Residential Radon Exposure and Risk of Lung Cancer in Missouri

Michael C. R. Alavanja, DrPH, Jay H. Lubin, PhD, Judith A. Mahaffey, MS, and Ross C. Brownson, PhD

ABSTRACT

Objectives. This study investigated residential radon exposure and lung cancer risk, using both standard radon dosimetry and a new radon monitoring technology that, evidence suggests, is a better measure of cumulative radon exposure.

Methods. Missouri women (aged 30 to 84 years) newly diagnosed with primary lung cancer during the period January 1, 1993, to January 31, 1994, were invited to participate in this population-based case–control study. Both indoor air radon detectors and CR-39 alpha-particle detectors (surface monitors) were used.

Results. When surface monitors were used, a significant trend in lung cancer odds ratios was observed for 20-year time-weighted-average radon concentrations.

Conclusions. When surface monitors were used, but not when standard radon dosimetry was used, a significant lung cancer risk was found for radon concentrations at and above the action level for mitigation of houses currently used in the United States (148 Bqm^{-3}). The risk was below the action level used in Canada (750 Bqm^{-3}) and many European countries (200–400 Bqm^{-3}). (*Am J Public Health.* 1999;89:1042–1048)

There is substantial variation in the annual mean concentration of radon in the same North American homes measured several years apart.[1,2] Such findings call into question the assumption that yearlong indoor air radon measurements offer a precise estimate of cumulative radon exposures in homes over a period of 15 to 25 years, the most biologically meaningful exposure period for lung cancer etiology. In a previous study of lung cancer risk among nonsmoking women in Missouri, we relied on detectors that measured current radon levels in indoor air for 1 year to estimate 30-year cumulative radon exposure and found no convincing association between lung cancer risk and residential radon.[3] The results of 7 other case–control studies of lung cancer and residential radon from the United States, Canada, Sweden, Finland, and China have also been reported.[4] Three have shown a statistically significant association between radon exposure and lung cancer, whereas the findings of the remaining 4 studies were consistent with no effect. Interpretation of the findings has been complicated by the methodological problems of estimating long-term residential radon exposure.[5,6] All previous studies used detectors that measured current radon in the air.[4]

In the case–control study described here, we carried out both standard yearlong indoor air radon measurements and measurements with CR-39 alpha-particle detectors (called surface monitors and made from an alpha-sensitive material, polyallydiglycol carbonate), which directly assess long-term (20-year and more) cumulative exposure by analyzing glass objects in the home. The surface monitors take advantage of the fact that the first long-lived radon progeny, lead 210 (half-life: 22 years), becomes embedded in glass surfaces in homes. The alpha activity of polonium 210, a decay product of lead 210, is measured in glass objects in the home and serves as a long-term retrospective exposure meter for residential radon.[7–10] This population-based case–control study of lung cancer was specifically designed to complement our earlier study[3] by evaluating the effects of cumulative residential radon exposure among Missouri women who were predominantly smokers and former smokers, by means of a control selection technique that minimized the inherent imbalance in smoking frequency between case patients and controls. In our earlier study,[3] exposure to domestic levels of radon was not convincingly associated with lung cancer risk among nonsmoking women in Missouri.

Methods

Case Patients

Between January 1, 1993, and January 31, 1994, 783 women were reported to the Missouri Cancer Registry with lung cancer; 41 were not eligible for the study either because they were not Missouri residents (7 women) or because they did not have primary lung cancer (34 women), leaving 742 case patients eligible for interview and radon measurement.

Michael C. R. Alavanja and Jay H. Lubin are with the Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Md. Judith A. Mahaffey is with Pacific Northwest Laboratories, Battelle Memorial Institute, Inc, Richland, Wash. Ross C. Brownson is with the Department of Community Health, School of Public Health, St. Louis University, St. Louis, Mo.

Requests for reprints should be sent to Michael C. R. Alavanja, DrPH, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Executive Plaza South, Room 8000, Mail Stop 8000, Bethesda, MD 20892.

This paper was accepted December 28, 1998.

Editor's Note. Please see related editorial by Nicholls (p 993) in this issue.

Physicians denied permission to interview 13 of these women, 19 died before the interview and no next of kin was available for an interview, and 13 refused to be interviewed. The remaining 697 case patients were interviewed and had some radon measurements made in their homes; 185 did not have at least 70% of the previous 25 years accounted for with actual radon dosimetry (i.e., air monitors or surface monitors, or both), which left 512 patients (73% of the study participants) available for analysis. This group included 41 women who had never smoked, 143 former smokers (stopped smoking 3 or more years before diagnosis), 235 light to moderate smokers (fewer than 30 cigarettes a day), and 93 heavy smokers (30 or more cigarettes a day). Among those younger than 65 years, 89% had a valid Missouri driver's license at the time of diagnosis (Table 1), and all of the women 65 years or older were registered with the Health Care Financing Administration. Tissue slides from all of the 512 case patients with complete radon dosimetry and questionnaire data were simultaneously reviewed by 3 pathologists for histological verification by means of standard histological classification criteria.[11,12]

