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Research Article

Radon and Lung Cancer in the American Cancer Society Cohort

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Abstract

Background: Case–control studies conducted in North America, Europe, and Asia provided evidence of increased lung cancer risk due to radon in homes. Here, the association between residential radon and lung cancer mortality was examined in a large-scale cohort study.

Methods: Nearly 1.2 million Cancer Prevention Study-II participants were recruited in 1982. Mean county-level residential radon concentrations were linked to study participants according to ZIP code information at enrollment [mean (SD) = 53.5 Bq/m^3 (38.0)]. Cox proportional hazards regression models were used to obtain adjusted HR and 95% CI for lung cancer mortality associated with radon. Potential effect modification by cigarette smoking, ambient sulfate concentrations, and other risk factors was assessed on both the additive and multiplicative scales.

Results: Through 1988, 3,493 lung cancer deaths were observed among 811,961 participants included in the analysis. A significant positive linear trend was observed between categories of radon concentrations and lung cancer mortality ($P = 0.02$). A 15% (95% CI, 1–31) increase in the risk of lung cancer mortality was observed per 100 Bq/m^3 increase in radon. Participants with mean radon concentrations above the EPA guideline value (148 Bq/m^3) experienced a 34% (95% CI, 7–68) increase in risk for lung cancer mortality relative to those below the guideline value.

Conclusions: This large prospective study showed positive associations between ecological indicators of residential radon and lung cancer.

Impact: These results further support efforts to reduce radon concentrations in homes to the lowest possible level. *Cancer Epidemiol Biomarkers Prev; 20(3); 438–48. ©2011 AACR.*

Introduction

Lung cancer is the leading cause of cancer mortality in the United States. In 2009, it was estimated that a total of 219,440 new lung cancer cases and 159,390 deaths occurred (1). Lung cancer is a highly fatal disease, with a 5-year survival ratio of 15% (1). Although incidence rates for lung cancer have been declining for males, they are only now leveling off after several decades of increase for females, most likely because of changes in cigarette smoking patterns in recent decades (1). Although the majority of lung cancer cases can be attributed to active cigarette smoking, residential radon and ambient air pollution also have been implicated as important risk factors for this disease in the general population (2–5).

Radon gas is formed during the radioactive decay of uranium-238, which is naturally present in rocks and soils in the environment. In 1988, the International Agency for Research on Cancer (IARC) determined that radon was a cause of human lung cancer, based on studies of underground miners historically exposed to high levels of the gas (2). It was also observed that α-particles emitted from radon decay products can damage DNA in human lung tissue (2). Bonner and colleagues (6) recently reported an interaction between glutathione-*S*-transferase M1 and radon, suggesting that radon may also induce lung cancer through oxidative mechanisms.

Radon gas enters homes through cracks and other openings in the foundation and accumulates largely in the basement and lower living areas (7). Although there have been more than 20 case–control studies examining the association between residential radon and lung

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cancer, results were limited by small sample sizes and disparate findings. Recent efforts to combine data from individual case–control studies have provided for the first time strong evidence for a link (8–11). In North America, data from 7 case–control studies, involving 3,622 lung cancer cases and 4,966 controls were combined, revealing that each 100 Bq/m^3 increase in radon was associated with an 11% (95% CI, 0–28) increase in lung cancer risk (10, 11). Results strengthened in a subset of the data with limited residential mobility and complete radon exposure histories [excess relative risk (ERR) = 21%; 95% CI, 3—52]. In Europe, data from a total of 7,148 lung cancer cases and 14,208 controls were also combined with similar findings observed (8, 9). Overall, each 100 Bq/m^3 increase in radon was associated with an 8% (95% CI, 3–16) increase in lung cancer risk. The evidence available to date suggests that radon may be responsible for 10% to 15% of the lung cancer burden, making radon the second leading cause of lung cancer after cigarette smoking (3).

Although there have been a number of residential case–control studies capturing retrospective data on individual smoking habits and other lung cancer risk factors, there has been only one prospective study in the general population. Ruano-Ravina and colleagues (12) recently followed up 241 control subjects from a previous case–control study of residential radon and lung cancer in Spain. An elevated, although imprecise, lung cancer risk was observed in subjects with radon concentrations above the guideline value of the U.S. Environmental Protection Agency (EPA; 4 pCi/L = 148 Bq/m^3; RR = 6.6; 95% CI, 1.2–38) relative to subjects below the guideline value.

There have also been few studies to examine the joint effects of residential radon and other inhalable environmental agents including passive smoke and ambient air pollution (13, 14). The question remains as to whether such agents may interact, thereby producing additive or multiplicative effects on lung cancer risk. Radon decay products may also attach to aerosols present in the environment, possibly influencing lung deposition and dose characteristics relevant for lung cancer (4, 15–16).

The purpose of this article is to examine the association between residential radon and lung cancer mortality in a large-scale prospective study. The American Cancer Society Cancer Prevention Study-II (CPS-II) is a large, well-established cohort, with detailed individual-level risk factor data collected at enrollment, including cigarette smoking, passive smoking, and occupational risk factors for lung cancer. It provides a unique opportunity to further strengthen the body of evidence for an association between residential radon and lung cancer and allows for an examination of the potential confounding or modifying effects of a range of individual and ecological-level risk factors including passive smoking and ambient air pollution. Results examining associations between residential radon and other malignant and nonmalignant mortality outcomes other than lung cancer will be presented separately (Turner and colleagues, unpublished data).

