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Residential Radon Gas Exposure and Lung Cancer

The Iowa Radon Lung Cancer Study

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Exposure to high concentrations of radon progeny (radon) produces lung cancer in both underground miners and experimentally exposed laboratory animals. To determine the risk posed by residential radon exposure, the authors performed a population-based, case-control epidemiologic study in Iowa from 1993 to 1997. Subjects were female Iowa residents who had occupied their current home for at least 20 years. A total of 413 lung cancer cases and 614 age-frequency-matched controls were included in the final analysis. Excess odds were calculated per 11 working-level months for exposures that occurred 5–19 years (WLM_{5-19}) prior to diagnosis for cases or prior to time of interview for controls. Eleven WLM_{5-19} is approximately equal to an average residential radon exposure of 4 pCi/liter (148 Bq/m^3) during this period. After adjustment for age, smoking, and education, the authors found excess odds of 0.50 (95% confidence interval: 0.004, 1.81) and 0.83 (95% percent confidence interval: 0.11, 3.34) using categorical radon exposure estimates for all cases and for live cases, respectively. Slightly lower excess odds of 0.24 (95 percent confidence interval: –0.05, 0.92) and 0.49 (95 percent confidence interval: 0.03, 1.84) per 11 WLM_{5-19} were noted for continuous radon exposure estimates for all subjects and live subjects only. The observed risk estimates suggest that cumulative ambient radon exposure presents an important environmental health hazard. *Am J Epidemiol* 2000;151:1091–1102.

case-control studies; dose-response relationship, radiation; lung neoplasms; radon; smoking; women's health

Lung cancer has been the leading cause of cancer death in US women since 1987 (1). Risk estimates derived from epidemiologic studies of underground miners attribute about 18,600 lung cancer deaths (range, 3,000–38,600) in the US population to residential ^{222}radon decay product (radon) exposure (2). Residential radon exposure risk estimates extrapolated from miners to the public are subject to many uncertainties (3) because of inherent differences between these populations and differences between the mine and home environments (4, 5).

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Abbreviations: IRLCS, Iowa Radon Lung Cancer Study; OR, odds ratio; WLM_{5-19}, working-level month of radon exposure for years 5–19 prior diagnosis for cases or time of interview for controls.

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Empirical evidence showing an increased lung cancer incidence from residential radon exposure is lacking. Numerous epidemiologic investigations using either ecologic (6–8) or case-control (9–19) designs have attempted to examine the relation between residential radon exposure and lung cancer. The case-control study design overcomes many of the limitations inherent in ecologic studies (20–24). Ten of the more rigorously designed case-control studies published to date (9–18) have not shown a consistent pattern regarding the association between radon exposure, cigarette smoking, and lung cancer. Poor radon exposure estimates have impeded the ability of case-control studies to detect underlying associations (19, 25). We conducted a population-based case-control study of Iowa women that incorporated a unique combination of study design and enhanced dosimetric techniques (19), including individual mobility assessment, population stability, expert histologic review, and a high percentage of live cases, to determine whether or not residential radon exposure exhibits a statistically significant positive association with lung cancer.

MATERIALS AND METHODS

The Iowa Radon Lung Cancer Study (IRLCS) had four major components: 1) rapid reporting of cases; 2) a mailed questionnaire followed by a face-to-face

interview; 3) a comprehensive radon exposure assessment; and 4) independent histopathologic review of lung cancer tissues. The IRLCS protocols received approval from the University of Iowa's Institutional Review Board in accordance with guidelines from the US Department of Health and Human Services.

Lung cancer cases

Lung cancer cases met the following inclusion criteria: 1) newly diagnosed with a microscopically confirmed primary invasive (not in situ) lung carcinoma, without any prior primary invasive lung carcinoma; 2) female Iowa resident at time of diagnosis; 3) age 40–84 years; and 4) residence in the current home for 20 consecutive years or more. A total of 1,974 female lung cancer cases were identified by the Iowa Cancer Registry between May 1, 1993 and October 30, 1996. The Iowa Cancer Registry has been a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute since 1973. The consent of each case's physician was obtained prior to contacting the subject. Rapid reporting identified 90.3 percent of the cases, with a median time between diagnosis and ascertainment of 20 days.

Forty-three percent of the 1,974 cases had lived in their current home for at least 20 years. Thirty-one percent ($n = 603$) of the 1,974 cases identified met all eligibility criteria. Of these, 440 cases (73 percent) consented to take part in the study. Each subject or her next of kin provided written informed consent prior to enrollment into the IRLCS. Of the consenting cases, 431 (98 percent) completed the process of filling out mailed questionnaires with follow-up in-person facilitation of the questionnaires and placement of radon detectors. The questionnaires included information concerning family health history, demographics, occupational exposures, smoking history, passive smoke exposure history, previous nonmalignant lung disease, diet, and a detailed section on characteristics of the home. Questionnaire data were manually double-entered into the computer, and a 10 percent random sample was selected to manually check against the original coded reports.

To obtain a reliable histologic diagnosis, we retrieved pathologic materials after obtaining signed permission from 423 of the 431 eligible lung cancer cases or their next of kin. Two board-certified surgical pathologists from the Department of Pathology at The University of Iowa Hospitals and Clinics reviewed the pathologic material upon which a diagnosis of lung cancer was made for these subjects. The reviewers were blinded to the diagnosis on the pathology report as well as to each other's review diagnosis. The major diagnostic groups were based on the World Health Organization's histologic typing of lung tumors and included the major categories of small cell carcinoma, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (26). Additional details concerning the histologic review are available elsewhere (27).

