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Brief Original Contribution

Radon and Nonrespiratory Mortality in the American Cancer Society Cohort

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Radon is a known cause of human lung cancer. Previously, the authors observed a significant positive association between mean county-level residential radon concentrations and lung cancer mortality in the Cancer Prevention Study II (CPS-II), a large prospective study of nearly 1.2 million participants recruited in 1982 by the American Cancer Society. There was also a significant positive association with mortality from chronic obstructive pulmonary disease. Because it is unclear whether radon is associated with mortality from other malignant or nonmalignant disease, the authors examined the association between radon and nonrespiratory mortality in the CPS-II. Mean county-level residential radon concentrations (mean = 53.5 (standard deviation: 38.0) Bq/m^3) were linked to participants by their zip code at enrollment. Cox proportional hazards regression models were used to estimate adjusted hazard ratios and 95% confidence intervals for all-cause (excluding lung cancer and respiratory mortality) and cause-specific mortality associated with radon concentrations. A total of 811,961 participants in 2,754 counties were analyzed, including 265,477 deaths through 2006. There were no clear associations between radon and nonrespiratory mortality in the CPS-II. These findings suggest that residential radon is not associated with any other mortality beyond lung cancer or chronic obstructive pulmonary disease.

cardiovascular diseases; cohort studies; neoplasms; radon; United States

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPS-II, Cancer Prevention Study II; HR, hazard ratio; LBL, Lawrence Berkeley National Laboratory.

Radon-222 is a naturally occurring gas formed during the radioactive decay of uranium-238. Radon further decays into a series of daughters, some of which emit alpha particles capable of damaging cellular DNA (1). Radon is found in the indoor and outdoor air, soil, and water and accumulates in confined spaces, including underground mines and in the lower living areas of homes (2). In 1988, radon and its decay products were designated a human lung carcinogen on the basis of experimental evidence and studies of underground miners exposed to high levels of the gas (3). Recent combined analyses of data from residential radon case-control studies conducted in North America and Europe have strengthened the epidemiologic evidence linking residential radon and lung cancer (4–8).

Although there have been a number of residential radon case-control studies, there have been few prospective studies in the general population. We recently observed a significant positive association between mean county-level residential radon concentrations and lung cancer mortality in the American Cancer Society Cancer Prevention Study II (CPS-II) (per 100 Bq/m^3: hazard ratio (HR) = 1.15, 95% confidence interval (CI): 1.01, 1.31) (9). Participants with mean radon concentrations above the US Environmental Protection Agency (EPA) guideline value (4 pCi/L ~ 148 Bq/m^3) (10) experienced a 34% (95% CI: 7, 68) increased risk of lung cancer death.

Although it is conceivable that radon may affect other malignant or nonmalignant diseases besides lung cancer,

the epidemiologic evidence is sparse (10, 11). A pooled analysis of data from 11 cohorts of underground miners reported excess mortality from stomach cancer, liver cancer, and leukemia that was unrelated to radon exposure (12). A French cohort study showed an increased mortality from lung and kidney cancer in uranium miners that was not associated with cumulative radon exposure (13). There was also a significant positive association between radon and mortality from cerebrovascular disease; however, potential confounding by cardiovascular risk factors could not be assessed (14). Mortality from multiple myeloma and non-Hodgkin's lymphoma was not related to cumulative radon exposure in the Colorado Plateau cohort (15). There was no strong evidence for an association between radon and death from extrapulmonary cancer in the German uranium miners' cohort (16). However, radon was positively associated with incident chronic lymphocytic leukemia (relative risk = 1.98, 95% CI: 1.10, 3.59) in Czech uranium miners (17).

Although ecologic analyses have reported positive associations between residential radon and leukemia, case-control studies have not supported a link (18). Excesses in total and site-specific (colorectal, breast, kidney, and prostate) cancer incidence were observed in census tracts with elevated groundwater uranium concentrations in a South Carolina study; however, there were no individual-level risk factor data (19). No association between radon or other drinking water radionuclides and leukemia, stomach, bladder, or kidney cancer was observed in Finland (20–22).