Materials and Methods

Study population

The CPS-II is a prospective study comprised of nearly 1.2 million participants enrolled by more than 77,000 volunteers in 1982. This cohort has been extensively studied to examine the long-term health effects of ambient air pollution (5, 17, 18). Ethics approval for the CPS-II was obtained from the Emory University School of Medicine Human Investigations Committee. Participants were recruited in all 50 U.S. states as well as the District of Columbia and Puerto Rico. Participants were largely friends and family members of the volunteers. For inclusion in CPS-II, participants were at least 30 years of age and had at least one family member ages 45 years or more. A 4-page self-administered questionnaire completed at enrollment captured data on a range of demographic, lifestyle, medical, and other personal and family characteristics including ZIP code of residence.

Because no updated information was collected on cigarette smoking status from enrollment, follow-up in the present study is restricted to the first 6 years of follow-up only (1982–1988; ref. 19). In CPS-II, follow-up of study participants for vital status has been conducted every 2 years. In 1984, 1986, and 1988, vital status was obtained from the study volunteers, confirmed by obtaining the corresponding death certificate. Subsequent to 1988, follow-up has been conducted through computerized linkage to the National Death Index (20). More than 99% of all known deaths have been assigned a cause. Lung cancer deaths were classified by the underlying cause of death according to ICD-9 162 (International Classification of Disease; ref. 21).

Of a total of 1,184,881 CPS-II participants, subjects were excluded due to missing vital status (419), prevalent cancer (except nonmelanoma skin cancer) at enrollment (82,329), missing ZIP code (99,479) or county data (22,872), or missing data on radon (5,836) or individual-level covariates of interest (161,985). A total of 811,961 participants in 2,754 counties were retained for analysis, among which 3,493 lung cancer deaths were observed.

Ecological measures of residential radon

Study participants were assigned to a primary county of residence using 5-digit ZIP code information provided at enrollment according to the ZIP code boundaries (STF3B) of the 1980 U.S. Census (22). Ecological indicators of residential radon concentrations were obtained from the Lawrence Berkeley National Laboratory (LBL) and the University of Pittsburgh.

Because long-term residential radon monitoring data in the United States is sparse, researchers at the LBL sought to estimate the annual average radon concentrations in the main living areas of homes by county using available data (23, 24). More specifically, both short-term

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and long-term indoor radon monitoring data were used along with a variety of geological, soil, meteorologic, and housing data to predict mean residential radon concentrations in a statistical model. Data from the EPA State Residential Radon Survey (SRRS), involving a random sample of approximately 60,000 short-term screening measurements from homes in the mid- to late 1980s, were combined with geological data, including estimated radium concentrations, and location of screening measurements within the home, as well as a short- to long-term radon monitoring data conversion factor estimated on the basis of the relationship between radon concentrations observed in the SRRS and in the U.S. National Residential Radon Survey (NRRS; 1989–1990), the only long-term residential radon survey conducted in the United States to date with representative data collected on nearly 5,700 homes in 125 counties (7), to predict annual average radon concentrations in homes in 3,079 U.S. counties.

At the University of Pittsburgh, Cohen (25, 26, 27) compiled a database of mean county-level residential radon concentrations for 1,601 U.S. counties based on a series of screening measurements made in a nonrandom sample of homes obtained from 3 independent data sources from the mid- to late 1980s: the University of Pittsburgh (272,000 measurements in 1,217 counties), the U.S. EPA (40,000 measurements in 1,141 counties), and measurements obtained from various other state-level sources (Florida, New Jersey, South Carolina, New Hampshire, New York, Iowa, Idaho, Ohio, Utah). Mean county-level residential radon concentrations were estimated by averaging all available data in each county with at least 10 available measurements. Data from the states of Florida, California, and Arizona were excluded in the final available county-level dataset by Cohen (25, 26) because of concerns surrounding the representativeness of data for individuals in states with high rates of migration (mainly due to retirement). Mean county-level residential radon concentrations were normalized to the data of the U.S. NRRS (7). Mean county-level residential radon concentrations from both data sources were linked to study participants as indicators of historic residential radon exposure.

Sociodemographic ecological covariates

Data on a range of social and demographic ecological covariates were compiled for 20,561 participant ZIP codes from the 1980 U.S. Census including median household income, and percent air conditioning, nonwhite, black, Hispanic, post–secondary education, unemployment, poverty, urban, moving, and homes with a well (22). The selection of ecological covariates was informed by previous air pollution studies in the CPS-II cohort (17, 18).

Air pollution

Average ambient sulfate (SO_4) data for 149 U.S. metropolitan statistical areas were previously compiled by members of our research team based on the data of the Inhalable Particle Monitoring Network and the National Aerometric Database for the years 1980 and 1981 (5, 17, 18). Sulfate air pollution was previously found to be associated with lung cancer mortality in the CPS-II cohort in the follow-up time period of interest here (28). Mean sulfate concentrations ranged from 1.4 to 15.6 $\mu g/m^3$ with an average value (SD) of 6.5 (2.8) $\mu g/m^3$.