TABLE 1—Characteristics of Women With Lung Cancer and Population Controls: Missouri, 1993–1994

Characteristic	Case Patients (n = 512), No.	Controls (n = 553), No.
Age, y[a]		
<65	186	203
65–74	216	239
>74	110	111
Smoking status		
Never	41	73
Stopped >3 years ago	143	170
Light to moderate	235	258
Heavy	93	52
Type of interview		
In person	350	553
Next of kin	162	0
Marital status		
Married	253	310
Widowed	180	188
Separated	9	3
Divorced	66	48
Never married	4	4
Education, y		
<12	186	145
12	226	260
>12	148	94
Missing	0	6
Previous lung disease		
No	142	257
Yes	362	293
Missing	8	3
Vegetable quartile, servings/wk		
1 (lowest intake)	145	139
2	205	216
3	65	56
4 (highest intake)	78	135
Missing	19	7
Current Missouri driver's license (among women <65 years)		
No	21	1
Yes	165	202
Cell type		
Adenocarcinoma	158	...
Small cell	117	...
Squamous	110	...
Other	127	...

[a]Mean ages: case patients, 66.5 years; controls, 66.4 years.

Controls

For women between the ages of 30 and 64 years, names and addresses were randomly selected from files of driver's licenses. For women between the ages of 65 and 84 years, names and addresses were randomly selected from lists provided by the federal Health Care Financing Administration, which included an estimated 95% of women in this older age group. Controls were age matched to case patients via 5-year age groups.

Case–control studies of lung cancer typically result in a sample of patients with lung cancer in which nearly all are smokers and a sample of controls in which very few people smoke. The extreme imbalance in smoking between case patients and controls limits the power of a study to assess subtle effects of smoking as well as interactions of smoking with other risk factors. The 2-stage randomized recruitment was developed to deal with this problem.[13,14] An initial screening interview is conducted to obtain information on selection covariates and disease. This information is then used with prespecified sampling probabilities to select subjects on whom further data are collected. An important feature of this sampling approach is that standard methods of analysis with commonly available computer software can be easily adapted for use.

We used a randomized recruitment procedure separately for Whites, Blacks, and other subjects on the basis of 4 categories of smoking: those who never smoked, former smokers, current light to moderate smokers, and heavy smokers. All case patients were enrolled; the randomized procedures were used for the selection of controls only. The controls were randomly selected for administration of the full questionnaire and radon measurements on the basis of the sampling probabilities described in an earlier article.[15] Potential controls also were frequency matched to cases via 5-year age strata. All White and non-White heavy smokers in the pool of potential controls were invited to participate (i.e., sampling probability of 1). Among Whites, 62% of light smokers and 26% of former smokers were invited to complete an entire interview. The corresponding percentages for non-Whites were 75% and 34%.

Screening interviews were administered to 4592 potential controls with telephone numbers or complete address information, or both. Of the 3886 controls who were found eligible by screening criteria, 730 were targeted for interview; 546 (75%) both completed a control interview and had comprehensive radon dosimetry (i.e., 70% of the previous 25 years accounted for by air monitors, surface monitors, or both).

Questionnaires and Administration

All interviews obtained information only on the period of life preceding the date of the diagnosis of lung cancer, and most (>94%) were conducted within 7 months of

diagnosis. Information on residential history, education, diet (food frequency questionnaire), and history of preexisting lung disease was obtained from a structured questionnaire administered by a trained interviewer. For women with lung cancer who could not be interviewed because of death or ill health, an interview with a knowledgeable next of kin was conducted (33% of the case patients and none of the controls).

A second questionnaire that focused on the age and placement history of glass objects in the home helped field interviewers identify 2 objects for cumulative residential radon measurement by surface monitors as described previously.[16] One object was sought in the kitchen and another in the bedroom or surrogate locations where study subjects spent most of their time.

TABLE 2—Odds Ratios of Lung Cancer, by Categories of Radon Concentration Based on Time-Weighted-Average Exposure CR-39 Surface Measurements: Missouri, 1993–1994

	Radon concentration ($Bq\,m^{-3}$)					
	<37	37–73	74–147	≥148	Total	P^a
Case patients	81	174	97	20	372	...
Controls	105	234	118	14	471	...
Mean[b]	24.6	55.3	96.6	192.4	64.6	...
Odds ratios	1.00	1.11	1.32	3.33	...	.02
95% confidence interval		0.8, 1.6	0.9, 2.0	1.5, 7.5	...	...

Note. Odds ratios were adjusted for age, educational level, previous lung disease, pack-years of smoking, and mean servings of vegetables per week. Time-weighted-average CR-39 surface measurements were averaged over an exposure period from 5 to 25 years prior to cancer diagnosis.

[a]*P* value for trend based on continuous value for radon. Trend statistics were similar when based on mean values within categories.