Final review of the 431 cases excluded 18 cases from the study because their detectors were discarded by next of kin after the case died. Radon measurements were completed for 413 of the cases. Histologic materials were not available for eight of these cases, and eight others refused to sign the consent form granting permission to obtain histologic materials. The registry-reported histologic subtype was used for classification of these 16 cases. The two surgical pathologists provided a consensus histologic diagnosis for 397 (96 percent) of the 413 cases. Thirty-three lung cancers included in the analyses were classified as carcinoma not otherwise specified because there was either insufficient pathologic material to review or the material was of poor quality. Risk analyses were performed on the 413 cases.

Controls

Controls met the following eligibility criteria: 1) no prior primary invasive lung cancer at the time of initial contact; 2) female Iowa resident at time of initial contact; 3) age 40–84 years; 4) alive at time of interview; and 5) residence in the current home for 20 consecutive years or more. Controls aged 40–64 were selected from current driver's license tapes provided by the Iowa Department of Transportation. Controls aged 65–84 were selected from a current tape made available through the Health Care Financing Administration. These two databases were chosen to provide a population-based sampling frame (28, 29). Both controls selected from driver's license tapes and those selected from Health Care Finance Administration records were age-frequency matched with the lung cancer cases by 5-year age groups. Additional information concerning contact with controls and the population representativeness is available elsewhere (27–29).

Forty-eight percent of the controls initially identified through either current driver's license tapes or Health Care Financing Administration records had lived in their current home for at least 20 years. A total of 1,337 eligible controls were identified between May 1, 1993 and October 30, 1996. Of the controls, 693 (52 percent) consented to take part in the study, and of these, 625 (90 percent) completed the process of filling out the mailed questionnaires with follow-up in-person review of the questionnaire and placement of radon detectors. All controls were alive at the time of the home visit. Risk analyses were performed on the 614 controls who completed yearlong radon measurements.

A follow-up questionnaire that compared smoking and working histories was routinely sent to eligible controls who refused to participate in the study ($n =$

644). A total of 224 controls returned their questionnaire. Comparisons were made between participating and nonparticipating controls on the basis of questionnaire responses to having ever worked outside of the home, current working status, and smoking history. In addition, the eligible controls who returned the short questionnaire were offered yearlong radon testing of their bedroom.

Radon dosimetry

The radon dosimetry assessment consisted of five components: 1) on-site residential assessment survey; 2) on-site radon measurements; 3) regional outdoor radon measurements; 4) assessment of subject's exposure when in another building; and 5) linkage of historical subject mobility with residential, outdoor, and other building radon concentrations. A detailed description of the radon dosimetry assessment is presented elsewhere (19, 27). Briefly, the first component was a residential assessment and dosimetry placement conducted in person at the subject's home. Historical 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 (19, 27, 30–32). The mobility assessment accounted for all of the time (168 hours/week) from when the participant moved into the current home until study enrollment.

The second component of the radon dosimetry assessment was on-site measurement of home radon gas concentrations for each case and control. At least one Radtrak Alpha Track Detector (Landauer, Inc., Glenwood, Illinois) was placed on each level of the home, in current and historical bedrooms, and in in-home work areas. Field technicians retrieved the detectors after the 1-year exposure period. In all, 4,626 alpha-track detectors were placed at the 1,027 study sites. Overall, 97 percent of all alpha-track detectors placed were retrieved 1 year later. Information describing the IRLCS's Dosimetry Quality Assurance Plan and information detailing the accuracy and precision of IRLCS alpha-track detector measurements are published elsewhere (33).

The third component of the radon dosimetry assessment was the measurement of annual average outdoor radon concentrations at 111 geographically dispersed locations in Iowa by using 129 US Environmental Protection Agency proficient alpha-track detectors. The outdoor radon concentrations and the radon concentrations from the participants' first floors were mapped by using a kriging procedure (figure 1). The outdoor radon exposure was estimated from the local average of the kriged grid values derived from direct outdoor measurements. The exposure model assumed that a subject was primarily exposed to radon outside the home at a variety of locations, and the exposure was weighted so that the radon concentration within 1 mile (1.6 km) of the home accounted for 50 percent of the exposure with incremental decreased weighting out to 20 miles (32 km). Additional information concerning outdoor radon concentrations in Iowa is presented elsewhere (34).

Estimated radon exposures in other buildings (work, schools, churches, stores, etc.) were the fourth component of our radon dosimetry assessment. We studied the relation between bedroom radon concentrations and radon concentrations in other buildings for approximately 100 women in nearby Minnesota. The results from this study suggested that the best estimate for the radon concentrations in other buildings is 0.5 times the first-floor residential radon concentration. Thus, we also constructed a kriged surface grid for the other buildings based on 0.5 times the first-floor radon concentrations within the controls' homes. The exposure model assumed that a subject spent time in many local buildings and assigned the average value of the other building kriged grid within a 20-mile (32-km) radius of her home as her average exposure in other buildings.