Statistical analysis

Cox proportional hazards regression models were used to examine the independent effects of residential radon on lung cancer mortality by using SAS PROC PHREG (29). The baseline hazard in the proportional hazards models was stratified by 1-year age categories, sex, and race (white, black, other). Follow-up time since enrollment (1982) was used as the time axis. The survival times of those still alive at the end of follow-up were censored. Residential radon concentrations were examined in 3 ways: as a continuous variable (per 100 Bq/m^3), as a 7-level categorical variable where the reference category was <25 Bq/m^3 (10, 11), and as a dichotomous variable where the cutpoint was at the U.S. EPA residential radon guideline value (148 Bq/m^3).

Estimated HRs and 95% CIs were adjusted for a range of individual-level risk factors including education, marital status, body mass index (BMI), BMI squared, cigarette smoking status, cigarettes per day (current and former smokers), cigarettes per day squared (current and former smokers), years smoked (current and former smokers),

Table 1. Distribution of mean county-level residential radon concentrations (LBL; Bq/m^3), at enrollment (1982), by region, CPS-II cohort, United States

Radon measure	Total (n = 811,961)	Northeast (n = 170,281)	South (n = 257,243)	Midwest (n = 234,952)	West (n = 149,485)
Mean (SD)	53.5 (38.0)	58.3 (42.3)	35.6 (21.7)	73.7 (36.6)	46.9 (40.3)
Minimum	6.3	17.8	6.3	18.9	9.6
First quartile	26.6	33.7	19.6	42.9	18.1
Second quartile	41.4	46.2	28.9	66.2	27.4
Third quartile	70.3	62.9	43.3	100.6	62.2
Maximum	265.7	265.7	143.9	221.6	232.0
Counties $\geq$ 148 Bq/m^3 (%)	3.1	3.7	0.0	7.0	2.9

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Table 2. Distribution (*n*, %) of selected participant characteristics at enrollment (1982), CPS-II cohort, United States

Characteristic	*n* (%)	Mean (SD) radon (Bq/m^3)
Age, y		
<40	37,262 (4.6)	50.1 (35.4)
40–49	173,768 (21.4)	54.0 (37.9)
50–59	297,108 (36.6)	54.2 (38.5)
60–69	213,231 (26.3)	53.1 (38.0)
70–79	76,633 (9.4)	52.4 (37.5)
≥80	13,959 (1.7)	51.9 (36.9)
Race		
White	770,352 (94.9)	54.2 (38.2)
Black	29,832 (3.7)	40.2 (28.3)
Other	11,777 (1.5)	39.3 (32.1)
Sex		
Male	362,600 (44.7)	53.8 (38.2)
Female	449,361 (55.3)	53.2 (37.8)
Education		
<High school	106,668 (13.1)	55.2 (38.9)
High school	262,853 (32.4)	56.8 (39.5)
≥High school	442,440 (54.5)	51.1 (36.6)
BMI, kg/m^2		
<18.5	13,685 (1.7)	50.3 (36.1)
18.5–24.9	402,003 (49.5)	52.2 (37.2)
25–29.9	299,755 (36.9)	54.6 (38.6)
≥30	96,518 (11.9)	55.6 (39.1)
Marital status		
Single	25,564 (3.2)	51.7 (36.7)
Married	691,267 (85.1)	54.1 (38.2)
Other	95,130 (11.7)	49.7 (36.0)
Cigarette smoking status		
Never	375,087 (46.2)	55.5 (39.0)
Current	152,033 (18.7)	51.5 (36.4)
Former	203,253 (25.0)	51.2 (36.9)
Pipe/cigar only	81,588 (10.1)	53.4 (37.9)
Passive smoking		
Yes	512,908 (63.2)	53.9 (38.4)
No	299,053 (36.8)	53.2 (37.7)
Vegetable/fruit/fiber consumption[a]		
First quintile	135,142 (16.6)	52.9 (37.8)
Second quintile	148,206 (18.2)	53.7 (37.9)
Third quintile	152,650 (18.8)	54.0 (38.1)
Fourth quintile	157,772 (19.4)	54.0 (38.4)
Fifth quintile	150,677 (18.6)	53.8 (38.5)
Fat consumption[a]		
First quintile	139,237 (17.2)	50.4 (36.9)
Second quintile	148,677 (18.3)	52.6 (37.8)
Third quintile	151,545 (18.7)	54.2 (38.6)
Fourth quintile	152,749 (18.8)	55.1 (38.6)
Fifth quintile	152,239 (18.8)	55.9 (38.5)
Industrial exposures		
Yes	166,660 (20.5)	55.5 (39.4)
No	645,301 (79.5)	53.0 (37.6)
Occupational dirtiness index[a]		
Level 0	394,828 (48.6)	52.3 (37.4)
Level 1	110,177 (13.6)	53.2 (37.4)
Level 2	90,595 (11.2)	52.1 (37.6)
Level 3	38,461 (4.7)	53.4 (38.1)
Level 4	66,029 (8.1)	62.9 (42.1)
Level 5	36,240 (4.5)	54.3 (38.5)
Level 6	9,525 (1.2)	57.6 (39.0)

