THE EFFECTS OF PROTOCOL CHOICES ON A RADON-LUNG CANCER EPIDEMIOLOGIC STUDY

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ABSTRACT

Exposure to radon progeny provides an opportunity to study the effects of low doses of ionizing radiation. Unfortunately, case control studies in the general population have failed to find a consistent association between radon and lung cancer. Since these studies did not use the same measurement and selection protocols, there may be differentially inaccurate assessment of the cumulative radiation dose between the studies. Radon concentration measurements for one year or less are the most commonly used lifetime dose surrogate. A Monte Carlo simulation was used to study the effects of protocol changes on the base design of the Iowa Radon Lung Cancer Study. Substantial loss of correlation and increase in misclassification occur when the simulation included shorter residency in the current home and less than complete, mobility-weighted radon exposure measurements. Substantial increases in correlation and decreases in misclassification occurred when airborne radon progeny dose surrogates substituted for radon measurements.

INDEX TERMS

Radon, Epidemiology, Sensitivity, Misclassification, Dose surrogates

INTRODUCTION

Airborne radon (^{222}Rn) progeny constitute the major source of radiation exposure for most people. The association between radon exposure and lung cancer in underground miners has led to a prediction of substantial numbers of lung cancers from non-occupational radon exposures (National Research Council, 1999). However, case control epidemiologic studies of residential radon exposures have failed to find a consistent association between radon and lung cancer. The failure to find an association in some environmental epidemiologic studies is understandable since those studies had only a few hundred subjects who lived in regions where only a few individuals would have significant cumulative exposures. Radon concentrations are highly variable indoors. Common radon dose assessment practices rely on the measurement of radon at one or two locations for a time period of one year or less. Radon-related lung cancer risk results from cumulative exposure over many years. The exposure during the period from 5 to 30 years prior to the present is thought to be most effective in creating lung cancer (National Research Council 1999). Additional uncertainties are introduced in studies that include individuals who occupy multiple houses during that 30-year period. Limited resources and owner refusals contribute to missing measurements in previously occupied houses. Measurement errors associated with trying to reconstruct radon-related dose of a mobile population over decades seriously limit the power of small studies to detect an association (Field *et al.* 1998, Field *et al.*1996, Fisher *et al.*1998, Lubin *et al.* 1990, Lubin *et al.*1995).

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Three case control studies have been completed in Central North America where radon concentrations are elevated and variable indoors and outdoors (Alavanja *et al.* 1999, Field *et al.* 2000, Létourneau *et al.* 1994, Steck 1992, Steck *et al* 1999). Figure 1 shows that two of the three studies found no association between radon and lung cancer.

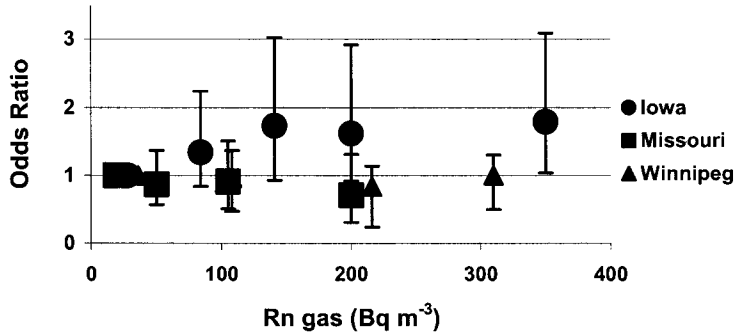

Figure 1.Odds ratios from three studies that use radon gas measurements as a dose surrogate.

A detailed model simulation of these three case-control studies was applied in an effort to understand the effects of a few specific choices on the sensitivity and misclassification of commonly used dose surrogates and selection protocols. The simulation used one of the studies as a base and then varied the characteristics of that study to be similar to the other studies.

METHODS

A Monte Carlo procedure used separate steps to (1) to generate the dose rates in 20,000 typical living spaces characteristic of the study area; (2) to simulate the exposure of individuals to a lifetime of radon in a variety of those occupied spaces (up to 7); and (3) to select subgroups of those individuals for 10 simulations of 400 case- 600 control studies. The input data and distributions were drawn from published case-control studies conducted in central North America; in Winnipeg (Létourneau *et al.* 1994), in Missouri (Alavanja *et al.* 1999), and in Iowa (Field *et al.* 2000). A partial listing of the variables modeled includes: radon concentration by floor; ventilation losses; surface deposition rates for radon progeny; smoking patterns; age; mobility; residency; occupancy; missing measurement rates, and measurement errors. Table 1 illustrates the level of detail included in the model by showing the radon distributions parameters.