This paper examines the association between residential radon and nonrespiratory mortality in the CPS-II. CPS-II is a large, well-established, prospective study, with detailed individual-level risk factor data collected at enrollment. In the CPS-II, we recently observed a significant positive association between mean county-level residential radon concentrations and chronic obstructive pulmonary disease (COPD) mortality (per 100 Bq/m^3: HR = 1.13, 95% CI: 1.05, 1.21) (23). It provides a unique resource to evaluate whether residential exposure to radon is associated with other nonrespiratory causes of death. Some of the results presented here were previously reported in an abstract (24).

MATERIALS AND METHODS

Study population

CPS-II is a prospective study of nearly 1.2 million participants enrolled in 1982. Participants, largely friends and family members of volunteer recruiters, were recruited in all 50 US states, the District of Columbia, and Puerto Rico. Participants were at least 30 years of age and had at least 1 family member aged 45 years or older. A 4-page self-administered questionnaire was completed at enrollment that captured data on a range of demographic, lifestyle, and medical factors, including zip code of residence at enrollment.

Follow-up for vital status is conducted every 2 years. In 1984, 1986, and 1988, vital status was obtained from volunteer recruiters and death certificate information. From 1989, follow-up has been conducted through computerized linkage to the National Death Index (25). In September 1988, follow-up was terminated for 2,840 (0.2%) participants because of insufficient information to link to the National

Table 1. Distribution of Selected Characteristics among Cancer Prevention Study II Cohort Participants at Enrollment in 1982

Characteristic	No.	%	Mean Radon, Bq/m^3 (SD)[a]
Overall	811,961	100	53.5 (38.0)
Age at enrollment, years			
<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			
Less than high school	106,668	13.1	55.2 (38.9)
High school	262,853	32.4	56.8 (39.5)
More than high school	442,440	54.5	51.1 (36.6)
Body mass index[b]			
<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)
Region			
Northeast	170,281	21.0	58.3 (42.3)
South	257,243	31.7	35.6 (21.7)
Midwest	234,952	28.9	73.7 (36.6)
West	149,485	18.4	46.9 (40.3)

[a] Lawrence Berkeley National Laboratory.
[b] Body mass index: weight (kg)/height (m)^2.

Table 2. Adjusted Hazard Ratios for All-Cause (Excluding Lung Cancer and Respiratory Mortality) and Cause-specific Mortality per Each 100-Bq/m^3 Increase in Mean County-Level Residential Radon Concentrations,[a] Cancer Prevention Study II Cohort Follow-up, 1982–2006

Cause of Death	ICD-9 and ICD-10 Codes	No. of Deaths	Minimally Adjusted[b]		Fully Adjusted[c]	
			HR	95% CI	HR	95% CI
All-cause mortality (excluding lung cancer and respiratory mortality)	All-cause mortality minus 162; C33–C34 and 460–519; J00–J98	265,477	0.96	0.95, 0.98	0.98	0.97, 1.00
Diseases of the circulatory system (plus diabetes)	250, 390–459; E10–E14, I 00–I99	142,272	0.96	0.94, 0.98	0.98	0.96, 1.00
Ischemic heart disease	410–414; I20–I25	61,790	0.95	0.92, 0.99	0.97	0.94, 1.01
Dysrhythmias, heart failure, cardiac arrest	420–429; I30–I51	25,172	0.95	0.90, 1.00	0.97	0.92, 1.02
Hypertensive disease	401–405; I10–I13	4,213	0.87	0.76, 0.99	0.89	0.78, 1.02
Other atherosclerosis and aortic aneurysms	440–441; I70–I71	4,964	0.86	0.76, 0.96	0.90	0.80, 1.01
Cerebrovascular disease	430–438; I60–I69	23,344	1.03	0.98, 1.09	1.05	0.99, 1.10
Diabetes	250; I10–E14	6,954	1.02	0.93, 1.12	1.02	0.93, 1.12
All other cardiovascular diseases	All not specified	15,835	0.94	0.88, 1.00	0.96	0.90, 1.02
All cancer (excluding lung cancer)	140–208; C00–C75, C80, C97 minus 162; C33–C34	62,309	0.96	0.93, 0.99	0.97	0.94, 1.00
Malignant neoplasms of lymphatic and hematopoietic tissue	200–208; C81–C96	10,142	0.96	0.89, 1.04	0.97	0.89, 1.04
Non-Hodgkin's lymphoma	200, 202; C82–C85	4,053	1.01	0.90, 1.14	1.02	0.90, 1.14
Hodgkin's disease	201; C81	172	0.98	0.55, 1.72	0.95	0.54, 1.68
Multiple myeloma	203; C88, C90	2,075	0.95	0.80, 1.13	0.93	0.78, 1.11
Leukemia	204–208; C91–C95	3,835	0.91	0.81, 1.04	0.93	0.82, 1.05
Malignant neoplasms of lip, oral cavity, and pharynx	140–149; C00–C14	834	0.74	0.55, 1.01	0.80	0.59, 1.08
Tongue and mouth	141, 143–145; C01–C06	370	0.83	0.55, 1.25	0.86	0.57, 1.30
Salivary gland	142; C07–C08	85	0.24	0.07, 0.84	0.24	0.07, 0.85
Pharynx	146–149; C09–C14	352	0.91	0.56, 1.47	0.99	0.62, 1.60
Malignant neoplasms of digestive organs and peritoneum	150–159; C15–C26, C48	20,854	0.94	0.89, 0.99	0.96	0.91, 1.02
Esophagus	150; C15	1,625	1.02	0.84, 1.23	1.08	0.89, 1.30
Stomach	151; C16	1,880	0.84	0.69, 1.01	0.85	0.70, 1.03
Colorectal	153–154; C18–C21	9,165	0.92	0.85, 1.00	0.94	0.87, 1.02
Liver	155; C22	1,526	0.86	0.70, 1.06	0.89	0.73, 1.10
Gallbladder	156; C23–C24	530	1.03	0.74, 1.45	1.07	0.77, 1.50
Pancreas	157; C25	5,441	1.01	0.90, 1.12	1.03	0.92, 1.14

