

Residential radon exposure and lung cancer: Variation in risk estimates using alternative exposure scenarios

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The most direct way to derive risk estimates for residential radon progeny exposure is through epidemiologic studies that examine the association between residential radon exposure and lung cancer. However, the National Research Council concluded that the inconsistency among prior residential radon case-control studies was largely a consequence of errors in radon dosimetry. This paper examines the impact of applying various epidemiologic dosimetry models for radon exposure assessment using a common data set from the Iowa Radon Lung Cancer Study (IRLCS). The IRLCS uniquely combined enhanced dosimetric techniques, individual mobility assessment, and expert histologic review to examine the relationship between cumulative radon exposure, smoking, and lung cancer. The *a priori* defined IRLCS radon-exposure model produced higher odds ratios than those methodologies that did not link the subject's retrospective mobility with multiple, spatially diverse radon concentrations. In addition, the smallest measurement errors were noted for the IRLCS exposure model. Risk estimates based solely on basement radon measurements generally exhibited the lowest risk estimates and the greatest measurement error. The findings indicate that the power of an epidemiologic study to detect an excess risk from residential radon exposure is enhanced by linking spatially disparate radon concentrations with the subject's retrospective mobility.

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Introduction

The National Research Council's BEIR VI Committee estimates that residential radon-222 (radon) decay product exposure causes between 3000 and 38,600 lung cancer deaths per year in the United States (NRC, 1999). These risk estimates for the public were derived from data obtained from radon-exposed underground miners, an occupationally exposed group. However, extrapolations from miners to the public introduce uncertainty because of differences in lifestyle factors between the miners and the public as well as differences between the mine and home environments. As suggested by the NRC (1999), a more direct way to derive risk estimates for residential radon exposure is to compare residential radon exposure among people in the general population who have lung cancer versus the exposure received by people in the population who have not developed lung cancer.

Epidemiologic research plays an important role in the understanding of environmentally related disease. When multiple valid observational epidemiologic studies demonstrate a consistent positive association between a specific environmental exposure and a human disease, their findings tend to strongly influence decisions concerning the environmental agent's toxicity and the need for regulation (USEPA, 1984). Twelve major case-control epidemiologic investigations have been published examining the relationship between residential radon gas exposure and lung cancer. While the risk estimates from some of these studies at radon exposures of 150 Bq/m³ are in general agreement with underground miner studies, they have not conclusively demonstrated that residential radon gas exposure poses a statistically significant increased lung cancer risk. Therefore, they have had minimal impact on decisions concerning radon's carcinogenicity.

The National Research Council's BEIR VI Committee concluded that the apparent inconsistency in findings among residential radon case-controls studies was largely a consequence of errors in dosimetry (NRC, 1999). Historic estimation of radon gas exposure presents a formidable challenge in studies evaluating the association between residential radon exposure and lung cancer. Because the

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doses from residential radon exposures are low compared with occupational radon exposures and the presumed lung cancer risk is relatively low compared with radon-exposed miners, inaccurate radon exposure estimates impede a case-control study's ability to examine whether or not an association exists between residential radon exposure and lung cancer.

The authors have previously postulated (Field et al., 1996) that misclassification of residential radon exposure arises primarily from (1) detector measurement error, (2) failure to consider temporal and spatial radon variations within a home, (3) missing radon measurement data from previously occupied homes that were inaccessible at the time of the study (NRC, 1988; Lubin et al., 1990; Weinberg et al., 1996), (4) failure to link radon concentrations with subject mobility, and (5) measuring radon gas as a surrogate for radon progeny exposure. We have already examined detector measurement error (Field et al., 1998a) and are actively exploring other factors that affect radon dose estimates such as measuring radon gas as a surrogate for radon progeny exposure and temporal radon variations (Field et al., 1999; Steck et al., 2002). This study focuses on the impact of applying various alternative commonly used exposure assessment methods, which differ in location of residential radon measurement and linkage of radon measurements with subject mobility, using a common data set from the Iowa Radon Lung Cancer Study (IRLCS) (Field et al., 2000).

