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Radon and COPD Mortality in the American Cancer Society Cohort

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ABSTRACT

Background: Although radon gas is a known cause of lung cancer, the association between residential radon and mortality from non-malignant respiratory disease has not been well characterized.

Methods: The Cancer Prevention Study-II is a large prospective cohort study of nearly 1.2 million Americans recruited in 1982. Mean county-level residential radon concentrations were linked to study participants' residential address based on their ZIP code at enrollment (mean (SD) = 53.5 (38.0) Bq/m^3). Cox proportional hazards regression models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for non-malignant respiratory disease mortality associated with radon concentrations. After necessary exclusions, a total of 811,961 participants in 2,754 counties were included in the analysis.

Results: Through 2006, there were a total of 28,300 non-malignant respiratory disease deaths. Radon was significantly associated with chronic obstructive pulmonary disease (COPD) mortality (HR per each 100 Bq/m^3 = 1.13, 95% CI 1.05 - 1.21). There was a significant positive linear trend in COPD mortality with increasing categories of radon concentrations ($p < 0.05$).

Conclusions: Findings suggest residential radon may increase COPD mortality. Further research is needed to confirm this finding, and to better understand possible complex inter-relationships between radon, COPD, and lung cancer.

Key Words: cohort study; pulmonary disease, chronic obstructive; radon; United States

INTRODUCTION

In 1988, the International Agency for Research on Cancer (IARC) designated radon a known cause of lung cancer, based on studies of underground miners exposed to high levels of the gas prior to the adequate ventilation of mines [1]. Radon itself further decays into a series of radon daughters, some of which emit alpha-particles capable of damaging cellular DNA [2]. Radon, formed during the radioactive decay of uranium-238, is present in the air, soil, and water. Upon release from the Earth's crust, radon enters homes through cracks in the foundation and accumulates primarily in the basement and lower living areas [3]. Combined analyses of case-control studies conducted in North America and Europe have also implicated residential exposure to radon as a risk factor for lung cancer [4-7].

Although radon may affect other non-malignant respiratory diseases, epidemiological evidence is sparse [2, 8]. Archer et al. [9] reported a positive association between radon and non-malignant respiratory disease mortality in an early study of uranium miners in the Colorado Plateau. Mapel et al. [10] reported an inverse association between underground mining duration and lung function in a cross-sectional study of New Mexico uranium miners. There are also reports of uranium miners with chronic diffuse interstitial fibrosis, although a causal link with radon could not be established [8, 11, 12].

This paper examines the association between residential radon and non-malignant respiratory disease mortality in the American Cancer Society Cancer Prevention Study-II (CPS-II). CPS-II is a large, well-established general population cohort, with detailed, individual-level risk factor

data collected at enrollment. We recently observed a positive association between mean county-level residential radon concentrations and lung cancer mortality in the CPS-II [13]. A 15% (95% confidence interval (CI) 1 - 31%) increase in lung cancer mortality was observed for each 100 Bq/m^3 increase in radon concentrations. CPS-II provides an excellent data resource to evaluate whether exposure to residential radon is associated with non-lung cancer mortality, including non-malignant respiratory disease mortality. Some of the results presented in this manuscript were included in a previous abstract [14].

METHODS AND MATERIALS

Study Population

CPS-II is a prospective study comprised of nearly 1.2 million subjects enrolled by over 77,000 volunteers in 1982. Ethics approval for the CPS-II was obtained from the Emory University School of Medicine Human Investigations Committee. Participants were recruited in all 50 US states as well as the District of Columbia and Puerto Rico. Participants were largely friends and family members of the volunteers, were at least 30 years of age, and had at least one family member aged 45 years or older. A four-page self-administered questionnaire completed at enrollment captured data on a range of demographic, lifestyle, and medical factors, including ZIP code of residence.

Follow-up of CPS-II participants for vital status has been conducted every two years. In 1984, 1986, and 1988, vital status was obtained from the study volunteers, confirmed by obtaining the

corresponding death certificate. Since 1989, follow-up is conducted through computerized linkage to the National Death Index [15]. A total of 2,840 (0.2 percent) participants had follow-up terminated in September of 1988 due to insufficient information to link to the National Death Index. Over 99 percent of all known deaths have been assigned a cause. Deaths were classified by the underlying cause of death according to the International Classification of Disease (ICD) 9 and 10 [16, 17].