Table continues

Death Index. Over 99% of all known deaths have been assigned a cause. Deaths were classified by the underlying cause according to the *International Classification of Diseases*, Ninth Revision and Tenth Revision (26, 27).

Of the total 1,184,881 participants, those with missing vital status ($n = 419$), prevalent cancer (except nonmelanoma skin cancer) at enrollment ($n = 82,329$), missing zip code ($n = 99,479$) or county data ($n = 22,872$), missing data on radon ($n = 5,836$), or any other individual-level covariates of interest ($n = 161,985$) were excluded. A total of 811,961 participants residing in 2,754 counties were retained for analysis. Through 2006, a total of 314,311 deaths in 16,554,617 person-years of follow-up were observed, of which 265,477 were due to causes other than lung cancer or respiratory mortality.

Ecologic measures of residential radon

Participants were assigned to a primary county of residence on the basis of the 5-digit zip code provided at enrollment, according to the boundaries (Summary Tape File 3B) of the 1980 US Census (28). Two ecologic measures of residential radon concentrations were linked to study participants as indicators of historical radon exposure. A detailed description is provided elsewhere (9). In brief, researchers at the Lawrence Berkeley National Laboratory (LBL) used a variety of short- and long-term indoor radon-monitoring data (mid to late 1980s) along with a variety of geologic, soil, meteorologic, and housing data, to predict the annual average radon concentrations in the main living areas of homes in 3,079 US counties using an empirical