Most of the published case-control studies (Blot et al., 1990; Schoenberg et al., 1990; Pershagen et al., 1992; Pershagen et al., 1994; Alavanja et al., 1994; Alavanja et al., 1999; Letourneau et al., 1994; Auvinen et al., 1996; Ruosteenoja et al., 1996; Darby et al., 1998; Kreienbrock et al., 2001) utilized radon measurements from one or two rooms to characterize the entire domestic exposure and did not attempt to link temporal and spatial home occupancy patterns with multiple radon measurements within a home in order to calculate retrospective cumulative radon exposures for a given time period. Because the study design of the Iowa study (Field et al., 2000) included multiple radon measurements in various areas where the subject spent time and the linkage of these measurements to the subjects' spatial and temporal mobility, the data from the IRLCS provide a unique opportunity to compare various exposure methods while using a common data set. In fact, the study design allows testing of our alternative *a priori* postulated methods (Field et al., 1996) of less rigorous exposure and evaluation of whether or not they produce lower risk estimates.

Methods

The IRLCS was a population-based case-control epidemiologic study that evaluated the lung cancer risk posed to

females by smoking and prolonged residential radon exposure (Field et al., 2000). The IRLCS combined enhanced dosimetric techniques, individual mobility assessment, and expert histologic review, within a population characterized by stability, high percentage of live cases, and potential for high radon exposure (White et al., 1992) to examine the relationship between cumulative radon exposure, smoking, and lung cancer. The IRLCS had four major components: (1) rapid reporting of cases, (2) a mailed questionnaire followed by a face-to-face interview, (3) a comprehensive retrospective radon exposure assessment, and (4) independent histopathologic review of lung cancer tissues. The retrospective radon dosimetry assessment consisted of five components that allowed calculation of individual radon exposures: (1) on-site residential assessment survey, (2) on-site radon gas measurements in multiple areas of the home (Fisher et al., 1998), (3) regional outdoor radon measurements (Steck et al., 1999), (4) assessment of subjects' exposure when in another building, and (5) linkage of historic subject mobility with

Table 1. Description of *a priori* defined radon dosimetry model (WLM₅₋₁₉) and alternative models.

Radon dosimetry model	Description of dosimetry models
IRLCS working level month (WLM ₅₋₁₉)	Multiple 1-year radon gas measurements in the home, outdoors, and in another building with linkage of these measurements to the subject's retrospective temporal and spatial mobility. Additional details concerning the mobility-linked WLM ₅₋₁₉ dosimetry model are presented elsewhere (Field et al., 2000).
First floor ^a	Mean first floor 1-year radon measurements with no linkage to the subject's spatial or temporal mobility. First floor is the story at ground level, usually above the basement.
Master bedroom ^a	Master bedroom 1-year radon measurements with no linkage to the subject's spatial or temporal mobility.
Master bedroom and living room (living area) ^a	Mean of the master bedroom and living room 1-year radon measurements with no linkage to the subject's spatial or temporal mobility.
Living room (living area) ^a	Mean of the living room 1-year radon measurements with no linkage to the subject's spatial or temporal mobility.
Basement ^a	Mean of the basement 1-year radon measurements with no linkage to the subject's spatial or temporal mobility.

^aAssumes a 70% home occupancy. Mobility refers to where the subject spends their time. Model does not include estimates of outdoor or other building radon gas concentrations.

radon concentrations in the residence, outdoor, and other buildings (Field et al., 1998b). The IRLCS limited enrollment of subjects to those individuals who lived in the current home a minimum of 20 years. Historic participant mobility within the home as well as time spent outside the home and in other buildings was ascertained by a face-to-face interview using a methodology described elsewhere (Brus, 1994; Field et al., 1998b). The mobility assessment accounted for all the time (168 h/week) from when the participant moved into their current home to study enrollment.

The IRLCS calculated a working level month (WLM₅₋₁₉) cumulative radon exposure assessment for the period 5 to 19 years prior to study enrollment (Field et al., 2000). This retrospective time window was chosen for three reasons. First, studies of underground miners demonstrated that the latency period for radiogenic cancer was 5 years (NRC, 1988; Lubin et al., 1994). Second, the 20-year interval eliminated any imputation of data for the current home. Third, radon risk has been shown to decline with time since exposure (NRC, 1988). Eleven WLM₅₋₁₉ is approximately equivalent to an average residential exposure of 150 Bq/m³ (4 pCi/l), assuming a 70% home occupancy and the other assumptions of the BEIR VI report (NRC, 1999). The IRLCS study design and methods are presented in detail elsewhere. The IRLCS protocols received approval from the University of Iowa's Institutional Review Board in accordance with guidelines from the U.S. Department of Health and Human Services.