[a]Does not sum to total due to missing data.

years smoked squared (current and former smokers), age started smoking less than 18 years (current and former smokers), passive smoking (hours), quintiles of vegetable/fruit/fiber and fat intake, occupational exposures (asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, and diesel engine exhaust), as well as a previously developed "occupational dirtiness index" specifically designed for the CPS-II cohort (5, 17, 30). To adjust for potential confounding by geography, results were also adjusted for state of residence at enrollment. Potential confounding by previous lung disease, a related occupational "lung carcinogen index" (17, 30), and alternate adjustments for cigarette smoking status were examined. Further the potential confounding influence of various sociodemographic ecological variables and sulfate air pollution concentrations was also assessed. Because radon exposures experienced from 5 to 25 years in the past are thought to be most relevant for lung cancer (4), results were also examined in individuals who reported living in their same neighborhood for at least the past 5 years at enrollment. The functional form of the relationship between residential radon and lung cancer mortality was assessed by the supremum test (31).

Effect modification was assessed on both the additive and multiplicative scales. On the additive scale, estimates of the relative excess risk due to interaction, attributable proportion, and synergy index (and associated 95% CIs) were calculated according to the "MOVER" method for the analysis of 4 × 2 tables (32). On the multiplicative scale, interaction terms between radon and each risk factor were entered into proportional hazards models. Two-sided *P* values were calculated to assess the significance of the interaction term by using the likelihood ratio statistic. To assess the impact of attained age, time-dependent variables were constructed by allowing participants

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to be included in the risk set at each death time only if they met the attained age criteria for the model (<70, 70–79, or ≥80 years). The proportional hazards assumption was tested by assessing the significance of an interaction term between radon and follow-up time.

Finally, sensitivity analyses of the main findings were undertaken using generalized relative risk models for survival data (33), and using a random-effects Cox model originally developed for air pollution research in the CPS-II cohort (18, 34). General relative risk models for survival time data were fitted to compare relative risk estimates obtained from linear versus log-linear models using SAS PROC NLP (33). For each lung cancer death, a risk set consisting of all at-risk controls was constructed, and matched according to the stratification criteria of the North American combined analysis of residential radon case–control studies (10, 11): 5-year age groups, sex, cigarettes smoked per day (never smoker, 1–9, 10–19, 20–29, ≥30), duration of cigarette smoking (never smoker, 1–24, 25–34, 35–44, ≥45 years), and state of residence. Analyses were also repeated using the stratification criteria of the European combined analysis (8, 9): 5-year age groups, sex, smoking [never smokers, current smokers' age started smoking (<15, 15–17, 18–20, ≥21 years) and cigarettes per day (<15, 15–24, ≥25), former smokers' amount smoked (<15, 15–24, ≥25 cigarettes per day) and years smoked (<10, ≥10)], and state of residence.

All analyses were conducted by SAS version 9.2 (35) and our random-effects Cox regression program (18). Ethics approval was obtained from the Ottawa Hospital Research Ethics Board.

Results

Table 1 presents the distribution of mean county-level residential radon concentrations by region (LBL data). Overall, mean concentrations ranged from 6.3 to 265.7 Bq/m^3 (1 pCi/L = 37 Bq/m^3) with an average value (SD) of 53.5 (38.0) Bq/m^3. Mean county-level residential radon concentrations were higher in the Northeast and the Midwest with the lowest concentrations observed in the South. Mean radon concentrations exceeded the EPA guideline value in 3.1% of counties.

Table 2 presents the distribution of selected CPS-II participant characteristics at enrollment (1982). The majority of participants were between 40 and 69 years of age, had more than a high school education, and were never smokers. Mean county-level residential radon concentrations varied by participant characteristics including race and cigarette smoking status, where higher mean radon concentrations were observed in white participants and in never smokers as compared with black participants or ever smokers.

Table 3 presents adjusted HR (95% CI) for lung cancer mortality in relation to mean county-level residential radon concentrations. In the final fully adjusted model (2), lung cancer risk increased with increasing categorical radon concentrations. There was no significant departure from a linear relationship ($P = 0.23$), and a significant positive linear trend was observed ($P = 0.02$). A HR of 1.15 (95% CI, 1.01–1.31) was observed for lung cancer mortality per 100 Bq/m^3 increase in radon. Participants in counties with mean radon concentrations above the EPA guideline value (148 Bq/m^3) experienced a 34% (95% CI, 7–68) increase in risk for lung cancer death relative to those below the guideline value. Figure 1 shows adjusted HRs (95% CIs) for lung cancer mortality according to continuous and categorical indicators of radon concentrations. There was no evidence that the proportional hazards assumption was violated ($P > 0.05$).