Table 2. Continued

Cause of Death	ICD-9 and ICD-10 Codes	No. of Deaths	Minimally Adjusted[b]		Fully Adjusted[c]	
			HR	95% CI	HR	95% CI
Malignant neoplasms of the respiratory and intrathoracic organs (excluding lung cancer)	160–165; C30–C39 minus 162; C33–C34	740	0.91	0.70, 1.19	0.95	0.73, 1.24
Nose	160; C30–C31	67	1.34	0.62, 2.87	1.47	0.69, 3.17
Larynx	161; C32	314	0.94	0.61, 1.45	1.06	0.69, 1.62
Malignant neoplasms of bone, connective tissue, skin, and breast	170–175; C40–C44, C46–C47, C49–C50	7,733	0.94	0.86, 1.02	0.95	0.87, 1.04
Bone	170; C40–C41	104	1.15	0.57, 2.32	1.19	0.60, 2.38
Connective tissue	171; C47, C49	538	1.10	0.80, 1.50	1.10	0.80, 1.51
Melanoma	172; C43	1,247	1.08	0.88, 1.33	1.08	0.88, 1.33
Other skin	173; C44, C46	313	0.67	0.40, 1.13	0.70	0.42, 1.19
Breast (female)[d]	174–175; C50	5,479	0.89	0.80, 0.99	0.91	0.82, 1.01
Malignant neoplasms of the genitourinary organs	179–189; C51–C68					
Uterus[d,e]	179, 182; C54–C55	906	1.15	0.90, 1.47	1.16	0.90, 1.48
Cervix[d,e]	180; C53	184	0.64	0.34, 1.20	0.70	0.37, 1.31
Ovary[d,e,f]	183; C56	1,316	0.91	0.74, 1.12	0.91	0.74, 1.13
Prostate[d]	185; C61	1,374	0.98	0.79, 1.23	0.99	0.79, 1.23
Bladder	188; C67	1,933	1.07	0.90, 1.27	1.11	0.94, 1.32
Kidney	189; C64–C66, C68	1,251	0.92	0.74, 1.14	0.94	0.76, 1.16
Malignant neoplasms of other and unspecified sites	190–199; C69–C80, C97	7,803	0.91	0.84, 1.00	0.94	0.86, 1.02
Eye	190; C69	46	0.64	0.19, 2.22	0.65	0.19, 2.25
Brain	191; C71	2,232	0.99	0.84, 1.16	0.98	0.83, 1.15
Thyroid	193; C73	55	1.05	0.32, 3.48	1.10	0.34, 3.53
Benign neoplasms	210–229; D10–D36	284	1.19	0.77, 1.83	1.18	0.77, 1.82
All other causes	All other not specified	60,612	0.98	0.95, 1.01	0.99	0.96, 1.03

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-9, *International Classification of Diseases,* Ninth Revision; ICD-10, *International Classification of Diseases,* Tenth Revision.

[a] Lawrence Berkeley National Laboratory.

[b] Age, race, gender, and state stratified.

[c] Age, race, gender, and state stratified and adjusted for education, marital status, body mass index, body mass index 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, and occupation dirtiness index.

[d] As above but not gender stratified.

[e] Females reporting a previous hysterectomy or an artificial menopause ($n = 143,991$) excluded here.

[f] Females reporting having undergone an ovarian surgery ($n = 9,232$) also excluded here.

statistical model (29, 30). Cohen (31–33) compiled a series of screening measurements in a nonrandom sample of homes in 1,601 US counties made by researchers at the University of Pittsburgh, the US Environmental Protection Agency, and other state-level sources (mid 1980s to the early 1990s). Counties with less than 10 measurements or states with high rates of migration (Florida, California, Arizona) were excluded, and data were normalized to the long-term US National Residential Radon Survey (2). County-level residential radon concentrations (LBL) ranged from 6.3 to 265.7 Bq/m^3 (1 pCi/L = 37 Bq/m^3), with a mean value of 53.5 (standard deviation: 38.0) Bq/m^3.

Statistical analysis

Cox proportional hazards regression models were used to examine the independent effects of radon on all-cause (excluding lung cancer and respiratory mortality) and cause-specific mortality (34). The baseline hazard in the proportional hazards model was stratified by 1-year age categories, sex, race (white, black, other), and state of residence. Follow-up time since enrollment in 1982 was used as the time axis. The survival times of those still alive at the end of follow-up were censored.

Estimated hazard ratios and 95% Wald-based confidence intervals were adjusted for a range of individual-level risk

factors including education, marital status, body mass index, body mass index squared, cigarette smoking status, and intensity (cigarettes per day, cigarettes per day squared, years smoked, and years smoked squared), age started smoking less than 18 years, passive smoking (home, work, other), quintiles of vegetable/fruit/fiber and fat intake, occupational exposures (asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, diesel engine exhaust), and an "occupational dirtiness index" (9, 23, 35).

The proportional hazards assumption was tested by assessing the significance of an interaction term between radon and follow-up time. Analyses were conducted by using SAS, version 9.2, software (36). Ethics approval was obtained from the Emory University Institutional Review Board and the Ottawa Hospital Research Ethics Board.