[b]Mean radon concentrations were 66.0 $Bq\,m^{-3}$ for case patients and 63.5 $Bq\,m^{-3}$ for controls.

Radon Dosimetry

In this study, the biologically meaningful period of exposure was defined as the time between 5 and 25 years before diagnosis for case patients and between 5 and 25 years before the interview for controls. Two radon dosimetry techniques were used.[7] Yearlong indoor air radon measurements were sought in the current dwelling occupied by the study subject. Annual time-weighted-average exposure was calculated by multiplying the mean radon level in a dwelling by the number of years that dwelling was occupied by the study subject. In each dwelling, a measurement was made in the kitchen and another measurement in the bedroom. We also used surface monitors, a technique newly applied to epidemiological investigations, to directly measure cumulative residential radon exposure for the previous 25 years, by affixing the detectors to selected household glass objects.

Cumulative radon values from CR-39 surface monitors were converted into annual time-weighted-average exposure readings by dividing the cumulative radon readings by the number of years the subject owned the glass object.[16] The surface monitors were not placed on ceramic objects or other decorated objects that might contain uranium or thorium glazes.[16] Flat-glass objects such as picture frames or mirrors that were at least 20 years old (preferably 30 years old or older), purchased new, and always displayed in the bedroom or kitchen of the study subject were ideal and frequently available in this population. A 2-in (5-cm) square of CR-39 was placed on each object that had been cleaned with nonabrasive window cleaner, sealed with tape on all sides, and left in place for a minimum 4-week period.[16] Radon exposures, measured by either surface or air radon monitors, occurring during the 5-year period immediately before the interview were considered biologically unimportant to lung cancer etiology and were not used in dose–response calculations.

Empirically derived correction factors for differential deposition rates were used to adjust for the effects of homes occupied by smokers and with study subjects for whom window glass was used.[7] Surface monitors detect alpha particles from decay of embedded polonium 210 (J. A. Mahaffey et al., unpublished data, 1999).[7–10] Polonium 210 from environmental tobacco smoke in the home is not embedded in glass and does not introduce measurement error if the glass is cleaned before measurement.[9] In addition, the level of polonium 210 from cigarette smoke is relatively small in comparison with the polonium 210 embedded in glass from residential radon.[9]

Missing data were imputed for subjects who had at least 70% of their person-years of exposure measured by indoor air measurements or surface monitors (e.g., exposure data for the time between 5 and 25 years before diagnosis for case patients or before the interview for controls). In control residences, the annual means for surface detectors and indoor air radon detectors were used in imputing missing data for the surface monitoring and air monitoring procedures, respectively.[17] Study subjects with less than 70% of their pertinent years of exposure measured by either monitoring procedure were excluded from the analysis to avoid excessive imputation. For the 512 case patients and 553 controls included in this analysis, 91% of the pertinent years had standard radon dosimetry, surface monitoring, or both, leaving only 9% of the pertinent years in need of imputation for missing radon values. In international units (SI), the activity of radon per unit mass of air is expressed as becquerels (Bq) per cubic meter, where 37 $Bq\,m^{-3}$ translates to 1 $pCi\,L^{-1}$. SI units are used in this article to express the activity of radon.

Analysis

Maximum likelihood procedures were used in computing odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate logistic regression models were used to adjust for potentially confounding variables: age, education (less than 12, 12, more than 12 years), previous lung disease (yes vs no), pack-years of smoking, and vegetable intake. Wald confidence intervals were computed on the basis of the estimated parameter, β_1, and its standard error: $\exp\{\beta_1 \pm 1.96 * \mathrm{SE}(\beta_1)\}$.[18]

We evaluated trends in the logistic analysis with a score test in which the continuous radon concentration and the mean value within categories were used as the quantitative values for exposure. Results were similar, and only the *P* values for the continuous values are presented. We also fit a linear odds ratio model, $\mathrm{OR} = 1 + \beta_2 X$, to estimate the trend, where β_2 is the excess odds ratio per unit $Bq\,m^{-3}$ and X is radon concentration in $Bq\,m^{-3}$. For the estimate of β_2, we computed likelihood-based confidence intervals.

Results

The mean ages were 66.5 years for case patients and 66.4 years for controls. We observed several significant differences between the 2 groups (Table 1). The potential confounding variables were consumption of vegetables, intensity of smoking, educational level, and previous lung disease.[19] The adjusted odds ratios for radon included these

TABLE 3—Odds Ratios (ORs) of Lung Cancer, by Radon Concentration Based on CR-39 Surface Measurements Within Categories of Other Variables: Missouri, 1993–1994

