking data were from the late 1960s and early 1970s. Age specific rates of lung cancer were calculated separately for never smoking and ever smoking miners from the NIOSH life table programme.⁵

Age specific rate ratios for radon exposure among never smokers were then calculated (RR_2), comparing never smoking uranium miners with never smoking United States veterans.

From these data, expected age specific death rates from lung cancer under either an additive or a multiplicative model were calculated, and these were then compared with observed age specific death rates from lung cancer for the ever smoking uranium miners.

Predicted rates were based on data with small numbers and hence exhibited variance. Confidence intervals (CIs) for the predicted rates under the additive model were calculated assuming the independence of summed rates and assuming that the observed deaths in these rates were Poisson variates. A logarithmic transformation and Taylor series approximation, as well as the assumption of independence and Poisson variance, were used in calculating the CIs for the predicted rates under the multiplicative model.

Observed and predicted rates of lung cancer for miners who smoke.

Table 2 Predicted and observed rates of lung cancer ($\times 10^5$) and deaths under additive and multiplicative models for ever smoking United States uranium miners (n = 3052)

Age	Predicted rate* additive model ($R_1 + R_2 - R_0$) (95% CI)	Predicted rate multiplicative model ($R_2 \times R_1 / R_0$) (95% CI)	Observed rate for smoking miners (95% CI)
30-50	66 (13-117)	207 (45-946)	164 (119-210)
50-59	299 (107-491)	1989 (697-5675)	723 (590-855)
60-69	455 (175-736)	2558 (937-6983)	1012 (797-1227)
70 +	610 (222-1008)	2276 (565-9161)	1704 (1213-2176)

* R_0 , R_1 , and R_2 are from table 1.

Results

Table 1 gives the rates for lung cancer for never smoking United States veterans (R_0), for ever smoking United States veterans (R_1), for never smoking miners exposed to radon (R_2), and for ever smoking miners (R_{12}). There were only 14 deaths among never smoking uranium miners, which dictated the choice of the rather broad age categories.

Table 2 presents the predicted death rates from lung cancer for ever smoking United States uranium miners under the additive and multiplicative models. The figure shows that the observed rates are clearly intermediate between those predicted by the additive and multiplicative models.

The figure indicates that the multiplicative model fits the data more closely than the additive at the youngest and oldest age categories. However, CIs (table 3) between the rates predicted for the additive and multiplicative models overlap at these same age categories.

Table 3 shows the ratio of the predicted rates under additive or multiplicative models compared with the all causes United States death rate in 1980. These ratios are particularly high for the multiplicative model for age 50-59, in which the predicted mortality from lung cancer is almost twice the 1980 United States death rate for all causes.

Discussion

These data are limited by small numbers and the lack of quantitative data on smoking and exposure to radon daughters for the development of rate ratios. The problem of small numbers (and the resulting unstable estimates) is almost always a problem in considering lung cancer among never smokers. In our data there were only 14 deaths from lung cancer among never smoking miners, and age specific rates based on these 14 deaths were used to derive predicted rates of lung cancer for miners who smoke under the additive and multiplicative models, resulting in low precision for the predicted rates.

Table 3 Ratio of predicted rates of lung cancer to the United States 1980 rate* for white men for all causes, under two models

Age	Multiplicative model	Additive model
30-50	0.73	0.23
50-59	1.78	0.27
60-69	0.96	0.17
≥ 70	0.29	0.08

*The 1980 United States death rate for white men for the four age categories from youngest to oldest was 282.2, 1190.0, 2673.1 and 7719.0 ($\times 10^5$).

The predicted rates for miners who smoke calculated in this paper are based on comparisons of exposed *v* non-exposed populations without reference to the amount of radon or tobacco exposure. If the age specific strata of our observed cohort of uranium miners who smoke differed greatly in the level of exposure to radon or smoking from the age specific strata of the populations used to develop predicted rates (the never smoking uranium miners or smoking United States veterans), then different levels of radon or smoking might confound our results. A similar problem might occur for latency (time since first exposure to radon). The predicted rates of lung cancer under additive or multiplicative models would then not be the appropriate ones to compare with the observed rates of lung cancer for uranium miners who smoke.

Some data are available to assess this problem for radon exposure and latency. Average radon exposures and average latencies (weighted by person-years) for the four age groups were reasonably similar for ever smoking *v* never smoking miners (643, 725, 740, and 725 *v* 502, 677, 749, and 829 working level months for radon exposure, and 16, 22, 26, and 28 years *v* 17, 23, 24, and 28 years for latency). These data suggest that radon exposures and latency do not confound the comparison of observed and predicted rates of lung cancer between age groups. On the other hand, no quantitative data were available for smoking either for the miners or the United States veteran referent group, leaving open the possibility of confounding due to smoking.

Other authors have used quantified data on smoking and radon exposure in assessing interaction. For example, Hornung and Meinhardt used regression analyses of continuous data (pack-years, working level months) with an internal referent group to assess interaction.² These authors did not, however, present age specific results for interaction. Furthermore, here I have used external rather than internal referent rates to present data on the absolute size of the rates in question as well as to use a completely non-exposed referent group.

Perhaps an even more important limitation to these data is our ignorance of underlying

mechanisms affecting rates at a biological level. The mechanism by which either smoking or radon cause lung cancer remains incompletely understood. Debate continues as to whether these exposures are initiators, promoters, or both. Our ignorance of the simultaneous effects of these exposures is more profound. The sequential timing of the respective exposures may also affect interaction.⁶ Differing patterns of risk by age for persons exposed to both tobacco smoke and radon may well reflect unknown underlying mechanisms, which would not be expected to conform consistently to either an additive or multiplicative model across different ages.

Despite these reservations, the results confirm the overall finding of a sub multiplicative effect of radon daughters and smoking reported by Hornung and Meinhardt.² The evaluation of age specific patterns suggests that the multiplicative model fits well at the youngest and oldest ages, but poorly for the middle age range (the additive model fits about equally well (or badly) across all ages). The multiplicative model fits particularly poorly when the predicted rate of lung cancer is highest in comparison with overall death rates expected for United States white men. This pattern conforms to what might be expected under the hypothesis that the multiplicative model is the true model, but that there is a limited susceptible pool of persons who can die of lung cancer, and that this pool is exhausted when death rate from lung cancer predicted by the multiplicative model is too high.

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