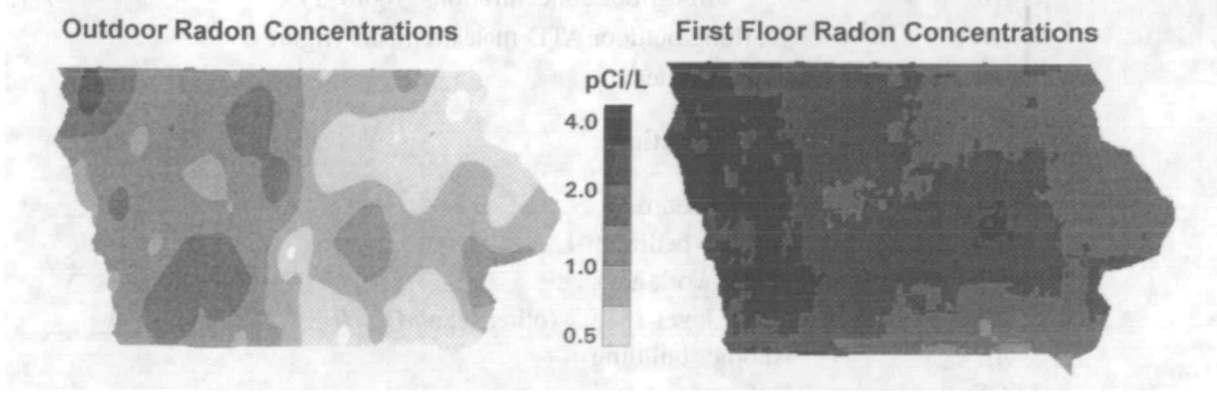

FIGURE 1. Maps of outdoor and first-floor radon concentrations in Iowa, IRLCS, 1993–1997.

The fifth component of the radon dosimetry assessment was the linkage between the various radon concentrations and both the subject's temporal and her spatial mobility (equation 1). A time-weighted average radon exposure for each subject was calculated based on average yearlong radon measurements performed in the current bedroom (and the historical bedroom, if applicable), each level of the home, and in-home work area (if applicable). For each subject, the average yearlong radon measurement was linked to percent time spent in the bedroom (and the historical bedroom, if applicable), each level of the home, in-home work area (if applicable), outdoors, in other buildings, and away on vacation or business travel. The current, average, yearlong radon measurement was assumed to be constant over the years that the participant lived in the home; however, the temporal and spatial activity (time spent in the bedroom, each level of the home, etc.) was allowed to vary for each subject by individual season and period of time as recorded in the face-to-face interview. A radon concentration of 0.95 pCi/liter (35 Bq/m^3) was assumed for the subject's radon exposure while the subject was away from home on vacation or business. This value (0.95 pCi/liter) represents the mean for the national average single-family home indoor (1.5 pCi/liter) and national average outdoor (0.4 pCi/liter) radon concentrations (35–37). Exposure estimates were available for all years that the subject had lived in the current home. Temporal and spatial mobility information was collected in a way that allowed estimation of exposures by time windows for the participants. The retrospective time window 5–19 years prior to diagnosis for cases or prior to initial contact for controls was chosen to compute a cumulative radon exposure for two reasons. First, studies of underground miners demonstrate that the latency period for radiogenic cancer is 5 years (3, 4). Second, the 20-year time interval inclusion criteria allowed a reasonable pool of eligible cases and eliminated the need to impute missing radon measurement data during this period. Previous studies of underground miners exposed to radon indicated that radon exposure occurring 5–15 years prior to the development of lung cancer carried the greatest risk per unit exposure (4).

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 percent

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

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

$$= \begin{cases} MB & \text{yearlong ATD measurement} \\ HB_1, HB_2, \ldots & \text{yearlong ATD measurements} \\ WA & \text{yearlong ATD measurement} \\ L_1, L_2, \ldots & \text{average of ATDs on } L_1, L_2, \ldots \text{ (other than } MB, HB_1, HB_2, \ldots, \text{ and } WA) \\ AB & 0.5 \times \text{first-floor concentrations (figure 1)} \\ OS & \text{yearlong outdoor ATD measurements (figure 1)} \\ AW & \text{0.95 pCi/liter} \end{cases}$$

Locations

MB	Master bedroom
$HB_1, HB_2, \ldots$	Historic bedroom 1, 2, ...
WA	Home work area
$L_1, L_2, \ldots$	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)

Statistical analyses

The associations between lung cancer risk and observed radon exposures were studied by using linear excess odds models in the form expressed in equation 2:

$$\frac{\pi}{1-\pi} = \exp\{\beta_0 + \sum \beta_i x_i\} \times [1 + \gamma w], \quad (2)$$

where π is the conditional probability of lung cancer, w is the cumulative working-level month radon exposure for years 5–19 prior to study enrollment, and the x_i are potential confounding variables. Under a rare-disease assumption, this model is of the same general form as the excess relative risk models developed for radon by the National Research Council (4).

Cumulative radon exposure was expressed in working-level months for exposures occurring 5–19 years prior to diagnosis (WLM_{5-19}) for cases or prior to the time of interview for controls. WLM_{5-19} exposure was analyzed both as a categorical and a continuous variable. Subjects were partitioned a priori into five exposure cells for the categorical analyses. The highest 15 percent of exposed cases and controls combined constituted the fifth cell. 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. For the continuous analyses, actual WLM_{5-19} exposure was used.