Of the 1,184,881 CPS-II participants, subjects were excluded due to missing vital status (419), prevalent cancer (except non-melanoma skin cancer) at enrollment (82,329), missing ZIP code (99,479) or county (22,872) data, missing data on radon (see below) (5,836), or other individual-level covariates of interest including cigarette smoking (161,985). A total of 811,961 participants in 2,754 counties were retained in the final analytic cohort. Through 2006, there were a total of 28,300 non-malignant respiratory deaths observed in 16,554,617 person-years of follow-up.

Ecological Measures of Residential Radon Exposure

Study participants were assigned to a primary county of residence using five-digit ZIP code information provided at enrollment, according to the ZIP code boundaries (STF3B) of the 1980 US Census [18]. Ecological indicators of residential radon concentrations were obtained from the Lawrence Berkeley National Laboratory (LBL) and the University of Pittsburgh. A detailed description is provided elsewhere [13]. In brief, at LBL, both short- and long-term indoor radon monitoring data were used, along with a variety of geological, soil, meteorological, and housing

data, including location of screening measurements within the home, to predict annual average radon concentrations in the main living areas of homes in 3,079 US counties [19, 20].

Cohen [21-23] compiled a database of mean county-level residential radon concentrations based on a series of screening measurements made in a nonrandom sample of homes in 1,601 US counties by researchers at the University of Pittsburgh, the US Environmental Protection Agency (EPA), and other state-level sources from the mid 1980s to the early 1990s. Data were excluded from counties where there were less than 10 radon measurements or from states with high rates of migration (Florida, California, and Arizona) [22, 23], and were normalized to the data of the US National Residential Radon Survey (NRRS), a long-term national residential radon survey conducted in 125 US counties [3].

Mean county-level residential radon concentrations were linked to study participants as indicators of historical residential radon exposure. Mean LBL county-level residential radon concentrations ranged from 6.3 to 265.7 Bq/m^3 (1 pCi/L = 37 Bq/m^3), with a mean value (SD) of 53.5 (38.0) Bq/m^3.

Social and Demographic Ecological Covariates

Data on a range of social and demographic ecological covariates were compiled for 18,484 participant ZIP codes from the 1990 US Census including: median household income, percent black, Hispanic, post-secondary education, unemployment, and poverty [24].

Statistical Analysis

Cox proportional hazards regression models were used to examine the independent effects of mean county-level residential radon concentrations on non-malignant respiratory disease mortality [25]. The baseline hazard in the proportional hazards model was stratified by one-year age categories, sex, race (white, black, other), and state of residence at enrollment [13]. 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.

Estimated hazard ratios (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, each of cigarettes per day, cigarettes per day squared, years smoked, years smoked squared, and age started smoking less than 18 years for both current and former smokers, passive smoking (hours exposed at home, work, or other), 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 an 'occupational dirtiness index' specifically designed for CPS-II [13, 26].

Potential effect modification was examined on the additive and multiplicative scales. On the additive scale, estimates of the relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (S) (and associated 95% CIs) were calculated according to the method of Zou [27] for the analysis of four by two tables. On the multiplicative scale, interaction terms between radon and selected risk factors were entered into proportional hazards

models. Two-sided *p* values were calculated to assess the significance of the interaction term using the likelihood ratio statistic. In order to assess the impact of attained age, time-dependent variables were constructed by allowing subjects to be included in the risk set at each death time if they met the age criteria for the model (<70, 70-79, or ≥80 years). The functional form of the relationship between residential radon and mortality was assessed using the Supremum test [28]. The proportional hazards assumption was tested by assessing the significance of an interaction term between radon and follow-up time.

Analyses were also undertaken using a random-effects Cox model originally developed to take into account complex spatial patterns in the data in air pollution research in the CPS-II [29, 30]. Analyses were conducted using SAS version 9.2 [31] and our random-effects Cox regression program [29, 30]. Ethics approval was obtained from the Ottawa Hospital Research Ethics Board.

RESULTS

The distribution of selected CPS-II participant characteristics is presented in Table 1. The majority of participants were aged 40 to 69 years at enrollment, had more than a high school education, and were never smokers. Mean county-level residential radon concentrations varied according to several participant characteristics: there was a tendency for higher radon concentrations to be observed among subjects who were white, had a lower level of education, a higher BMI, or who were never smokers. Radon concentrations tended to be higher in the Northeast and Midwest and lowest in the South.