Mean county-level residential radon concentrations were weakly correlated with sociodemographic ecological variables ($r = 0.12$ to -0.29). Results strengthened somewhat with the inclusion of 4 ecological variables in the model that were each independently associated with lung cancer mortality ($HR_{/100} = 1.18$; 95% CI, 1.04–1.35; Supplementary Table 1). Results were virtually unchanged with the inclusion of sulfate air pollution concentrations in the model in the 439,297 participants with data available on both radon and sulfate ($r = 0.06$; $HR_{/100} = 1.15$; 95% CI, 0.97–1.37).

Table 4 presents adjusted HRs for lung cancer mortality stratified according to selected participant characteristics at enrollment. There was no significant effect modification observed by cigarette smoking status, passive smoking, or sulfate air pollution concentrations on the additive (Supplementary Table 2) or multiplicative scale (Table 4). However, results did vary by geographic region ($P = 0.004$), with a significant positive association observed between radon and lung cancer mortality in the Northeast only ($HR_{/100} = 1.31$; 95% CI, 1.12–1.53; Table 4; Supplementary Figure 1). Results also strengthened

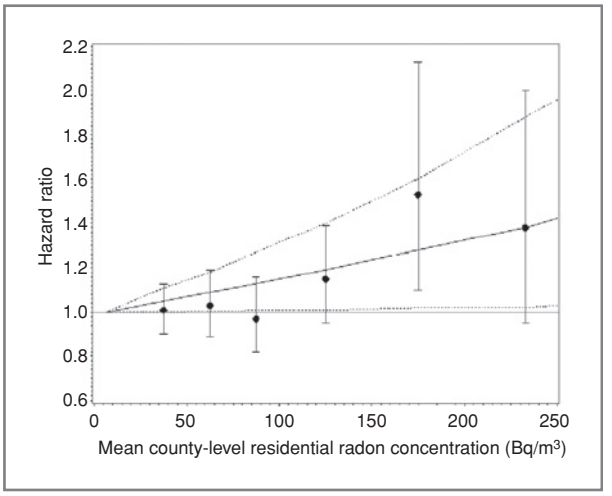

Figure 1. Adjusted HRs (95% CIs) for lung cancer mortality in relation to continuous (solid line, 95% CIs dashed lines) and categorical (reference category < 25 Bq/m^3) indicators of mean county-level residential radon concentrations (LBL) at enrollment (1982), follow-up (1982–1988), CPS-II cohort, United States.

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somewhat when restricting the analysis to individuals who reported living in the same neighborhood for at least the past 5 years at enrollment ($HR_{/100}$ = 1.19; 95% CI, 1.04–1.36).

Figure 2 presents a comparison of the exposure–response relationship using linear or log-linear general relative risk models. Little difference was observed. Results were also insensitive to the inclusion of clustering at the ZIP code–, county-, or state-level in the model with random effect variances being negligible ($\sim 10^{-6}$).

Mean county-level residential radon concentrations were strongly correlated between the LBL and Cohen [mean (SD) = 54.4 (32.5) Bq/m^3] data sources ($r = 0.89$), and similar findings were observed for lung cancer mortality (Supplementary Table 3). Using Cohen's data, in the final fully adjusted model (2), a HR of 1.22 (95% CI, 1.05–1.42) was observed per 100 Bq/m^3 increase in radon. Results were robust to the inclusion of various county-level sociodemographic risk factors compiled by Cohen (refs. 25, 26; results not shown). Results were also found to vary by geographic region ($P_{interaction} = 0.03$) with a significant positive association observed in the Northeast only ($HR_{/100}$ = 1.37; 95% CI, 1.13–1.67). On restriction of the analysis to participants who lived in 1,515 counties with data available from both the LBL and Cohen, overall HRs per 100 Bq/m^3 radon were 1.19 (95% CI, 1.04–1.36) and 1.22 (95% CI, 1.05–1.42), respectively.

Discussion

Overall, the findings of this large prospective study showed a positive association between residential radon and lung cancer mortality. A 15% increase in the risk of lung cancer mortality was observed per 100 Bq/m^3 increase in radon across the United States; in the Northeast the increase was 31%. Participants in counties with mean radon concentrations above the EPA guideline value (148 Bq/m^3) experienced a 34% increase in risk of lung cancer mortality relative to those below the guideline value. Findings were robust to adjustment of a variety of sociodemographic ecological risk factors and sulfate air pollution concentrations. Results showed no effect modification by cigarette smoking status or other risk factors on either the additive or multiplicative scales. Results were similar using either the radon data from the LBL (23, 24) or Cohen's data (25, 26, 27).