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 prior to study enrollment (assumed latency period for lung cancer) for controls or lung cancer diagnosis for cases. Results are also presented for never, light, and heavy smokers, where "light" and "heavy" are based on the median pack-year rate (208.2 median pack-years) among those who smoked at least 100 cigarettes or who smoked for a period of at least 6 months in their lifetime. Pack-year rate was chosen for this categorization because it was most strongly and significantly associated with lung cancer risk. The data were analyzed using the S-PLUS statistical package (38). Model parameters were estimated via maximum likelihood techniques. Trend tests, tests for heterogeneity, and 95 percent confidence intervals are two-sided and are based on the likelihood ratio statistic.

RESULTS

The mean age at lung cancer diagnosis was 67.9 years, and, as expected, was comparable with the age at contact for controls, 67.4 years (table 1). Cases had a slightly higher median residency time within their current home at time of contact. The percent of subjects who attained a postsecondary education and the number of children were both slightly higher for controls. All of the controls were alive at the time of interview. Rapid reporting led to a high percentage (68.5 percent) of live cases. For the remaining cases, next of kin participated. The next of kin who completed questionnaires consisted of husbands (58.0 percent), daughters (16.7 percent), sons (14.7 percent), sisters (2.6 percent), brothers (1.3 percent), and other relatives or friends (6.7 percent). Fifteen percent of the time, more than one relative helped to complete the proxy questionnaires. A slightly higher percent of cases resided in urban areas. A significantly higher frequency of previous lung disease was seen for cases. As expected, the greatest difference observed between cases and controls was the proportions of ever smokers, with 86.4 and 32.5 percent of the cases and controls, respectively, smoking for either at least 6 months or 100 cigarettes in their lifetime. Among ever smokers, the pack-year exposure was much higher for cases compared with controls. Among former smokers, cases stopped smoking more recently than did controls. The odds ratio (OR) for lung cancer for women who smoked at least 100 cigarettes or who smoked for a period of at least 6 months in their lifetimes versus women who never smoked was 13.2 (95 percent confidence interval: 9.5, 18.3). In addition, ORs of 8.1 (95 percent confidence interval: 5.6, 11.7) and 29.0 (95 percent confidence interval: 19.1, 43.9) were found for light and heavy smokers, respectively, compared with the never smokers. These findings are consistent with previous risk estimates from large-scale, population-based studies examining the relation between smoking and lung cancer in women (39–41).

Data from the follow-up questionnaire found no differences between participation and refusals among controls for the categories ever-worked, current worker, ever smoked, and current smoker. In addition, no significant differences were noted in the bedroom radon concentrations (Wilcoxon rank-sum test, $p = 0.17$) between participating controls and the control refusals (21 percent) who performed radon testing.

Radon dosimetry

Home radon concentrations. An average of four radon detectors were placed at each study home. The measurements followed an approximately log-normal

TABLE 1. Demographic characteristics of cases and controls in the IRLCS*, Iowa, 1993–1997

	Cases			Controls		
	No.	%	Years	No.	%	Years
Total	413			614		
Age (years)						
40–49		2.2			2.8	
50–59		16.9			19.2	
60–69		38.0			37.6	
70–84		42.9			40.4	
Mean age at diagnosis (cases) or contact (controls)			67.9			67.4
Residency in home (median)			33			31
Mean no. of children	3.0			3.2		
Education (years)						
<12		10.2			7.7	
12		57.2			48.7	
>12		32.6			43.6	
In-person interview		68.5			100.0	
Urban residential setting		82.3			71.7	
Previous lung disease		43.6			26.5	
Ever-smokers†	357			200		
Smoking (pack-years)						
0–19		13.2			49.5	
20–39		37.2			30.0	
40–59		28.6			16.5	
≥60		21.0			4.0	
Former smokers‡	104			128		
Years since cessation of smoking						
<10		70.5			29.8	
10–19		17.3			21.9	
20–29		7.1			20.5	
≥30		5.1			27.8	

* IRLCS, Iowa Radon Lung Cancer Study.
† Individuals who smoked at least 100 cigarettes or for a period of at least 6 months in their lifetime.
‡ Former smokers were individuals who had quit smoking for at least 5 years before diagnosis for cases or for at least 5 years before time of interview for controls.

distribution. Geometric mean radon concentrations by level of the home are presented in table 2. The mean first- and second-story radon concentrations were approximately half the concentrations detected in the basements of homes. The mean radon concentrations found in the basement of case and control homes were similar, while slightly higher radon concentrations were noted for the first and second story of case homes. Detailed information concerning the spatial variation of radon concentrations in IRLCS homes is presented elsewhere (42). The majority of basement radon concentrations and a significant percentage of first- and second-story radon concentrations exceeded the US Environmental Protection Agency's action level of 4 pCi/liter (148 Bq/m^3) for both cases and controls. Geographic areas that exhibited the highest first-floor radon concentrations were located in areas of western and central Iowa (figure 1).