Table 2 presents adjusted HRs (95% CIs) for non-malignant respiratory disease mortality in relation to a 100 Bq/m^3 increase in mean county-level residential radon concentrations. In the fully-adjusted model, a significant positive association was observed between radon and non-malignant respiratory disease mortality overall (HR = 1.08, 95% CI 1.03 - 1.13) and chronic obstructive pulmonary disease (COPD) specifically (HR = 1.13, 95% CI 1.05 - 1.21) using the LBL data. There was a significant positive linear trend of increasing categories of radon concentrations with both non-malignant respiratory and COPD mortality ($p < 0.05$). However, the association with non-malignant respiratory death was not apparent upon exclusion of COPD (HR = 1.03, 95% CI 0.96 - 1.09). Figure 1 shows adjusted HRs (95% CIs) for COPD mortality according to continuous and categorical indicators of radon concentrations. There was no significant departure from a linear exposure-response relationship ($p > 0.05$). Similar results were obtained using the Cohen data [21-23].

Results for COPD mortality were similar when excluding individuals who reported a history of any previous lung disease (asthma, emphysema, or chronic bronchitis) at enrollment (HR = 1.12, 95% CI 1.03 - 1.22). Results were robust to the adjustment of six socio-demographic ecological covariates (n = 811,373; HR = 1.11, 95% CI 1.04 - 1.19) and ambient ozone concentrations (average of 1977-2000 annual spring and summer daily maximum [32], correlation with radon = -0.09) (n=404,519; HR = 1.16, 95% CI 1.03-1.31) in the model. Results were also insensitive to allowance for spatial clustering at either the ZIP, county, or state level in analysis using the random-effects Cox model. Similar results were observed upon exclusion of participants (n = 104,821) who lived in their current neighborhood at enrollment for less than five years (HR =

1.13, 95% CI 1.05-1.22). There was no evidence that the proportional hazards assumption was violated ($p > 0.05$).

There was no significant effect modification of the radon-COPD association by cigarette smoking, passive smoking, or ambient ozone concentrations on either the additive (Table 3) or multiplicative scales (Table 4). However, results varied by age at enrollment and region ($p < 0.05$) with a somewhat stronger association observed in participants aged at least 65 years at enrollment, compared to participants aged 64 years or less, and among participants in the Northeast and West; no association was observed in the South (Table 4).

DISCUSSION

Findings of this large prospective study showed a significant positive association between residential radon and COPD mortality (HR per each 100 Bq/m^3 = 1.13, 95% CI 1.05 - 1.21). Findings were robust to the control of a variety of socio-demographic ecological variables, ambient ozone concentrations, and potential spatial clustering in the data. Similar results were obtained upon exclusion of individuals who reported a history of any previous lung disease at enrollment.

COPD includes chronic bronchitis and emphysema. It leads to a progressive loss of airflow and can ultimately be fatal [33]. Although cigarette smoking is a major known risk factor, other risk factors include occupational dusts and fumes, air pollution, and genetic susceptibility [33, 34]. COPD is also associated with multiple co-morbidities, such as other respiratory, cardiovascular,

and malignant diseases including lung cancer, possibly due to chronic pulmonary and systemic inflammation [33, 35-37]. Jerrett et al. [32] recently reported a positive association between long-term ambient ozone concentrations and non-malignant respiratory disease mortality in the CPS-II.

Early research findings provide limited evidence of an association between radon and non-malignant respiratory disease [2, 8]. Results from animal studies have shown pulmonary fibrosis and emphysema with exposure to either radon progeny alone or in combination with uranium ore dust [8, 12]. In recent epidemiological studies, a significant excess in mortality from non-malignant respiratory disease was observed in a cohort of French uranium miners [38]. There was however, no trend in mortality with cumulative radon exposure and, when excluding silicosis, the excess in mortality disappeared. Excesses in mortality due to silicosis, other and unspecified pneumoconiosis, and pulmonary fibrosis were observed among uranium miners in the Colorado Plateau [39]. There was also a significant increasing trend in pulmonary fibrosis with increasing categories of cumulative radon exposure. However, occupational dust exposure could confound these associations. We found a significant positive association between radon and COPD mortality in a large general population study. There were also no clear associations observed between radon and mortality from any other malignant or non-malignant disease beyond lung cancer [13] and COPD (reported herein) in the CPS-II [14].