The Iowa Radon Lung Cancer Study (IRLCS) characteristics were used as a base as they represented the most comprehensive data set available. Changes from this base case were made in (1) the surrogate for lifetime radon dose (2) the residency selection requirements. All studies used yearlong alpha track detectors to measure radon concentrations. The *a priori* dose surrogate used by the IRLCS was a time weighted radon exposure that included participant mobility patterns within the house, in another building (work, shopping), and outdoors. This dose surrogate is labeled "Complete Rn" in the figures. The Missouri study used the average of the kitchen-bedroom (Kitch_Bed Rn) radon, while the Winnipeg study used the average of the basement and first floor radon concentration as one of their dose surrogates (Base_1st Rn). In addition to these three dosimetric surrogates, we studied two hypothetical measurement surrogates; the dose rate in the current house (Doserate) without measurement error and the dose rate measured to within ±25% using surface deposited radon

progeny (Glassdose). The IRLCS required 20 years of occupancy in the participant's current home while the Missouri and Winnipeg studies had 5 and 1-year requirements respectively. The results of a Missouri-like residency requirement on the IRLCS base case are labeled IAMO in the Figures.

Table 1. Temporal and spatial and variations of radon observed[a] in central North America.

Variation	COV[b] %	Mean (Deviation) Bqm^{-3}	Region
Temporal: Year-to-Year	25		Minnesota
Spatial:			
Within a house			
-Room-to-room on a floor	10; 11		Iowa; Minnesota
-First floor-to-basement ratio[c]		0.55 (0.25); 0.64 (0.16)	Iowa; Minnesota
-First -to-second floor ratio[c]		1.02 (0.24)	Iowa
House to house[c]			
(Mobility weighted Rn in living spaces; 7% basement residency)	120	90 (2.2)	Iowa
	85	100 (1.8)	Minnesota
	120	44 (2.2)	Missouri
	150	120 (2.5)	Winnipeg
Workplaces[d]	170	70(2.7)	Minnesota
Outdoors[d]	40	29(1.4)	Iowa
	80	19(1.8)	Minnesota

[a] Alavanja *et al.* 1999, Field *et al.* 1998, Field *et al.* 2000, Fisher *et al.* 1998, Létourneau *et al.*1994, Steck 1992, Steck *et al* 1999

[b] Coefficient Of Variation expressed as a percentage

[C]Normal distribution: Mean value (Standard deviation)

[d] Lognormal distribution: Geometric mean value (Geometric Standard deviation)

The BEIR VI age weighted lifetime dose model was used as the standard for lung cancer risk (National Research Council, 1999). The radon exposure was converted to radon-related dose using a recent conversion model that incorporate typical atmospheric parameters to account for activity size distribution and dose effectiveness variations in different residential conditions (Porstendorfer and Reineking 1999). The radon -based dose surrogate's sensitivity was assessed using its correlation coefficient with the BEIR VI model weighted lifetime dose. The degree of misclassification was judged by shifts from the lifetime dose quintile of an individual to the surrogate quintile.

RESULTS AND DISCUSSION

The best available model suggests that radon-related lung cancer risk depends on radiation doses to the lung received over a lifetime (National Research Council, 1999). However, radon-related dose measurements are difficult and expensive. As a compromise, recent retrospective case-control studies have decided to make risk estimates based on a small number of measurements of dose surrogates, usually the contemporary radon concentrations in recently occupied home (s). These protocol choices raise serious questions about the effects of measurement error, missing data, and correlation on the sensitivity of the study to detect an effect. For example, how good are contemporary radon measurements for reconstructing past radon-related dose; how much does floor-to-floor variation within the home or year-to-year radon variation distort the dose estimates; could we improve the sensitivity if we measured dose rather than gas; even if the dosimeter was only 25% accurate? To try to get answers specific to the Iowa study, we focused on the differences between the Iowa study where a radon-lung cancer association was found and those in Missouri and Winnipeg were one was not detected. Those studies had somewhat similar protocols and participants since they took

place in geographically comparable areas. The Iowa study design included the most comprehensive radon measurement protocol to cover every occupied room within the home and the local average values for outdoors and in workplaces.

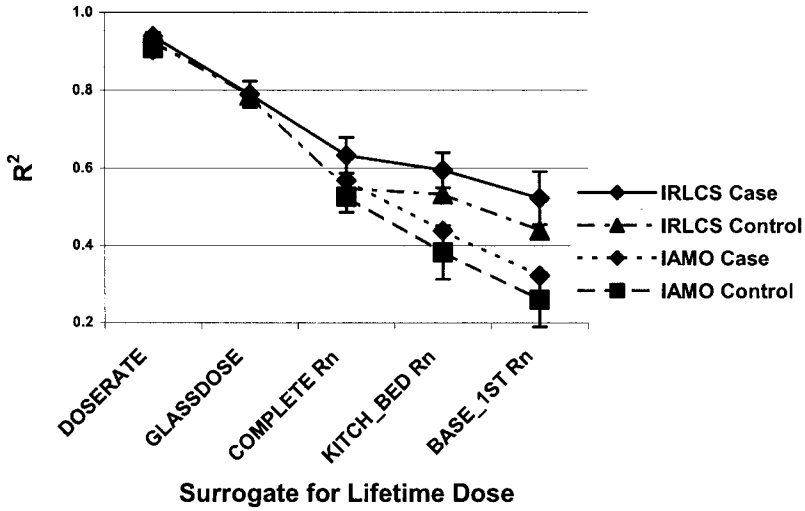

Figure 2. Correlation coefficients (R^2) for the simulated performance in Iowa for two hypothetical (DOSERATE and GLASSDOSE) and the actual Iowa (COMPLETE Rn), Missouri(KITCHEN_BED Rn), Winnipeg(BASE_1stRn)dosimetric surrogates with a 20 year (IRLCS) and a 5 year (IAMO) current home residency inclusion criterion.