A major limitation of this study is the use of an area-based (county) indicator of residential radon concentrations. Previous studies using area-based indicators of residential radon have tended to follow an ecological design, linking mean county-level residential radon

Table 3. Adjusted HRs (95% CIs) for lung cancer mortality in relation to mean county-level residential radon concentrations (LBL; Bq/m^3) at enrollment (1982), follow-up 1982–1988, CPS-II cohort, United States

Radon concentration (Bq/m^3)	Lung cancer deaths	Person-years	Death rate[a]	Minimally adjusted HR (95% CI)[b]	Fully adjusted HR (1) (95% CI)[c]	Fully adjusted HR (2) (95% CI)[d]
Categorical						
<25	856	1,062,216.23	77.79	1.00	1.00	1.00
25-<50	1,312	1,767,001.74	75.59	0.97 (0.89–1.06)	0.96 (0.88–1.04)	1.01 (0.90–1.13)
50-<75	632	863,881.31	74.09	0.96 (0.86–1.06)	1.00 (0.90–1.10)	1.03 (0.89–1.19)
75-<100	274	428,430.94	64.47	0.82 (0.72–0.94)	0.90 (0.79–1.03)	0.97 (0.82–1.16)
100-<150	332	526,638.30	62.49	0.80 (0.70–0.90)	0.97 (0.85–1.10)	1.15 (0.95–1.39)
150-<200	53	62,903.34	83.53	1.07 (0.81–1.41)	1.27 (0.96–1.68)	1.53 (1.10–2.13)
≥200	34	42,084.48	82.20	1.07 (0.76–1.50)	1.24 (0.88–1.75)	1.38 (0.95–2.00)
P_{trend}[e]				*0.006*	*0.44*	*0.02*
EPA guideline value						
<148	3,396	4,631,071.50	73.31	1.00	1.00	1.00
≥148	97	122,084.84	80.82	1.10 (0.90–1.34)	1.24 (1.02–1.52)	1.34 (1.07–1.68)
Continuous						
per 100 Bq/m^3	3,493	4,753,156.34	73.49	0.88 (0.80–0.96)	1.03 (0.94–1.13)	1.15 (1.01–1.31)

[a]Per 100,000 person-years, age-standardized to the age distribution of the entire cohort.
[b]Age, race, gender stratified.
[c]Age, race, gender stratified and adjusted for education, marital status, BMI, BMI squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index.
[d]As footnote c above, but also state stratified.
[e]Tests for linear trend used Wald χ^2 tests, with categorical medians modeled as ordinal variables.

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Table 4. Adjusted[a] HRs (95% CIs) for lung cancer mortality per 100 Bq/m^3 mean county-level residential radon concentrations (LBL) at enrollment (1982) stratified by selected risk factors, effect modification multiplicative scale, follow-up 1982–1988, CPS-II cohort, United States

Characteristic	*n*	Lung cancer deaths	Fully adjusted HR (2) (95% CI)	*P*
Age, y				
<65	633,932	1,922	1.12 (0.95–1.33)	
≥65	178,029	1,571	1.13 (0.93–1.38)	0.16
Attained age[b], y				
<70	615,247	2,228	1.18 (1.01–1.38)	
70–79	153,901	1,033	1.03 (0.80–1.32)	
≥80	42,813	232	0.88 (0.51–1.53)	0.56
Race				
White	770,352	3,332	1.14 (1.00–1.30)	
Other	41,609	161	1.77 (0.79–3.94)	0.10
Sex				
Male	362,600	2,423	1.14 (0.98–1.33)	
Female	449,361	1,070	1.17 (0.93–1.48)	0.59
Education				
<High school	106,668	946	1.20 (0.93–1.56)	
High school	262,853	1,115	0.95 (0.74–1.20)	
>High school	442,440	1,432	1.33 (1.09–1.64)	0.64
BMI, kg/m^2				
18.5–24.9	408,322	1,938	1.20 (1.00–1.43)	
25–29.9	302,762	1,208	1.12 (0.90–1.39)	
≥30	87,192	226	1.11 (0.67–1.84)	0.69
Marital Status				
Married	691,267	2,911	1.11 (0.96–1.27)	
Other	120,694	582	1.35 (0.96–1.90)	0.69
Cigarette Smoking				
Never Smoker	375,087	271	0.77 (0.47–1.25)	
Current	152,033	1,792	1.20 (1.00–1.44)	
Former	203,253	941	1.09 (0.84–1.41)	0.66
Cigarettes/day[c]				
1–19	128,212	479	1.14 (0.80–1.62)	
20–29	124,600	1,042	1.23 (0.97–1.57)	
≥30	102,474	1,212	1.15 (0.92–1.45)	0.67
Years smoked[c]				
1–34	250,099	723	1.11 (0.83–1.48)	
35–44	74,434	1,040	1.25 (0.99–1.59)	
≥45	30,753	970	1.21 (0.93–1.57)	0.59
Years since quitting[c]				
0	158,122	1,856	1.20 (1.01–1.44)	
1–9	57,601	434	1.06 (0.71–1.59)	
≥10	139,560	443	1.31 (0.90–1.91)	0.26
Age started smoking[c], y				
<18	140,360	1,397	1.26 (1.02–1.57)	
≥18	214,926	1,825	1.14 (0.93–1.40)	0.55
Passive smoking in home[d]				
Yes	54,532	24	1.20 (0.22–6.46)	
No	320,552	247	0.72 (0.43–1.21)	0.76
Vegetable/fruit/fiber consumption				
First tertile	313,799	1,766	1.08 (0.88–1.34)	
Second tertile	243,922	965	1.26 (0.98–1.60)	

(Continued on the following page)

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Table 4. Adjusted[a] HRs (95% CIs) for lung cancer mortality per 100 Bq/m^3 mean county-level residential radon concentrations (LBL) at enrollment (1982) stratified by selected risk factors, effect modification multiplicative scale, follow-up 1982–1988, CPS-II cohort, United States (Cont'd)