The IRLCS investigators identified several dosimetry models prior to initiating the data collection for the study (Table 1). The IRLCS selected the WLM₅₋₁₉ dosimetry model (Eq. 1) as the preferred model to minimize radon exposure uncertainty. This model links radon measured on separate floors of the home and at sites outside of the home with the subjects' retrospective mobility for the 15-year time period of interest.

Eq. 1: mobility-linked working-level month exposure for year *y*

$$WLM_y = \frac{\lambda}{170 \times 100} \sum_l h_{ly} r_l \tag{1}$$

Mobility and radon concentrations

λ = assumed equilibrium ratio of 50%

h_{ly} = total hours spent at location *l* during the *y*th year prior to enrollment

r_l = radon concentration (pCi/l) at location *l*

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OS	year – long outdoor ATD measurements														
AW	0.95 pCi														

Locations

MB	Master bedroom
HB ₁ , HB ₂ , ...	Historic bedroom 1, 2, ...
WA	Home work area
L ₁ , L ₂ , ...	Home level 1, 2, ... (other than MB, HB ₁ , HB ₂ , ..., and WA)
AB	Another building
OS	Outside
AW	Away from home (other than AB and OS)

The detailed data collected also allowed for the calculation of risk estimates based on the other general dosimetry models used in many of the previous case-control epidemiologic studies (Blot et al., 1990; Schoenberg et al., 1990; Pershagen et al., 1992; Pershagen et al., 1994; Alavanja et al., 1994; Alavanja et al., 1999; Letourneau et al., 1994; Auvinen et al., 1996; Ruosteenoja et al., 1996; Darby et al., 1998). The risk estimates obtained for the IRLCS were compared with the risk estimates that would have been obtained if the alternative models (Table 1) were used. The associations between lung cancer risk and observed radon exposures for each model were studied using linear excess odds of the same general form as the excess relative risk models developed for radon by the National Research Council (NRC, 1988). The risk estimates were adjusted for age, active smoking, and education (Field et al., 2000). Exposure was analyzed as a categorical

Table 2. Sample size and geometric mean WLM exposure for the six competing radon dosimetry models and percent of subjects who remained in the original IRLCS radon-exposure categories.

Radon dosimetry model	<i>N</i>	Geometric mean WLM	Percent of subjects that remained in the original IRLCS exposure categories
IRLCS	1027	8.42	100.0
First floor	1025	7.30	75.0
Master bedroom	1027	7.08	77.6
Master bedroom and living room	1027	7.19	77.0
Living room	1015	7.21	72.4
Basement	930	13.31	59.1