Outdoor radon concentrations. The outdoor radon concentrations at the 111 geographically dispersed sampling stations throughout Iowa ranged from 0.2 pCi/liter (7.4 Bq/m^3) to 1.5 pCi/liter (56 Bq/m^3), with

TABLE 2. Residential radon gas concentrations for the 1,027 IRLCS* homes, Iowa, 1993–1997

Subjects and level of home	No. of homes	Geometric mean (pCi/liter) (GSD*)	% exceeding 4 pCi/liter (148 Bq/m³)
Controls			
Basement	567	4.6 (2.2)	58.4
1	614	2.4 (2.2)	28.0
2	298	1.9 (2.1)	17.1
Cases			
Basement	363	4.5 (2.2)	58.7
1	413	2.7 (2.2)	32.7
2	209	2.1 (2.1)	20.6

* IRLCS, Iowa Radon Lung Cancer Study; GSD, geometric standard deviation.

a mean and a geometric mean of 0.82 pCi/liter (0.27 standard deviation) and 0.78 pCi/liter (1.4 geometric standard deviation), respectively. Geographic spatial similarities between the first-floor and outdoor radon concentrations were apparent (figure 1). Detailed information concerning the modeling of outdoor radon concentrations in Iowa and its impact on radon exposure assessment is available elsewhere (34).

Spatial and temporal occupancy patterns. Temporal longitudinal trends in the mobility patterns for cases and controls varied modestly over time (table 3). The mean time spent at home for the controls ranged from a low of 69.4 percent at age 50–59 years to a high of 81.5 percent at age 80–84 years. The mean time spent at home for cases ranged from a low of 70.5 percent at age 40–49 years to a high of 81.6 percent at age 80–84 years. Both controls and cases who lived in either one- or two-story homes with basements spent the majority of their residential occupancy on the first story. Trends across age for both cases and controls varied for other subgroups by number of children, education, and urban/rural status. Additional information concerning the spatial and temporal mobility patterns of study subjects is published elsewhere (32).

Risk estimates

The WLM_{5-19} cumulative radon exposures followed a log-normal distribution. Table 4 presents the estimated odds ratio for lung cancer and tests of linear trend for WLM_{5-19} cumulative radon exposure for all controls and cases and subset analyses of controls and cases who were alive at the time of interview. The risk estimates were adjusted for age, active smoking, and education. For all lung cancer subjects, there was a positive categorical trend ($p = 0.05$). Analyses restricted to the 283 live cases and 614 live controls noted both a strong categorical ($p = 0.01$) and a continuous ($p = 0.03$) trend. The fifth exposure category was also statistically significant (OR = 2.14, 95 percent confidence interval: 1.12, 4.15).

Table 5 displays the 15-year cumulative radon exposure risk at 11 WLM_{5-19} for all subjects and for live subjects categorized by both the continuous and categorical variables. Eleven WLM_{5-19} is roughly equivalent to an average residential exposure of 4 pCi/liter (148 Bq/m³), assuming a 70 percent home occupancy and the other assumptions of the BEIR VI report (2). Excess odds of 0.24 (95 percent confidence interval: –0.05, 0.92) and 0.50 (95 percent confidence interval: 0.004, 1.81) per 11 WLM_{5-19} were calculated for all cases by using the continuous and categorical variables, respectively. Higher excess odds of 0.49 (95 percent confidence interval: 0.03, 1.84) and 0.83 (95 percent confidence interval: 0.11, 3.34) were noted per 11 WLM_{5-19} for the live case subset for both the continuous and the categorical risk estimates, respectively.

The effect of the urban or rural status of subjects was examined by classifying them as living within or out-

TABLE 3. Mean percent time spent at home, in another building, outside, and away on vacation or business*, IRLCS,† Iowa, 1993–1997

Age (years)	Cases				Controls			
	Home	Another building	Outside	Away	Home	Another building	Outside	Away
All	73.2	14.2	7.6	5.0	72.1	14.4	8.5	5.0
40–49	70.5	17.1	7.7	4.7	70.1	16.7	9.0	4.2
50–59	70.7	16.7	7.5	5.1	69.4	17.2	8.4	5.0
60–69	74.6	11.6	7.2	6.6	73.2	12.3	7.6	6.9
70–79	78.9	7.8	6.7	6.6	78.0	8.2	6.7	7.1
80–84	81.6	7.0	5.9	5.5	81.5	6.2	6.8	5.5

* The category "another building" represents time spent in another building at work, volunteer work, shopping, etc. The category "away" represents vacation time or work assignments at a geographic location significantly away from the usual residence or place of employment. The category "outside" represents time spent in the outdoors, but also includes time spent in a vehicle.

† IRLCS, Iowa Radon Lung Cancer Study.

TABLE 4. Estimated odds ratios* for lung cancer and tests of a linear trend for WLM_{5-19}† cumulative radon exposure, IRLCS†, Iowa, 1993–1997

	Median	All			Alive		
		OR†	95% CI†	Cases/controls	OR	95% CI	Cases/controls
WLM_{5-19} cumulative radon exposure‡							
0–4.23	3.16	1.00		56/104	1.00		37/104
4.24–8.47	6.18	1.34	0.81, 2.22	147/229	1.31	0.75, 2.31	98/229
8.48–12.70	10.50	1.73	0.99, 3.04	87/118	1.79	0.97, 3.33	61/118
12.71–16.94	14.58	1.62	0.88, 2.99	56/75	1.74	0.88, 3.43	39/75
>16.95	21.16	1.79	0.99, 3.26	67/88	2.14	1.12, 4.15	48/88
p for trend							
Continuous		0.14			0.03		
Categorical		0.05			0.01		

* Estimates are adjusted for age, active smoking, and education.