Characteristic	*n*	Lung cancer deaths	Fully adjusted HR (2) (95% CI)	*P*
Third tertile	254,240	762	1.03 (0.78–1.36)	0.55
Fat consumption				
First tertile	299,311	1,319	1.11 (0.87–1.42)	
Second tertile	258,329	1,005	1.12 (0.87–1.43)	
Third tertile	254,321	1,169	1.26 (1.00–1.59)	0.94
Industrial exposures				
Yes	166,660	920	1.05 (0.82–1.35)	
No	645,301	2,573	1.17 (1.01–1.37)	0.28
Occupational dirtiness				
Yes	351,027	1,915	1.04 (0.86–1.27)	
No	394,828	1,578	1.24 (1.02–1.50)	0.33
Asthma				
Yes	36,679	157	1.12 (0.43–2.93)	
No	775,282	3,336	1.15 (1.01–1.31)	0.40
Hay fever				
Yes	97,141	254	1.35 (0.79–2.32)	
No	714,820	3,239	1.12 (0.98–1.28)	0.56
Chronic bronchitis/emphysema				
Yes	39,016	611	0.99 (0.68-1.43)	
No	772,945	2,882	1.15 (1.00-1.33)	0.25
Region[e]				
Northeast	170,281	710	1.31 (1.12–1.53)	
South	257,243	1,246	0.95 (0.73–1.24)	
Midwest	234,952	954	1.07 (0.89–1.27)	
West	149,485	583	0.83 (0.65–1.04)	0.004
Sulfate air pollution[f]				
$<$6.4 μg/m^3	221,453	897	1.29 (0.94–1.77)	
$\geq$6.4 μg/m^3	217,844	946	1.08 (0.88–1.32)	0.57

[a]Age, race, gender, state stratified and adjusted for education, marital status, BMI, BMI squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index where appropriate.

[b]Race, gender, state stratified and adjusted for cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking only.

[c]Ever smokers. Additional participants with missing information were excluded for years since quitting. *P* values calculated with never and ever smokers.

[d]Never smokers.

[e]HRs and 95% CIs by region unadjusted for state.

[f]Participants with missing sulfate information excluded. Cutpoints were based on median participant sulfate value.

concentrations with county-level lung cancer death rates with conflicting results observed. In the ecological study of Cohen (25), a strong negative association between radon and lung cancer was reported. However, because there was a negative correlation between smoking prevalence and radon concentrations at the ecological level, such studies are subject to confounding by cigarette smoking (36, 37). There are also other potential limitations for the studies such as cross-level bias (36, 37). Here, mean county-level residential radon concentrations were linked to individuals in the CPS-II cohort and with detailed adjustment for a variety of individual-level risk factors, including cigarette smoking; positive associations between radon and lung cancer mortality were observed.

Mean county-level residential radon concentrations were linked to CPS-II participants as indicators of historic residential radon exposure. Radon data were estimated either on the basis of available short- and long-term monitoring data, as well as a variety of geological, meteor-

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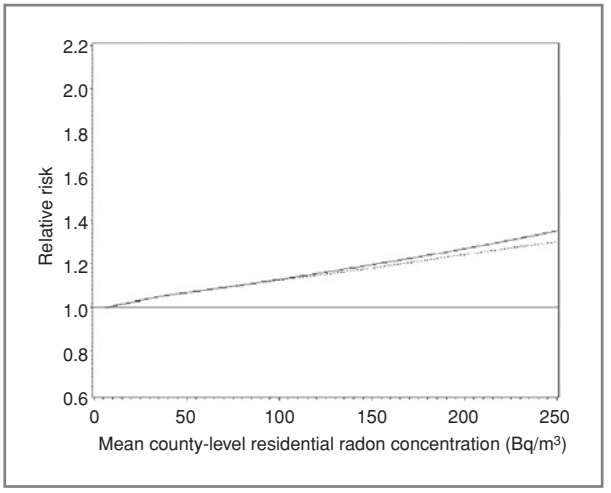

Figure 2. Comparison of linear and log-linear general relative risk models for the association between lung cancer mortality and mean county-level residential radon concentrations (LBL) at enrollment (1982), follow-up (1982–1988), CPS-II cohort, United States. According to the stratification criteria of Krewski and colleagues (10, 11) little difference in relative risk estimates obtained from either a linear (ERR = 1 + 0.00121 X; dotted line) or log-linear [Cox regression analysis; RR = exp(0.00119 X); solid line] model was observed. Relative risk estimates were also similar using the stratification criteria of Darby and colleagues [refs. 8, 9; ERR = 1 + 0.00108 X, RR = exp(0.00109 X)].

ologic, and housing data (LBL), or on the basis of a series of aggregated short-term screening measurements from several different sources normalized to the data of the U.S. NRRS (Cohen). Estimates of radon concentrations in individual homes are subject to a number of sources of uncertainty, including detector measurement error, variation due to detector placement, and changes in radon concentrations over time (seasonal and year-to-year variability; refs. 4, 38–43). However, these measurement errors are most likely to be nonsystematic. Mean county-level residential radon concentrations are also subject to sampling error (44). Residential radon concentrations can exhibit considerable variability due to individual housing characteristics (building materials, presence of a basement, age of construction, ventilation, water supply), soil permeability, and underlying geology (4, 7, 42, 45). The extent to which ecologic indicators of residential radon exposures are representative of the exposure experience of individuals in the CPS-II cohort is also not known.