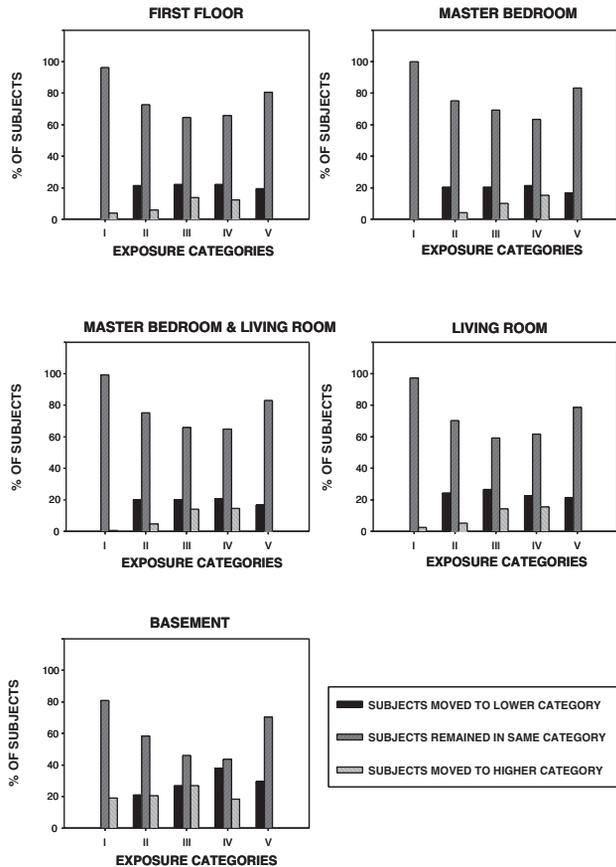


Figure 1. Movement of subjects as compared with the original IRLCS radon exposure categories.

variable. Subjects were partitioned into five *a priori* defined exposure percentile cells for the analyses with the highest 15% of exposed cases and controls, combined, constituting the fifth cell (Field et al., 2000). The remaining subjects were divided among four equal width intervals of WLM_{5-19} exposure. The median exposure within each of the five categories was used as the quantitative value in analysis.

Continuous variables were included in the regression models to adjust for the effects of age, active smoking, and attained education level. The measures of “active smoking” most significantly associated with lung cancer risk, years since smoking cessation and cigarette pack-year rate were selected for the regression model. Pack-year rate was defined as the average number of packs smoked per year from birth until 5 years (assumed latency period for lung cancer) prior to study enrollment for controls or lung cancer diagnosis for cases. In addition to all cases ($n=413$) and controls ($n=614$), subset analyses using the cases ($n=283$) and controls ($n=614$) alive at time of interview were also performed. The use of living subjects provided the maximal opportunity to obtain accurate information (e.g., mobility, smoking history, etc.) as well as representative radon measurements (Field et al., 2000).

Christensen and Blackwood (1993) proposed a model for assessing the relative quality of multiple methods used to make a particular measurement. Their model allows one to test for the equality of measurement error variance across methods and, if applicable, to determine where the variances differ. We used this methodology to compare the measurement error variances across the competing dosimetry models, under the necessary assumption that

$$\log(y_{ij}) = \log(x_i) + \alpha_j + e_{ij}$$

where y_{ij} is the exposure estimate from the j th dosimetry model for the i th subject, x_i is the true exposure, and α_j is the fixed bias of the j th dosimetry model. The e_{ij} 's represent the zero mean errors due to the individual dosimetry models with $\text{var}(e_{ij}) = \sigma_j^2$. A log transformation was used to satisfy the model requirements of independent and normally distributed errors and true (log-transformed) exposures.

Results

Table 2 presents the sample size, geometric mean WLM exposures, and percent of subject movement between radon exposure categories. The basement model yielded the highest geometric mean WLM (13.31), followed by the IRLCS model (8.42). The geometric means for the WLMs were similar (range 7.08–7.30) for the remaining models. As compared with the IRLCS model, there was similar movement (range 22.4–27.6%) of subjects between exposure categories for the first floor, master bedroom, master bedroom/living room, and living room models. The basement model had the highest degree (40.9%) of movement as compared with the original IRLCS categories. Figure 1 displays the movement of

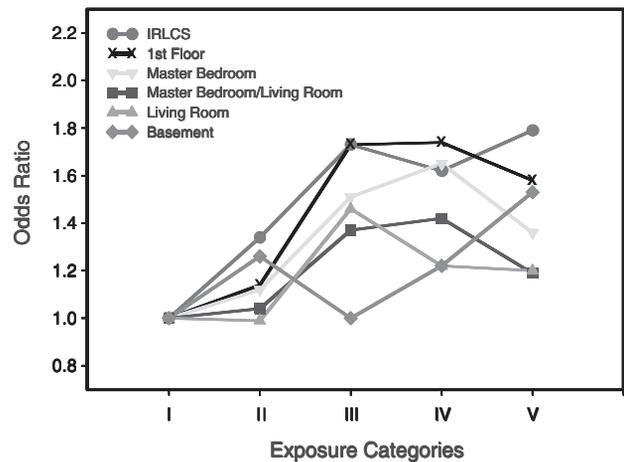


Figure 2. Estimated odds ratios under alternative radon dosimetry models for all subjects.