RESULTS

The distribution of participant characteristics at enrollment is presented in Table 1. The majority of participants were between 40 and 69 years of age, had more than a high school education, and were never smokers. There was a tendency for higher radon concentrations to be observed among participants who were white, had a lower level of educational attainment, had a higher body mass index, or were never smokers. The highest radon concentrations were observed in the Midwest and Northeast and the lowest in the South.

Table 2 presents adjusted hazard ratios for all-cause (excluding lung cancer and respiratory mortality) and cause-specific mortality in relation to each 100-Bq/m^3 increase in radon concentrations (LBL). In the fully adjusted model, there was no significant association between radon and all nonrespiratory mortality (per each 100 Bq/m^3: HR = 0.98, 95% CI: 0.97, 1.00). There was also no association between radon and any other specific cause of death category, with the exception of mortality from salivary gland tumors where a significant inverse association was observed (per each 100 Bq/m^3: HR = 0.24, 95% CI: 0.07, 0.85). There was no evidence that the proportional hazards assumption was violated for any specific cause of death category ($P \geq 0.05$), with the exception of ischemic heart disease mortality with hazard ratios of 0.91 (95% CI: 0.85, 0.97) (1982–1989), 0.95 (95% CI: 0.90, 1.00) (1990–1999), and 1.04 (95% CI: 0.99, 1.09) (2000–2006) observed per each 100 Bq/m^3 of radon.

Results using Cohen's data are presented in Web Table 1. In the fully adjusted model, there was no association between radon and all-cause mortality (excluding lung cancer and respiratory mortality) (per each 100 Bq/m^3: HR = 0.99, 95% CI: 0.97, 1.01). However, significant positive associations were observed between radon and mortality from cerebrovascular disease (per each 100 Bq/m^3: HR = 1.07, 95% CI: 1.01, 1.14) and benign neoplasms (per each 100 Bq/m^3: HR = 1.69, 95% CI: 1.05, 2.75). There were also significant inverse associations observed for mortality from hypertensive disease (per each 100 Bq/m^3: HR = 0.78, 95% CI: 0.66, 0.91) and stomach cancer (per each 100 Bq/m^3: HR = 0.74, 95% CI: 0.59, 0.93).

DISCUSSION

We previously observed significant positive associations between mean county-level residential radon concentrations and mortality from both lung cancer and COPD in the CPS-II (9, 23). Results from the present study provided no clear evidence of associations between radon and nonrespiratory mortality. Although there was a significant inverse association between radon and mortality from cancer of the salivary gland (LBL), there is little biologic plausibility to support this finding, and there were few salivary tumor deaths. Some significant increases in mortality (cerebrovascular disease, benign neoplasms) with radon were observed by using Cohen's data; however, they were not replicated in the larger LBL cohort.

Strengths of this study include its large prospective design, the ability to examine multiple endpoints other than lung cancer, and detailed individual-level risk factor data collected at enrollment. Limitations include a mortality-based design and the use of ecologic measures of radon concentrations estimated in a statistical model (LBL) or based on a nonrandom series of short-term measurements (Cohen). Errors in radon detector measurements, seasonal and yearly variability in radon concentrations, changes in housing characteristics over time, and sampling errors may occur (37–39). Residential radon concentrations within counties can also exhibit considerable variability due to differential construction and underlying geologic characteristics of individual homes (37, 38, 40, 41). Radon exposures may also be experienced outside the home (workplace, outdoor exposures). However, estimates of increased lung cancer mortality in the CPS-II were compatible with estimates from combined analyses of case-control studies (9). No updated data on cigarette smoking or residential mobility were available beyond enrollment in the full CPS-II, nor were any time-activity data collected, such as individual mobility within or outside the home (6, 7, 42). However, with a mean age of 57 years at enrollment, it is unlikely that participants would begin smoking during follow-up. Radon concentrations and cigarette smoking are also inversely related (4, 5, 9, 43). Participants also tended to be long-term residents of their current neighborhood at enrollment (9).

These findings suggest that residential radon is not associated with mortality beyond lung cancer or COPD. Although the lung and respiratory tract experience the highest doses of ionizing radiation from the inhalation of radon and its decay products, the kidney, bone, bone marrow, and breast are also exposed, as well as the stomach (ingestion) and skin (external radiation), although to a lesser degree (10, 44). Further research examining associations between radon and nonrespiratory disease incidence may be useful to further confirm these findings.

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