	Radon concentration (Bqm^{-3})						
	<37	37–73	74–147	≥148	P^a	Fitted OR at 150 Bqm^{-3}[b]	P^c
Age, y, at disease incidence (case patients) or interview (controls)							.84
<65	1.00	1.02	1.27	8.89	.08	2.2	
65–74	1.00	1.52	1.43	2.49	.33	1.7	
≥75	1.00	0.73	1.08	2.57	.25	1.8	
Education, y							.67
<12	1.00	1.34	1.62	5.07	.10	2.6	
12	1.00	1.21	1.53	1.71	.19	1.9	
≥13	1.00	0.68	0.71	4.80	.32	1.6	
Previous lung disease							.05
No	1.00	1.47	1.95	5.82	.08	4.4	
Yes	1.00	0.99	1.09	2.23	.42	1.3	
Vegetable consumption, servings/wk							.05
<7	1.00	0.77	0.75	0.25	.46	0.6	
7	1.00	1.26	2.13	8.33	.01	4.3	
≥8	1.00	1.35	0.98	4.19	.25	1.7	
Smoking status							.84
Never	1.00	0.49	0.49	1.35	.66	1.3	
Former	1.00	1.83	1.45	2.60	.53	1.4	
Light to medium	1.00	0.89	1.32	6.57	.08	2.1	
Heavy	1.00	2.42	2.52	∞	.07	4.8	

Note. ORs were adjusted for age, educational level, previous lung disease, pack-years of smoking, and mean servings of vegetables per week.
[a]*P* value for trend based on continuous value for radon.
[b]Estimate of the fitted OR at 150 Bqm^{-3} based on the model $OR = 1 + \beta_2 X$, where X is in Bqm^{-3}. The overall estimate of OR at 150 Bqm^{-3} was 1.95 (95% CI = 1.1, 3.9).
[c]*P* value for test of homogeneity of excess OR per Bqm^{-3} across levels of other factor.

variables in the logistic model to mitigate confounding. Saturated fat, which was a risk factor for lung cancer in our earlier study of nonsmoking women, was not found to be a risk factor in this study[20] and was not included in the logistic model. Few women with lung cancer did not have a current Missouri driver's license. Because there was little difference in our risk estimates if we included or excluded case patients without a Missouri driver's license, we kept these patients in our study.

The mean indoor air radon detector reading (± SE) in subjects' current kitchens was 58 ± 2.8 Bqm^{-3}, with a range of 3.7 (detection level) to 1500 Bqm^{-3}. The mean in subjects' current bedrooms was 56 ± 2.6 Bqm^{-3}, with a range of 3.7 to 1300 Bqm^{-3}; this mean value was not significantly different from that for the kitchen. The mean surface monitor readings were 65 ± 1.6 Bqm^{-3} in the kitchen and 65 ± 1.5 Bqm^{-3} in the bedroom; these values were not significantly different from each other but were significantly higher than results based on use of indoor air radon measurements. Because the 2 dosimetry procedures resulted in different estimates of historic radon exposure, we report separate dose–response analyses for the 2 dosimetry procedures and do not report a dose–response analysis for a combined estimate of radon exposure. Neither dosimetry procedure revealed a meaningful difference between the 2 locations in the house, so we used the simple arithmetic average of the results from both rooms as our radon exposure measure for that procedure. Surface monitoring results were based on measurements of objects aged 31.7 ± 0.32 and 31.1 ± 0.31 years for controls and case patients, respectively. More details of the exposure assessment have been described elsewhere.[7,15]

Dose–Response Pattern With Surface Monitors (CR-39)

Four percent of the study population was exposed to time-weighted-average radon concentrations above 148 Bqm^{-3}, the current US Environmental Protection Agency action level. In comparison with the lowest exposure category (<37 Bqm^{-3}), the odds ratios of lung cancer among women exposed to higher radon categories—20-year time-weighted-average radon concentrations (i.e., the exposure assessment period of 5 to 25 years before cancer diagnosis) of 37 to 73, 74 to 147, and 148 Bqm^{-3} or higher—were 1.11, 1.32, and 3.33, respectively, with a statistically significant trend ($P = .02$, continuous [Table 2]). Subjects who did not have a history of previous lung disease had a significantly greater risk from residential radon exposure than those who had such a history (i.e., the *P* value for homogeneity of trends was .05) (Table 3). Likewise, there was significant heterogeneity of radon risk associated with vegetable consumption, with the greater trends in radon risk associated with vegetable consumption of 7 or more servings per week (vs fewer servings in a week). Significant differences in patterns of radon risk were not observed for categories of other potential effect modifiers: age, educational level, and smoking status.

Overall, the slope of the dose–response trend was similar to the slope for each cell type (i.e., adenocarcinoma, small cell carcinoma, squamous carcinoma, and other cell types) (Table 4), and a similar dose–response trend was found among women who occupied homes with complete surface monitor dosimetry during the previous 25 years (for radon levels below 37, 37–73, 74–147, and 148 Bqm^{-3} or higher, odds ratios were 1.18, 1.39, and 4.29, respectively, with a statistically significant trend, $P = .02$ [not shown in table]).