† WLM_{5-19}, working-level months for exposures that occurred 5–19 years prior to diagnosis for cases or time of interview for controls (1 working-level month is equivalent to 3.5×10^{-3} Jh/m³); IRLCS, Iowa Radon Lung Cancer Study; OR, odds ratio; CI, confidence interval.

‡ The temporally and spatially weighted median WLM cumulative exposure over 5–19 years was 7.9 WLM and 8.6 WLM for all controls and cases, respectively.

side of city limits, as well as by county type of residence (large urban, small urban, and rural counties). After control for age, education, and active smoking, the urban/rural status was not significantly associated with radon exposure and lung cancer risk ($p > 0.6$); likewise, subjects who worked outside the home were not at a significantly higher risk of lung cancer than were those who did not ($p > 0.5$). No individual occupation was found to be at an increased risk.

Figure 2 compares the IRLCS odds ratios with odds ratios calculated using radon exposure methodologies similar to some of the previously published residential radon studies. The odds ratios labeled as the master bedroom and living area (level 1) were based on a simple arithmetic average of the radon measurements from the two rooms. The odds ratios labeled as the basement were based on the average yearlong radon concentration in the basement. The IRLCS radon exposure methodology produced higher odds ratios than did the other two commonly utilized radon exposure methods.

TABLE 5. Excess risk estimates* for WLM_{5-19} cumulative radon exposure, IRLCS†, Iowa, 1993–1997

Subjects (cases/controls)	Continuous		Categorical	
	Excess risk	95% CI†	Excess risk	95% CI
All (413/614)	0.24	−0.05, 0.92	0.50	0.004, 1.81
Live (283/614)	0.49	0.03, 1.84	0.83	0.11, 3.34

* Estimated excess odds are for an exposure of 11 working-level months for exposures that occurred 5–19 years prior to diagnosis for cases or time of interview for controls (WLM_{5-19}) and are adjusted for age, active smoking, and education (1 working-level month is equivalent to 3.5×10^{-3} Jh/m³)

† IRLCS, Iowa Radon Lung Cancer Study; CI, confidence interval.

Table 6 presents the estimated odds ratios by lung cancer subtype. Large cell carcinoma exhibited a statistically significant trend for both the continuous ($p = 0.04$) and categorical ($p = 0.03$) risk estimates. A suggestive dose-response trend was also observed for the squamous cell carcinoma subset (categorical p for trend = 0.06) with a significant categorical risk estimate of 3.17 for the fifth exposure category. However, the differences in the linear excess odds between histologic types was not statistically significant (continuous $p = 0.58$, categorical $p = 0.65$).

Additional analyses were performed to examine whether or not the effect of radon differed according to smoking status, education, and age (table 7). There was no evidence of heterogeneity for these three factors using either continuous or categorical analyses. The test statistics (continuous p value = 0.83, categorical p value = 0.66) for heterogeneity among the categories of smoking failed to reject a multiplicative effect between radon and smoking on lung cancer risk.

DISCUSSION

IRLCS data were analyzed by using both continuous and categorical modeling of cumulative radon exposure. Analyses based on continuous exposure variables have the advantage of avoiding the discretionary nature of choosing cutpoints. On the other hand, trend statistics based on categorical measures tend to reduce the influence of extreme values. Similar

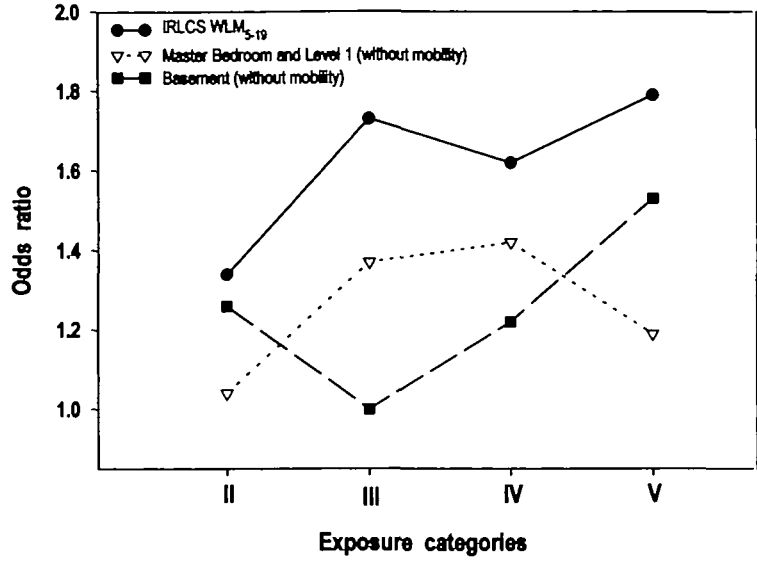

FIGURE 2. Plots of risk estimates for the all cases and controls calculated by using alternative radon exposure estimate scenarios, IRLCS, Iowa, 1993–1997. IRLCS odds ratios, as reported in table 4, are presented for comparison. The odds ratios plotted as the master bedroom and living area are based on a simple arithmetic average of the radon measurements from the two rooms. The odds ratios plotted for the basement are based on the average yearlong radon concentration in the basement without consideration of retrospective subject mobility. An average home occupancy of 70 percent time was assumed for the master bedroom and level 1 (living area) plot and the basement plot.