The simulation showed that the Iowa study's *a priori* surrogate (Complete_Rn in Figures 2 and 3) performed somewhat better than the Missouri-style surrogate (Kitch-Bed) and a Winnipeg-style surrogate (Base_1st Rn). This relative performance result agrees with a comparative analysis of the surrogates using actual radon measurements in the Iowa study (Field et al. 2001). The correlation coefficient (R^2) between the IRLCS dose surrogate and the lifetime-weighted dose generated by the full Monte Carlo model is 0.63 for cases (400) and 0.55 for controls (600). When the 25% year-to-year radon variability was left out of the model, the correlation improves only slightly, to 0.67 for cases. When the residency requirement was relaxed from 20 years to 5 years (IAMO simulation), the absolute performance of all the radon surrogates was reduced but the relative performance order was retained. The correlation of the last two surrogates fell below 50%. It is hard to believe that an epidemiologic study in Iowa using those surrogates would have much of a chance of detecting an effect. From the simulation, it appears that a direct measuring radon progeny dosimeter with an instrumental error of 25% would make a better surrogate than any of the radon surrogates. If the instrumental error is increased to 50%, the dosimeter performance is comparable to the best radon surrogate.

Figure 3 shows the shift and bias of surrogates relative to the real risk factor in a uniform quintile categorical analysis of the IRLCS simulation. In each of the 10 study simulations, the average misclassification was calculated from the difference between the lifetime dose quintile and the surrogate quintile value for each subject. The radon surrogates show very little bias but a shift of roughly one quintile for each individual. This high shift rate suggests that even pooling of the currently-completed studies may not yield meaningful results unless very large numbers of well-characterized cases and controls are included in the pooling. The realistic dosimeter surrogate shows a little more bias but a little lower shift rate.

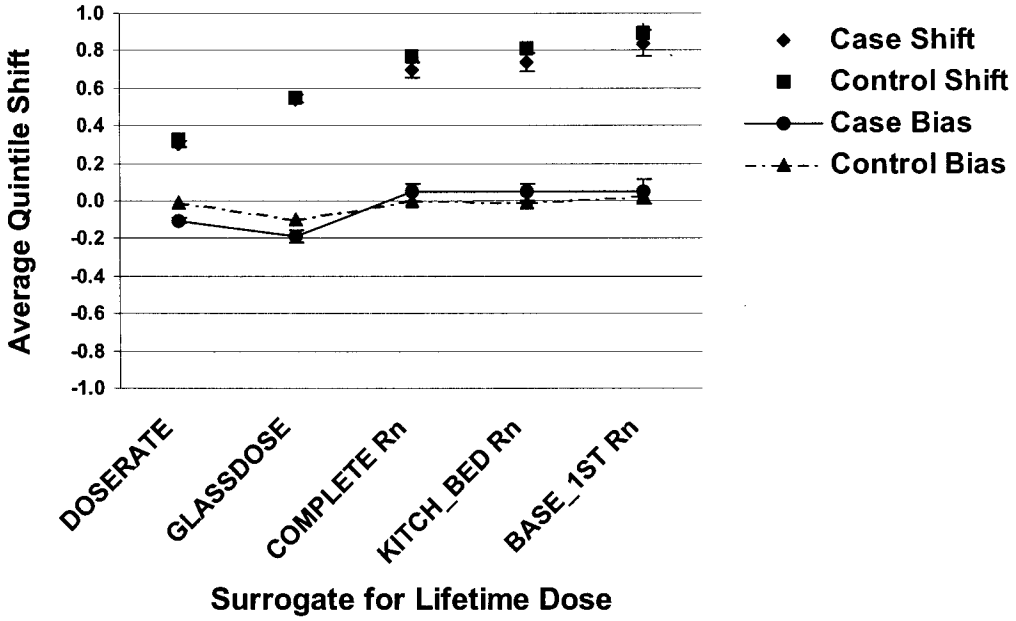

Figure 3. Average of the shift between the surrogate classification and lifetime dose quintile per individual (S-L). Shift is the term used for the average of the absolute values and Bias is the term used for the average arithmetic sum.

CONCLUSIONS

The *a priori* dose surrogate used in the Iowa study had higher correlation and less misclassification than other radon surrogates analyzed in this simulation. The performance seems to be most sensitive to the relative completeness of direct measurements of the radon in all occupied spaces during the 25-year window when radon exposure is thought to be most effective. Airborne radon progeny dosimeter measurements accurate to within ±25% outperformed the *a priori* Iowa risk surrogate.

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