Although it is difficult to predict the total potential cumulative impact of such errors on the results observed in the current study, the observed relative risk estimates may be subject to some degree of downward bias (38, 46, 47). Mallick and colleagues (48) examined the impact of adjusting for plausible levels of exposure measurement error associated with ecological measures of ambient air pollution under a cohort design and found the relative risk estimates were subject to downward bias. Jerrett and colleagues (49) observed that air pollution mortality relative risk estimates increased by nearly 3-fold in research in the CPS-II cohort examining within- as opposed to between-city contrasts in fine particulate matter concentrations.

Two studies (50, 51) have directly examined the impact of using either individual (measured in subject's homes) or ecological (aggregating individual-level measures) indicators of residential radon concentrations in case–control studies. Findings using ecological measures of radon resulted in notably less precise relative risk estimates, compared with those based on individual measures of radon. Results using ecological radon measures also required the inclusion of an additional indicator for geographical location, which takes into account broad spatial patterns in both radon concentrations and risk factors for lung cancer, for compatibility with results using individual data.

Despite these uncertainties, our findings are consistent with results obtained from combined analyses of residential case–control studies (8–11). In North America, ERR per 100 Bq/m^3 radon were found to range from 11% (95% CI, 0–28) overall to 21% (95% CI, 3–52) in subjects with complete historic radon data and limited residential mobility. In Europe, results ranged from 8% (95% CI, 3–16) overall to 16% (95% CI, 5–31) when adjusting for exposure measurement error. A pooled analysis of 2 residential radon case–control studies conducted in China reported an ERR of 13% (95% CI, 1–36) at 100 Bq/m^3 (52). A recent prospective study in Spain also reported elevated, although imprecisely determined, lung cancer risks for subjects with higher residential radon concentrations; however, only 5 lung cancer cases were observed in this cohort (12).

Results for the United States as a whole were largely due to a significant positive association between radon and lung cancer observed in the Northeast. Although this could conceivably be an artifact of the choice of administrative data boundaries, this finding may also be due to higher residential radon concentrations in the Northeast and other factors unaccounted for in the analysis including possible regional differences in time spent at home (53). Although there is no information on time-activity patterns for characterizing time spent at home for individuals in the CPS-II cohort, results from the U.S. National Human Activity Pattern Survey showed that time spent in a residence was consistent across all 10 regions of the United States (54). However, the Iowa Radon Lung Cancer Study reported that time spent at home varied by age from a low of 69.4% in women ages 50 to 59 years up to 81.6% in women ages 80 years or more (55); differences in time spent at home were also observed according to number of children in this study.

Updated information on neither cigarette smoking status nor residential mobility from enrollment was available for individuals in the full CPS-II cohort. In an attempt to control for changes in cigarette smoking over time, a major risk factor for lung cancer, it was decided *a priori* to restrict the follow-up time period for the analysis

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to the first 6 years of follow-up only (19). There was no detailed information on address history prior to enrollment; however, study participants did report living in their current neighborhood at enrollment for a mean (SD) of 19.4 (14.1) years. Radon–lung cancer associations strengthened somewhat when restricting the analysis to individuals who reported living in the same neighborhood for at least the past 5 years ($HR_{/100} = 1.19$; 95% CI, 1.04–1.36). No information was available on lung cancer histologic subtype.

Mean county-level residential radon concentrations for black individuals in the CPS-II cohort (mean = 40.2 Bq/m^3) tended to be lower than those for white individuals (mean = 54.2 Bq/m^3). This could be because of the tendency for black individuals in the cohort to live in ZIP codes that were more highly urbanized, where radon concentrations tend to be lower (8, 9). Urban areas also tend to have higher smoking rates (8, 9).

Few studies have examined potential interrelationships between residential radon and other inhalable environmental agents. Lagarde and colleagues (56) reported that residential radon may be a more important risk factor for lung cancer in never smokers with a smoking spouse. However, in the combined analysis of European case–control studies, lung cancer risk did not vary according to spousal smoking status (8, 9). In China, increased lung cancer risk associated with radon did not vary according to level of indoor smokiness (52). Brauner and colleagues (57) reported that the association between residential radon and childhood leukemia in Denmark strengthened in the presence of exposure to traffic-related air pollution, although further research is needed to clarify this finding. Here the association between county-level residential radon concentrations and lung cancer mortality did not vary according to exposure to passive cigarette smoke or ambient sulfate concentrations.

In conclusion, this large prospective study showed positive associations between ecological indicators of residential radon and lung cancer mortality. Current data suggest that residential radon is the second leading cause of lung cancer after tobacco smoking (3). The results of this study further support the need for continued efforts to reduce radon concentrations in homes to the lowest possible level (58).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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