Dose–Response Pattern With Indoor Air Detectors

In comparison with the lowest category of radon exposure (<37 Bqm^{-3}), the relative risk of lung cancer among women exposed to the highest concentration was 0.71 (95% CI = 0.3, 1.3), and the *P* value for trend was not significant (Table 5). Similar patterns of odds ratios were observed for subjects stratified by age, educational level, previous lung disease, and smoking status (data not shown). However, among individuals who consumed 7 or more servings of vegetables per week, the lung cancer risk rose with radon exposure, and the gradient of risk was significantly different from the gradient among those who consumed fewer vegetables. A positive dose–response gradient of lung cancer risk was observed with increasing radon exposure among heavy smokers, but the number of cases in each strata was relatively small, and the pattern of risk in heavy smokers was not statistically different from that in light to moderate smokers or those who did not smoke at all.

Discussion

Our population-based case–control study used 2 different radon dosimetry technologies to estimate cumulative and annual

TABLE 4—Odds Ratios (ORs) for Histological Types of Lung Cancer, by Categories of Radon Concentration Based on CR-39 Surface Measurements: Missouri, 1993–1994

	Radon Concentration, Bqm^{-3}						
	<37	37–73	74–147	≥148	Total	P[a]	Fitted OR at 150 Bqm^{-3}[b]
			No. of subjects				
Adenocarcinoma	26	52	30	7	115	...	...
Small cell	14	41	25	2	82	...	...
Squamous cell	21	38	17	5	82	...	...
Other	20	43	25	5	93	...	...
Controls	105	234	118	14	471	...	...
			Odds ratios				
Adenocarcinoma	1.00	1.02	1.22	3.33	...	.10	1.9
Small cell	1.00	1.65	2.21	3.33	...	.30	2.2
Squamous cell	1.00	1.19	1.12	7.09	...	.06	2.3
Other	1.00	1.09	1.34	3.03	...	.07	2.2

Note. ORs were adjusted for age, educational level, previous lung disease, pack-years of smoking, and mean servings of vegetables per week.
[a]P value for trend based on continuous value for radon.
[b]Estimate of the OR at 150 Bqm^{-3}.

TABLE 5—Odds Ratios of Lung Cancer, by Categories of Radon Concentration Based on Time-Weighted Indoor Air Track-Etch Measurements: Missouri, 1993–1994

	Radon Concentration, Bqm^{-3}					
	<37	37–73	74–147	≥148	Total	P[a]
Case patients	113	84	40	10	247	...
Controls	120	108	53	18	299	...
Mean[b]	24.1	51.2	102.8	246.8	58.5	...
Relative risk	1.00	0.87	0.91	0.71	...	.79
95% confidence interval		0.6, 1.3	0.5, 1.5	0.3, 1.3	...	...

Note. Odds ratios were adjusted for age, educational level, previous lung disease, pack-years of smoking, and mean servings of vegetables per week.
[a]P value for trend based on continuous value for radon. Trend statistics were similar when based on mean values within categories.
[b]Mean radon concentrations were 57.1 Bqm^{-3} (1.5 pCi L^{-1}) for case patients and 59.6 Bqm^{-3} (1.6 pCi L^{-1}) for controls.

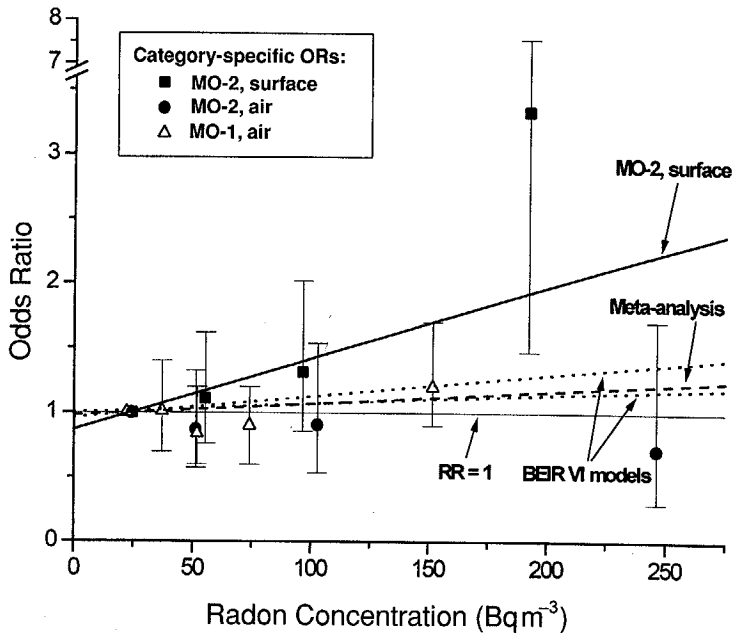
average residential radon exposures. On the basis of the fitted odds ratio model, there was a 2-fold increased lung cancer risk (OR = 1.95, 95% CI = 1.1, 3.9) at 150 Bqm^{-3} when radon was measured with surface monitors. The value exceeds the fitted values from a recent meta-analysis of residential radon case–control studies, although the difference is not statistically significant (Figure 1), and is similar to values in the Stockholm (OR = 1.8) and New Jersey (OR = 1.8) studies.[4] The fitted trend in our study was consistent with extrapolation estimates from miners (Figure 1).[21] No excess risk was observed when standard indoor air radon monitoring procedures (track-etch detectors) were used to assess residential radon exposure.