Table 3. Estimated odds ratios and linear excess risks (p values) under alternative radon dosimetry models for all subjects.

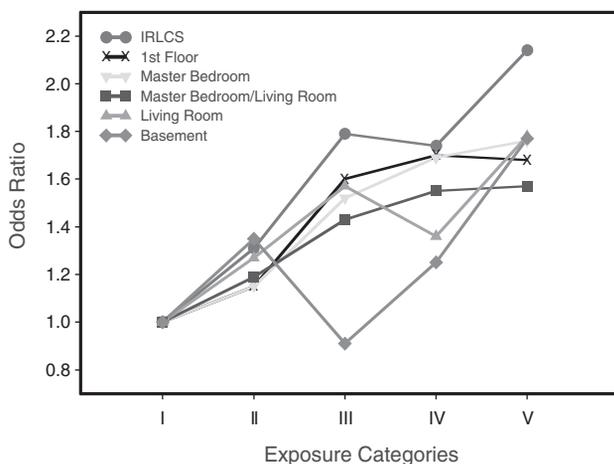
Radon dosimetry model	Exposure category percentiles				Excess risk ^a (p value)
	II	III	IV	V	
IRLCS WLM ₅₋₁₉	1.34	1.73	1.62	1.79	0.382 (0.047)
First floor	1.14	1.73	1.74	1.58	0.352 (0.026)
Master bedroom	1.12	1.51	1.65	1.36	0.238 (0.096)
Master bedroom and living room	1.04	1.37	1.42	1.19	0.141 (0.264)
Living room	0.99	1.46	1.22	1.2	0.125 (0.031)
Basement	1.26	1.00	1.22	1.53	0.146 (0.213)

Category I used as the reference cell.

^aEstimated excess odds correspond to the geometric mean WLM radon exposure, which fell within the second exposure category for each model. Odds ratios and excess risk estimates are adjusted for age, active smoking, and education.

subjects (all-subjects analysis) as compared with their placement in the IRLCS radon-exposure categories. As compared with the IRLCS model, a slightly higher percentage of subjects moved to lower exposure categories than higher exposure categories. A similar finding was also obtained when just the live subject subset was used for the analysis (not shown).

The Christensen and Blackwood model indicated that the measurement error variances were not significantly different among the models: master bedroom, living room, master bedroom/living room, and first floor exposure models ($p=0.98$). The measurement error variances for the basement and IRLCS models did differ from one another, as well as from the rest of the models at the 5% level of significance. The measurement error variance was largest for the basement model and smallest for the IRLCS model.

**Figure 3.** Estimated odds ratios under alternative radon dosimetry models for live cases and controls.**Table 4.** Estimated odds ratios and linear excess risks (p values) under alternative radon dosimetry models for live cases and controls.

Radon dosimetry model	Exposure category percentiles				Excess risk ^a (p value)
	II	III	IV	V	
IRLCS WLM ₅₋₁₉	1.31	1.79	1.74	2.14	0.636 (0.012)
First floor	1.15	1.60	1.70	1.68	0.365 (0.032)
Master bedroom	1.15	1.52	1.69	1.76	0.409 (0.023)
Master bedroom and living room	1.19	1.43	1.55	1.57	0.279 (0.080)
Living room	1.27	1.57	1.36	1.78	0.306 (0.059)
Basement	1.35	0.91	1.25	1.77	0.202 (0.162)

Category I used as the reference cell.

^aEstimated excess odds correspond to the geometric mean WLM radon exposure, which fell within the second exposure category for each model. Odds ratios and excess risk estimates are adjusted for age, active smoking, and education.

The IRLCS dosimetry model produced the highest odds ratios and excess risk estimates for both the all subjects (Figure 2, Table 3) and the live subset of subjects (Figure 3, Table 4). The IRLCS p value for the linear excess risk was statistically significant for all subjects ($p<0.05$) and for the live case and control subjects ($p=0.01$) at the geometric mean WLM radon exposure.

For all subjects (Table 3), statistically significant p values for the excess risk at the geometric mean WLM categorical radon exposure were also noted for the dosimetry models first floor and living room. In addition to the statistically significant p values for the linear excess risk at the geometric mean WLM categorical radon exposure detected for the live subject IRLCS model (Table 4), statistically significant p values were detected for the live subject models including first floor and master bedroom.