Radiation-induced lung damage, including radiation pneumonitis and lung fibrosis, is also observed following radiation therapy for lung or other thoracic tumours [40]. Alpha radiation exposure was associated with respiratory dysfunction in Mayak nuclear workers [41]. The

Japanese Life Span Study of atomic bomb survivors also yielded significant increases in respiratory mortality in relation to acute, whole body, gamma and neutron radiation exposure [42]. In contrast, there was no association between external radiation and respiratory mortality in a 15-country collaborative study of nuclear workers [43].

The present study is based on ecological indicators of residential radon. Previous studies have examined associations between county-level residential radon concentrations and county-level mortality rates [2, 22]. However, such studies are limited by cross-level bias and confounding due to cigarette smoking and other individual-level risk factors that may vary across counties [8, 44, 45]. Here, mean county-level residential radon concentrations were assigned to individual CPS-II participants and mortality health effects estimated with detailed adjustment for individual-level cigarette smoking status (including both linear and square terms for amount and duration of smoking) and other potential confounders.

Ecological radon data were either estimated using a statistical model based on available short- and long-term monitoring, geological, meteorological, and housing data (LBL), or were based on a non-random series of short-term screening measurements normalized to the data of the US NRRS (Cohen). These data are subject to radon measurement error, seasonal and yearly variability, and within-county variability, likely resulting in some degree of downwards bias and reduced precision of relative risk estimates [13, 46-48]. However, our previous estimates of increased lung cancer mortality associated with ecological indicators of residential radon were compatible with estimates obtained from combined analyses of residential case-control studies [13]. There were also no data on time-activity patterns or residential mobility from enrollment.

Results from an Iowa study revealed that attempts to minimize misclassification through restricting participant selection to long-term household residents and compiling detailed retrospective mobility assessments with measures of radon in multiple locations both within and outside of the home resulted in an improved ability to detect associations with lung cancer [49]. In the combined analysis of seven North American case-control studies of residential radon and lung cancer, restriction of the analysis to subjects with limited residential mobility (reporting at most two addresses in the previous 5-30 years) also tended to strengthen the association between residential radon exposure and lung cancer risk [4, 5]. Although participants here reported living in their current neighborhood at enrollment for a mean number (SD) of 19.4 (14.1) years, results were virtually unchanged upon restriction of the analysis to participants who lived in the same neighborhood at enrollment for at least five years.

There was no updated information on cigarette smoking available beyond enrollment in the full CPS-II. Previously, results for radon associated lung cancer mortality were restricted *a priori* to the first 6 years of follow-up (1982-1988) in order to most accurately control for smoking status [13]. However here, an extended follow-up period (1982-2006) was used in an attempt to maximize statistical power to detect possible associations with causes of death other than lung cancer by maximizing the number of observed deaths. With a mean age at enrollment of 57 years, it is unlikely that participants would begin smoking during follow-up. Results for COPD mortality in the first 6 years of follow-up (1982-1988) were also similar, although less precise (HR = 1.18, 95% CI 0.96 - 1.44), to those obtained in the full follow-up time period, and there was no evidence that the proportional hazards assumption was violated. Residential radon concentrations and cigarette smoking are also inversely correlated [6, 7, 13, 45] and negative

confounding of both radon associated lung cancer [13] and COPD mortality by cigarette smoking was observed. Although findings were somewhat stronger in current, as opposed to never or former smokers, there was no significant effect modification by cigarette smoking status observed on either the additive or multiplicative scales.

Another limitation of the present study is the mortality-based design. Inferences for less fatal diseases may be less reliable to those that are more highly fatal. COPD on death certificates is also likely underreported [36, 50], which may result in non-differential misclassification that is more pronounced in younger subjects. Although respiratory failure typically accounts for the majority of deaths in patients with severe COPD, lung cancer and cardiovascular disease are reported in patients with mild disease [36].

This large prospective study suggests that residential exposure to radon may increase COPD mortality. Although it is unclear whether radon may lead to the induction or exacerbation of COPD (or both), radon may lead to pulmonary inflammation and damage associated with both COPD and lung cancer. The present findings require replication in other settings. If confirmed, airway dysfunction may represent an early indicator of the radon effect. Further research is needed to confirm this finding, and to better understand possible complex inter-relationships between radon, COPD, and lung cancer.