When standard indoor air radon monitoring procedures are used, there is the implicit assumption that a measurement today accurately reflects exposure conditions over the previous 20 to 30 years. Changes to homes due to structural aging, remodeling, new furnaces, storm windows, and other alterations could introduce systematic biases and invalidate this assumption even with complete coverage of current and all previous residences. Year-to-year variability in radon concentrations increases random error in exposure assessment. Such variability has been observed in selected homes in the Midwest. In 2 houses with no structural alterations, monitored over a 7-year period, the year-to-year variation in radon concentration was 55%, while a 300% annual radon concentration increase was observed in a home where a relatively minor change in the solar heating was made.[1,2]

While the reasons for the differences between results using exposures based on indoor air measurements and surface measurements in our study are unclear, long-term exposure estimates based on contemporary indoor air measurements are potentially subject to increased random error owing to year-to-year variability and to systematic error owing to modifications in residence over time. To evaluate the consequences of increased random error with indoor air measurements, we carried out a Monte Carlo study in which we fit a linear odds ratio model to radon exposures based on surface measurements augmented with random errors. We assumed a multiplicative, log-normally distributed error with geometric standard deviation $\exp(\tau)$. Figure 2 shows frequency distributions at τ taking on values of 0.1, 0.5, and 1.0, corresponding to multiplicative errors of 11%, 64%, and 170%. We conducted 500 simulations for each error distribution. The excess odds ratios per Bqm^{-3} based on surface measurements and on indoor air measurements were 0.0065 (95% CI = 0.001, 0.020) and 0.0006 (95% CI = –0.001, 0.006), respectively. Figure 2 indicates that our results could be due to increased random error for indoor air measurements relative to surface measurements.

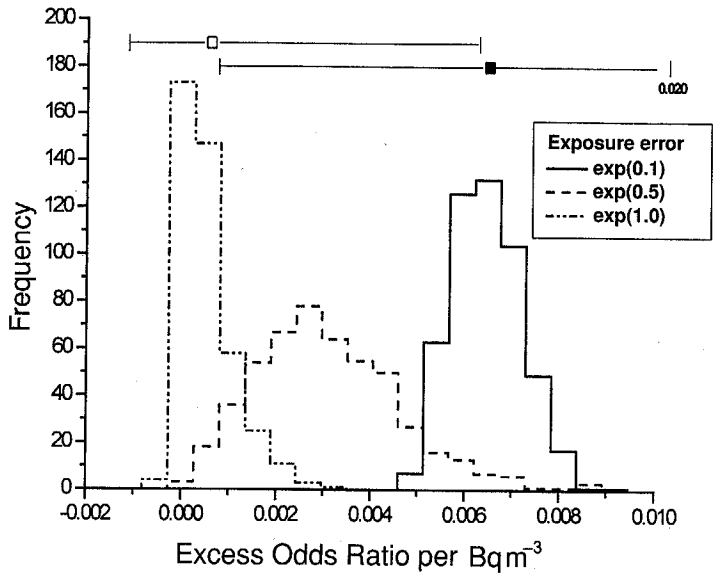
In our study, the significant positive dose–response trend in lung cancer odds ratios when surface monitors were used was consistent across age and education and when cases were analyzed by cell type. Heterogeneity in trends in odds ratios with previous lung disease and vegetable consumption was observed, with the lower risk found among those with previous lung disease and lower weekly vegetable consumption. For these variables, radon had a greater effect in high-risk categories. These results may be due to chance, and without an a priori hypothesis they are difficult to interpret. A significant interaction between radon and smoking was not seen in our data, whereas a submultiplicative pattern is suggested in studies of radon exposure in miners.[22]

A strength of our population-based case–control study is that it complements our earlier study of lung cancer among nonsmoking women, being specifically designed to evaluate the effect of radon exposure among study subjects who were predominantly smokers. Only recently diagnosed case patients were included to minimize the gap between radon measurement and cancer diagnosis and to eliminate potential inaccuracies in death certificate diagnoses. A unique feature of our study is the use of cumulative radon dosimeters, CR-39 surface monitors, that have been developed and validated in the laboratory and in limited field testing but have never been used in an epidemiological investigation.



Note. The data are for our previous study in Missouri of nonsmoking women using air monitors (MO-1, air) and the current study using CR-39 surface monitors (MO-2, surface) and air radon monitors (MO-2, air). Also shown are plotted curves from the fitted excess odds ratio model for the surface monitor concentrations, the meta-analysis of indoor radon studies,[4] and the extrapolations from miner data (BEIR VI models).[21]

FIGURE 1—Odds ratios of lung cancer and 95% confidence intervals for categories of time-weighted-average radon concentrations: Missouri.