Discussion

The *a priori* defined IRLCS radon-exposure model produced slightly higher odds ratios and the lowest measurement error as compared with the other *a priori* selected (Field et al., 1996) methodologies that did not link the subject's retrospective mobility with multiple, spatially diverse radon concentrations. The enhanced dosimetry model used in the IRLCS, which reduced exposure misclassification, likely contributed to its higher risk estimates. Alternatively, the finding of increased risk estimates using the IRLCS model may be attributable to some unidentified systematic or differential bias. However, this alternative explanation is less likely, because we used a common data set. Any potential confounding factor should operate similarly in all models since the only factor we changed in the analysis was the variable used for radon

exposure, and the only difference between the construction of the radon variables was in the amount of weight given to the rooms in which radon was measured. In most cases, nondifferential misclassification of exposure results in a bias toward the null in estimates of relationships between exposure and disease (Kelsey et al., 1986). Other researchers have also noted that increased radiation exposure misclassification leads to risk estimates biased toward showing no association (Lubin et al., 1990; Pierce et al., 1990).

The similarity in movement of subjects between exposure categories for the first floor, master bedroom, master bedroom/living room, and living room models as compared with the IRLCS model are not surprising. We have previously shown that the radon concentrations on the levels above the basement are fairly homogenous (Fisher et al., 1998) and that the subjects in the IRLCS spent a large percentage of their time, while in the home, in nonbasement areas (Field et al., 1998b).

The basement dosimetry model generally produced the lowest odds ratios and the greatest measurement error. Our findings suggest that the use of basement radon concentrations for risk assessment may substantially underestimate the risk posed by residential radon exposure. The lower risk estimates obtained for the basement dosimetry model are likely attributable to the increased misclassification of radon exposure. This finding is also not surprising since the IRLCS subjects spent limited time in the basement (Field et al., 1998b) and the basement radon concentrations were significantly higher than the concentrations encountered in nonbasement residential areas (Fisher et al., 1998).

Because of differences in the spatial distribution of radon in a home by geography, the findings of this study are most generalizable to geographic areas with similar housing stock and climate. The comparative findings of this paper may have differed slightly, if exposure categories were selected other than the categories *a priori* defined for the IRLCS. It should be noted that the findings of this paper do not address the effects of missing radon data within the past 20 years that frequently occur in other residential radon studies (Weinberg et al., 1996). As previously discussed, these gaps in radon measurements seriously decrease a study's statistical power to detect an association, especially if the gaps occur 5 to 15 years prior to study enrollment (NRC, 1988; Lubin et al., 1990). In the majority of residential radon case-control studies, subjects were included that had lived in several homes in the 20 years prior to enrollment that were inaccessible at the time of the study. In this study, this uncertainty was eliminated by the IRLCS inclusion criteria that limited subject enrollment to individuals that had spent a minimum of 20 years in their current residence.

In addition to the contemporary radon gas measurements, the IRLCS dosimetry also included the placement of novel glass-based retrospective radon detectors at each study

home (Field et al., 1999; Steck and Field, 1999). The retrospective reconstruction detectors analyze the alpha activity deposited on and implanted in glass surfaces to reconstruct past residential radon progeny concentrations. We hope to further improve radon dose estimate for the IRLCS by controlled laboratory and field calibration of the novel retrospective detectors under various depositional environments followed by reanalyses of risk estimates for the IRLCS.

The BEIR VI Committee concluded (NRC, 1999) that the power of a residential radon study to detect an excess risk could be augmented by targeting populations that have high radon exposures and low residential mobility. The ability of the IRLCS to detect an association was enhanced by a study population characterized by low residential mobility and the potential for high radon exposure (Field et al., 2000). However, the findings of this paper indicate that the power of a residential radon study to detect an excess risk is also enhanced by linking spatially disparate radon concentrations with the subject's retrospective mobility, especially when live subjects can supply mobility information. In addition, our findings suggest that the dosimetry model used by some of the previous residential radon studies may have underestimated the true risk posed by radon progeny exposure.

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