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FIGURE LEGENDS

Figure 1. Adjusted HRs (95% CIs) for COPD 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 1982-2006, CPS-II cohort, US.

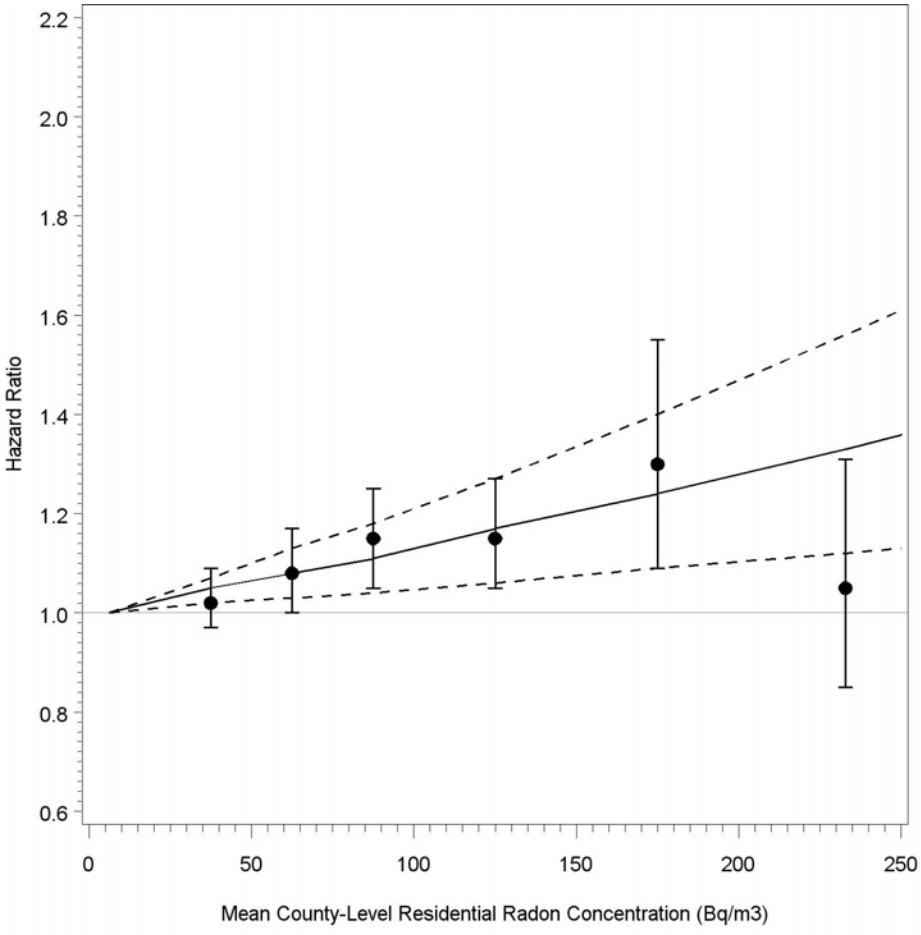

Table 1. Distribution (%) of selected participant characteristics at enrollment (1982), CPS-II cohort, US.

Characteristic	No. (%)	Mean (SD) radon (Bq/m^3) (LBL data)
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 HS	106,668 (13.1)	55.2 (38.9)
HS	262,853 (32.4)	56.8 (39.5)
More than HS	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)
25.0-29.9	299,755 (36.9)	54.6 (38.6)
30.0+	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)

Table 2. Adjusted HRs (95% CIs) for non-malignant respiratory disease mortality per each 100 Bq/m^3 mean county-level residential radon concentrations at enrollment (1982), follow-up 1982-2006, CPS-II cohort, US.

		Cohen Data			LBL Data		
Cause of Death	ICD 9; 10	No. of Deaths	Minimally-adjusted HR (95% CI)[a]	Fully-adjusted HR (95% CI)[b]	No. of Deaths	Minimally-adjusted HR (95% CI)[a]	Fully-adjusted HR (95% CI)[b]
Diseases of the respiratory system	460-519; J00-J98	20,406	1.04 (0.98-1.09)	1.11 (1.05-1.17)	28,300	1.01 (0.96-1.06)	1.08 (1.03-1.13)
Pneumonia and influenza	480-487; J10-J18	6,440	1.06 (0.96-1.17)	1.08 (0.98-1.19)	9,058	0.99 (0.91-1.07)	1.01 (0.92-1.10)
COPD and allied conditions	490-496; J19-J46	9,664	1.02 (0.94-1.11)	1.14 (1.05-1.23)	13,541	1.02 (0.95-1.09)	1.13 (1.05-1.21)
All other respiratory diseases	all not specified	4,302	1.03 (0.92-1.16)	1.07 (0.95-1.20)	5,701	1.02 (0.92-1.13)	1.05 (0.95-1.16)

[a] Age, race, gender, state stratified.