Note. The error distribution was distributed log-normally with geometric mean 1.0 and geometric standard deviation exp(τ). The excess relative risk per Bqm^{-3} and the 95% confidence interval for exposures based on surface measurements (solid square) and on indoor air measurements (open square) are also shown.

FIGURE 2—Frequencies of the estimated excess relative risks per Bqm^{-3} based on a linear excess relative risk model using data obtained by augmenting the exposure estimates from surface measurements with multiplicative random errors.

Accurate cumulative measures of exposure are important for valid estimates of true effects. Surface monitors may offer a more accurate measure of the radon environment in the previous 20 to 30 years. Serious radon measurement error due to the use of surface monitors was unlikely because of the consistent results obtained when we compared radon measurements made on 2 different pieces of glass in each home included in this study.[7] We carefully selected appropriate glass objects on the basis of age, composition, and history of exposure to the living area of the homes occupied, and we thoroughly cleaned each object used for dosimetry to eliminate other sources of polonium 210.

Weinberg has suggested that because particulate air pollution from cigarette smoke and other sources retards the plate-out of radon progeny, the calibration curve relating the actual historical radon exposure to surface monitor results would be different for smoky vs nonsmoky homes.[23] This "measurement confounding" would be expected to distort inferences about the effect of radon and may spuriously result in evidence of synergism (i.e., statistical interaction) between radon exposure and smoking cigarettes. We avoided this potential problem by using 2 different calibration curves for smoky homes (i.e., those with 1 or more smokers) and nonsmoky homes (i.e., those with no smokers),[7] and we found no evidence of statistical interaction between radon and cigarette smoking in our data.

Another potential source of bias with surface monitors could be the differential underestimation of the age of the glass object used for radon dosimetry by case patients vs controls, resulting in higher estimates of radon exposure for case patients. This scenario is plausible because 33% of the case interviews were conducted with next of kin, whereas none of the control interviews were conducted with next of kin. When we restrict the analysis to in-person interviews, however, the trend of lung cancer risk with increasing radon levels is greater (odds ratios are 1, 1.23, 1.49, and 4.57, respectively, for the below 37, 37–73, 74–147, and 148 or higher Bqm^{-3} categories, with a statistically significant trend [$P = .01$]) than when we include next-of-kin interviews (Table 2).

For an average indoor radon concentration of about 46 Bqm^{-3} (1.25 pCi L^{-1}), approximately 1 in 400 basal cell nuclei in the lung is traversed by a single alpha particle in a year, and far fewer will be traversed by 2 or more alpha particles.[20] Data of this type have suggested to some that residential radon concentrations lie below a threshold and provide little danger to the public health.[24,25] Recent work by Hei et al., however, found

that a single alpha particle was only slightly cytotoxic (survival fraction of 82%) but was highly mutagenic, with an induced mutation fraction of 110 mutant cells per 100 000 surviving cells.[26] These laboratory data provide direct evidence that a single alpha particle traversing a nucleus will have a high probability of resulting in a mutation, and the data provide additional biological support for the case that radon concentrations typical of the residential environment may be an important public health problem.

This is the first epidemiological study to provide lung cancer risk estimates for domestic radon exposure derived from monitor radon dosimetry, and therefore our results must be interpreted cautiously. If surface monitors do give more precise estimates of historical radon levels than indoor air measurements, our results suggest that current air measurements may be understating the actual risk associated with residential radon exposure. At present, the exact slope of the dose–response curve remains an open question, and replication of our results in another epidemiological study is needed. Nonetheless, extrapolations from miner data, along with the meta-analysis of residential radon studies using air monitoring data and recent epidemiological and laboratory studies, tend to support the conclusion that after cigarette smoking, residential radon is the second leading cause of lung cancer in the general population. □

Contributors

M. C. R. Alavanja designed the study, managed the study during the field phase, analyzed the data, and was principal author of the article. J. H. Lubin was the principal statistician and wrote the statistical analysis section. J. A. Mahaffey managed the field and laboratory phase of surface monitoring dosimetry and helped write the dosimetry section of the article. R. C. Brownson designed and managed the cancer registry/data acquisition phase of the study and helped write and edit the overall article.

Acknowledgments

This project received National Cancer Institute (NCI) Institutional Review Board approval. It was conducted as an NCI intramural project, and fieldwork was funded by contract N01-CP-21102 with Battelle Memorial Institute, Inc.

We are indebted to Dr John D. Boice, Jr, for his support in helping to initiate this study; to Drs Tim Loy and Ellis Ingram of the University of Missouri School of Medicine (Columbia, Mo) and Dr Jeffrey Myers of the Mayo Clinic (Rochester, Minn) for their pathology review; to Marianne A. Parkhurst of the Pacific Northwest National Laboratory, Battelle Memorial Institute, Inc, for reading and processing CR-39 detectors; to Dr Jang Chang of the Missouri Department of Health for ascertainment of lung cancer cases through the state cancer registry; to Joan Huber and Patsy Henderson of Battelle Memorial Institute, Inc, for contributions in data collection and data management support; and to Eric Berger for computer support.