findings were noted for both the continuous and categorical analyses. Excess odds of 0.24 (95 percent confidence interval: –0.05, 0.92) and 0.49 (95 percent confidence interval: 0.03, 1.84) per 11 WLM_{5-19} were calculated by using the continuous variables for all subjects and for live subjects, respectively. Slightly higher excess odds of 0.50 (95 percent confidence interval: 0.004, 1.81) and 0.83 (95 percent confidence interval: 0.11, 3.34) per 11 WLM_{5-19} were noted for the categorical variables for all subjects and for live subjects. The results for the continuous and categorical variables were in general agreement. Furthermore, there is no significant correlation between radon exposure and active smoking (a combination of years since smoking cessation and pack-year rate) ($p > 0.45$). Thus, it is unlikely that the observed excess odds for radon exposure are due to residual confounding with smoking. Overall, these results suggest that cumulative radon exposure is a significant risk factor for lung cancer in women.

A major advantage of the IRLCS was the rapid-reporting mechanism of the study, which obtained a high percentage (69 percent) of live cases. The use of living subjects provided the maximal opportunity to obtain valid information (e.g., mobility, residence, education, smoking history, etc.) as well as represen-

TABLE 6. Estimated odds ratios* and 95% confidence intervals for lung cancer and tests of a linear trend for WLM_{5-19}† cumulative radon exposure by cancer subtype, IRLCS†, Iowa, 1993–1997‡

No. of cases	WLM_{5-19} cumulative radon exposure								*p* for trend	
	0–4.23 (OR†)	4.24–8.47		8.48–12.70		12.71–16.94		≥16.95		
		OR	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI	Continuous	Categorical
Adenocarcinoma (*n* = 175)	1.00	1.21	0.67, 2.24	1.57	0.81, 3.09	1.86	0.90, 3.85	1.35	0.64, 2.83	0.20	0.21
Squamous (*n* = 82)	1.00	2.06	0.79, 5.90	2.20	0.77, 6.75	2.40	0.77, 7.90	3.17	1.08, 10.06	0.18	0.06
Small cell (*n* = 74)	1.00	1.16	0.49, 2.86	1.83	0.70, 4.95	1.36	0.40, 4.44	1.44	0.47, 4.35	0.33	0.41
Large cell (*n* = 32)	1.00	1.13	0.33, 4.51	1.87	0.50, 7.90	1.99	0.42, 9.56	3.42	0.93, 14.53	0.04	0.03
Other (*n* = 50)§	1.00	1.60	0.60, 4.82	1.33	0.39, 4.64	1.75	0.48, 6.45	2.95	0.96, 9.82	0.10	0.09

* Estimates are adjusted for age, active smoking, and education.

† WLM_{5-19}, working-level months for exposures that occurred 5–19 years prior to diagnosis for cases or time of interview for controls (1 working-level month is equivalent to 3.5×10^{-3} Jh/m^3); IRLCS, Iowa Radon Lung Cancer Study; OR, odds ratio; CI, confidence interval.

‡ All 614 controls were included in each subtype analysis.

§ Thirty-three lung cancers were classified as carcinoma not otherwise specified and 17 as adenosquamous. Histologic materials were not available for eight cases, and eight cases refused to sign the consent form granting permission to obtain histologic materials. The registry-reported histologic subtype was available and used for these 16 cases.

TABLE 7. Excessive risk estimates* for 5–19 working-level months (WLM_{5-19})† cumulative radon exposure within categories of other covariates for all cases and controls, IRLCS‡, Iowa, 1993–1997

	Continuous			Categorical		
	Excess risk	95% CI‡	Test for heterogeneity (*p* value)	Excess risk	95% CI	Test for heterogeneity (*p* value)
Age (years)						
40–59	0.18	−0.13, 1.19	0.93	0.29	−0.25, 1.88	0.79
60–69	0.20	−0.13, 0.97		0.43	−0.09, 1.76	
70–84	0.32	−0.08, 1.57		0.71	−0.003, 2.85	
Education (years)						
<12	−0.07	−0.34, 1.20	0.71	0.08	−0.39, 1.91	0.69
12	0.21	−0.07, 0.92		0.48	−0.03, 1.80	
>12	0.34	−0.10, 1.47		0.65	−0.05, 2.59	
Smoking category						
Never	0.22	−0.20, 1.93	0.83	0.88	−0.05, 6.01	0.66
Light	0.33	−0.05, 1.30		0.51	−0.07, 2.10	
Heavy	0.14	−0.12, 1.04		0.20	−0.24, 1.48	

* Estimated excess odds are for an exposure of 11 working-level months for exposures that occurred 5–19 years prior to diagnosis for cases or time of interview for controls (WLM_{5-19}). Eleven WLM_{5-19} is approximately equivalent to an average residential exposure of 4 pCi/liter (148 Bq/m^3), assuming a 70 percent home occupancy and the other assumptions of the BEIR VI report (4). Separate risk estimates are presented for the categories listed above to test for departures from the multiplicative effects of the covariates in the excess odds model.

† One WLM is equivalent to 3.5×10^{-3} Jh/m^3.