[b] Age, race, gender, 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, occupation dirtiness index.

Table 3. Three measures of additive interaction[a] (95% CIs) between mean county-level residential radon concentration (LBL data), cigarette smoking, and other inhalable agents for COPD mortality, follow-up 1982-2006[b], CPS-II cohort, US.

	RERI (95% CI)	AP (95% CI)	S (95% CI)
Cigarette Smoking	0.61 (-0.38, 1.73)	0.08 (-0.06, 0.20)	1.11 (0.94, 1.31)
Industrial Exposures	-0.06 (-0.34, 0.25)	-0.05 (-0.38, 0.14)	0.76 (0.19, 3.08)
Passive Smoke	-0.075 (-0.17, 0.03)	-0.06 (-0.17, 0.01)	0.70 (0.39, 1.26)
Ambient Ozone	-0.04 (-0.18, 0.11)	-0.04 (-0.22, 0.07)	0.29

[a] Relative excess risk due to interaction (RERI), attributable proportion (AP), synergy index (S).
[b] Exposures categorized as: mean county-level residential radon concentrations: <148 Bq/m^3, ≥148 Bq/m^3; cigarette smoking: never, ever; industrial exposures: no, yes; passive smoking in home: none, any; ambient ozone concentrations < 57.1 ppb, ≥ 57.1 ppb. Cox regression models were fitted with the baseline hazard stratified by age, race, gender, and state, 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, occupation dirtiness index where appropriate.

Table 4. Adjusted HRs (95% CIs) for COPD mortality per each 100 Bq/m^3 mean county-level residential radon concentrations (LBL data) at enrollment (1982) interacted with selected risk factors on the multiplicative scale, follow-up 1982-2006, CPS-II cohort, US.

Characteristic	No. Deaths	Fully-adjusted HR[a] (95% CI)	*p* value
Age at Enrollment			
<65 years	7,800	1.10 (1.01-1.19)	
≥ 65 years	5,741	1.20 (1.08-1.33)	*<0.01*
Attained Age[b]			
<70	2,376	1.06 (0.91-1.24)	
70-79	5,500	1.18 (1.07-1.31)	
≥80	5,665	1.11 (1.00-1.23)	*0.12*
Sex			
Male	7,414	1.07 (0.98-1.17)	
Female	6,127	1.20 (1.09-1.33)	*0.27*
Education			
< High School	2,923	1.14 (0.99-1.33)	
High School	4,589	1.18 (1.05-1.32)	
> High School	6,029	1.06 (0.95-1.19)	*0.38*
Cigarette Smoking			
Never Smoker	1,797	1.03 (0.86-1.25)	
Current	6,585	1.13 (1.02-1.24)	
Former	3,912	1.08 (0.94-1.24)	*0.24*
Industrial Exposures			
No	10,268	1.16 (1.07-1.26)	
Yes	3,273	1.03 (0.89-1.18)	*0.21*
Passive Smoking (Home)[c]			
None	1,570	1.04 (0.85-1.27)	
Any	227	1.03 (0.56-1.90)	*0.89*
Region[d]			
Northeast	2,646	1.20 (1.10-1.31)	
South	4,359	0.94 (0.81-1.08)	
Midwest	3,695	1.12 (1.02-1.22)	
West	2,841	1.21 (1.10-1.32)	*0.02*
Ambient Ozone Concentrations[e]			
<57.1 ppb	3,232	1.21 (0.97-1.53)	
≥57.1 ppb	3,311	1.17 (1.01-1.36)	*0.32*

[a] Age, race, gender, 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, 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.
[c] Never smokers.
[d] HRs (95% CIs) and *p* value were calculated without stratification by state.
[e] Participants with missing ozone data excluded, cutpoints based on median participant ozone value.