References

1. Steck DJ. Spatial and temporal indoor radon variations. *Health Phys.* 1993;62:351–355.
2. Steck DJ, Lively R, New E. Epidemiological implications of spatial and temporal radon variations. In: *29th Hanford Symposium on Health and the Environment, 16–19 October 1990.* Richland, Wash: Battelle Pacific Northwest Laboratories; 1990:889–904.
3. Alavanja MCR, Brownson RC, Lubin JH, Berger E, Chang J, Boice JD. Residential radon exposure and lung cancer among nonsmoking women. *J Natl Cancer Inst.* 1994;86:1829–1837.
4. Lubin JH, Boice JD. Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. *J Natl Cancer Inst.* 1997;89:49–57.
5. Lubin JH, Samet JM, Weinberg C. Design issues in epidemiological studies of indoor exposure to radon and risk of lung cancer. *Health Phys.* 1990;59:807–817.
6. Lubin JH, Boice JD Jr, Samet JM. Errors in exposure assessment, statistical power and the interpretation of residential radon studies. *Radiat Res.* 1995;144:329–341.
7. Mahaffey JA, Alavanja MCR, Parkhurst MA, Berger E, Brownson RC. Estimation of past radon exposure history for analysis of a residential epidemiological study. *Radiat Protection Dosimetry.* In press.
8. Samuelsson C. Retrospective determination of radon in houses. *Nature.* 1988;334:338–340.
9. Lively RS, Stock DJ. Long-term radon concentrations estimated from 210Po embedded in glass. *Health Phys.* 1992;64:485–490.
10. Fews AP, Henshaw DL. High resolution alpha particle spectroscopy using CR-39 plastic track detectors. *Nucl Instrum Methods.* 1982;197:517–529.
11. The World Health Organization Histological Typing of Lung Tumors, 2nd ed. *Am J Clin Pathol.* 1982;77:123–136.
12. Koss LG. *Diagnostic Cytology and Its Histologic Bases.* 3rd ed. Philadelphia, Pa: JB Lippincott; 1979.
13. Weinberg C, Wacholder S. The design and analysis of case-control studies with biased sampling. *Biometrics.* 1990;46:963–975.
14. Weinberg C, Sandler DP. Randomized recruitment in case-control studies. *Am J Epidemiol.* 1991;134:421–432.
15. Alavanja MCR, Brownson RC, Berger E, Lubin JH, Modigh CM. Avian exposure and the risk in women in Missouri: population based case-control study. *BMJ.* 1996;313:1233–1235.
16. Mahaffey JA, Parkhurst MA, Hui TE, Brownson RC, Alavanja MCR. Factors affecting use of CR-39 surface monitor technology to estimate past exposure to indoor radon. *J Exp Anal Environ Epidemiol.* 1996;4:425–437.
17. Weinberg CR, Moledor ES, Umbach DM, Sandler DP. Imputation of exposure histories with gaps, under an excess relative risk model. *Epidemiology.* 1996;7:490–497.
18. Breslow NE, Day NE, eds. *Statistical Methods in Cancer Research: Volume 1. The Analysis of Case-Control Studies.* Lyon, France: International Agency for Research on Cancer; 1980. IARC Scientific Publication 32.
19. Swanson C, Brown C, Singha R, Alavanja MCR. Dietary fat and lung cancer risk among women: the Missouri Women's Health Study (the United States). *Cancer Causes Control.* 1997;8:883–893.
20. Alavanja MCR, Brown CC, Swanson C, Brownson RC. Saturated fat intake and lung cancer risk among nonsmoking women in Missouri. *J Natl Cancer Inst.* 1993;85:1906–1915.
21. Committee on the Health Risks of Exposure to Radon, National Research Council. *Health Effects of Exposure to Radon (BEIR VI).* Washington, DC: National Academy Press; 1998.
22. Lubin J, Boice JD, Edling C, et al. *Radon and Lung Cancer Risk: A Joint Analysis of 11 Underground Miner Studies.* Washington, DC: Public Health Service; 1994. NIH publication 94-3664.
23. Weinberg CR. Potential for bias in epidemiologic studies that rely on glass-based retrospective assessment of radon. *Environ Health Perspect.* 1995;103:1042–1046.
24. Abelson PH. Mineral dusts and radon in uranium mines [editorial]. *Science.* 1991;254:777.
25. Cohen BL. Lung cancer rate vs. mean level in U.S. counties of various characteristics. *Health Phys.* 1997;72:114–119.
26. Hei TK, Wu LJ, Liu SX, Vannais D, Waldren CA, Pehrson GR. Mutagenic effects of a single and an exact number of alpha particles in mammalian cells. *Proc Natl Acad Sci U S A.* 1997;94:3765–3790.