‡ IRLCS, Iowa Radon Lung Cancer Study; CI, confidence interval.

tative radon measurements. The degree of temporal and spatial radon variation is of particular concern in other studies in which a high percentage of lung cancer participants are deceased and in studies that measure historical homes the participant lived in at some time in the past. The radon concentrations that exist after the participant moves out of the home may not reflect radon concentrations that prevailed when she lived there. Structural changes in the home or behavior differences between the new and the former occupants, such as opening the windows more frequently, may affect residential radon concentrations. Radon measurements were performed for a second year in the basement and bedroom of 280 IRLCS homes. Compared with first-year measurements, second-year measurements performed in homes of proxy respondents had greater radon variation (coefficient of variation = 21.9 percent, n = 27 measurements) compared with nonproxy homes (coefficient of variation = 15.4 percent, n = 487 measurements). Retrospective subject mobility information, used to derive radon exposure, is obtained more accurately from the subject herself than from the next of kin, resulting in less error in exposure measures and stronger dose-response trends. Therefore, the live-case subset provides a better estimate of the risk posed by cumulative radon exposure.

The IRLCS had several other advantages over previous residential radon studies. The study was carried out in Iowa, which has the highest mean radon concentrations in the United States (43). Approximately 60 percent of the study participants' basement radon concentrations and 30 percent of the first-floor radon concentrations exceeded the US Environmental Protection Agency action level of 4 pCi/liter (148 Bq/m^3). Western Iowa appeared to have uniformly higher indoor and outdoor radon concentrations compared with eastern Iowa. In fact, large areas of western Iowa had outdoor radon concentrations comparable with the national average indoor value for single-family homes of 1.5 pCi/liter (56 Bq/m^3). The high radon concentrations in conjunction with a strict quality assurance protocol contributed to accurate and precise radon measurements (33). While previous residential radon studies have imputed from 17 to 40 percent of their radon measurements (9–15, 17, 18), the IRLCS criteria requiring occupancy in the current home for at least the previous 20 years eliminated the need to impute radon measurements from missing homes. Lubin et al. (21) have pointed out that these gaps in radon measurements seriously decrease the statistical capacity of a study to detect an association, since the impact of the imputation decreases the overall power of a study.

A limitation of the IRLCS was the lower than expected response rate for controls, which was likely attributable to the inclusion criterion of a 20-year residency in the current home. We have previously shown that as time spent living in a home increases, concern about radon decreases (44). The findings of

the follow-up questionnaire support the representativeness of the participating controls. The residency requirement was imperative in order to reduce radon exposure misclassification. However, it is noteworthy that the IRLCS findings are most generalizable to Midwest women who have smoked at some time in their lives and have spent at least the last 20 years in their current home.

The advancement of linking multiple radon measurements with individual retrospective mobility provided a comprehensive assessment of radon exposure. Since the participants' spatial and temporal mobility trends were nonlinear (32), exposure misclassification increases when assuming a constant, such as a 75 percent home occupancy factor, which was common practice in previous studies. The IRLCS linkages between radon concentrations and individual mobility minimized exposure misclassification attributable to spatial radon variation (42) and changes in the participant's retrospective mobility (32). The failure to link spatially disparate concentrations of radon with the subject's retrospective mobility probably introduces random misclassification of radon exposure that leads to risk estimates biased toward showing no association (45). To support this assertion, we found that the a priori IRLCS radon exposure methodology produced higher odds ratios than did those methodologies that did not link the subject's retrospective mobility with multiple spatially diverse radon concentrations (figure 2).

Previous case-control studies were performed in Canada, China, Finland, Germany, Sweden, the United Kingdom, and the United States (New Jersey and Missouri). Lubin et al. have combined the relative risks of eight of these studies (9–16, 46) in a meta-analysis using weighted linear regression to provide a summary excess odds of 0.14 at 4 pCi/liter (148 Bq/m^3). The excess odds at 4 pCi/liter (148 Bq/m^3) obtained in two other recent studies in Germany (17) and the United Kingdom (18) were in close agreement with the risk estimates obtained from the meta-analysis. The estimated excess odds of the IRLCS at 11 WLM_{5-19} (roughly equivalent to a 15-year exposure at an average radon exposure of 4 pCi/liter) ranged from 0.24 for all cases to 0.83 for live cases only. These observed excess odds were slightly higher than those reported in most of the previous residential radon studies. The enhanced dosimetry techniques used in the IRLCS, which reduced exposure misclassification, probably contributed to the higher risk estimates. The IRLCS risk estimates are in general agreement with the National Research Council's predicted cancer risk associated with indoor radon exposure (2).

Independent pathologic review was performed for 96 percent of the cases. The review provided for more reliable classification of lung cancer cases by morphology. While a positive dose-response trend was noted for large cell carcinoma and squamous cell carcinoma, no significant differences were noted for radon risk estimates between the lung cancer subtypes. However, the morphologic findings from the IRLCS require cautious interpretation because of the limited sample size for some of the subtypes.

In conclusion, the IRLCS examined the relation between cumulative radon exposure and lung cancer by uniquely combining enhanced dosimetric techniques, individual mobility assessment, and expert morphologic review with a population characterized by stability, a high percentage of live cases, and a potential for high radon exposure. Our findings suggest that the ability to detect an association between cumulative radon exposure and lung cancer requires 1) a rigorously designed study minimizing radon exposure misclassification and 2) a study location with relatively high radon concentrations. Overall, the risk estimates obtained in this study suggest that cumulative radon exposure in the residential environment is significantly associated with lung cancer risk.

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