A Review of Residential Radon Case-Control Epidemiologic Studies Performed in the United States

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SUMMARY

Lung cancer is the leading cause of cancer death in the United States for both men and women. Although most lung cancer deaths are attributable to tobacco usage, even secondary causes of lung cancer are important because of the magnitude of lung cancer incidence and its poor survival rate. This review summarizes the basic features and major findings from the published U.S. large-scale residential radon case-control studies performed in New Jersey, Iowa, and Missouri (two studies). The methodology from an unpublished study covering Connecticut, Utah, and Southern Idaho is also presented. Overall, the higher categorical risk estimates for these published studies produced a positive association between prolonged radon exposure and lung cancer. Two studies (Missouri-II and Iowa) that incorporated enhanced dose estimates produced the most compelling evidence suggesting an association between prolonged residential radon exposure and lung cancer. The prevailing evidence suggests that the statistically significant findings may be related to improved retrospective radon exposure estimates. The general findings from the U.S. studies, along with extrapolations from radon-exposed underground miners, support the conclusion that after cigarette smoking, prolonged residential radon exposure is the second leading cause of lung cancer in the general population.

KEYWORDS

radon, lung cancer, United States, case-control, epidemiology

INTRODUCTION

Lung cancer is the leading cause of cancer death for both men and women in the U.S. population, accounting for an estimated 157,400

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deaths in the United States during 2001 /1/. In fact, lung cancer (including bronchus) in the United States is responsible for 31% and 25% of all cancer deaths in males and females, respectively /1/. The majority of these lung cancer deaths are attributable to the voluntary practice of cigarette smoking. Because of the magnitude of lung cancer incidence and poor lung cancer survival rates, however, even secondary causes of lung cancer present a major public health concern. Radon-222 (radon), a naturally occurring radioactive noble gas generated by the radioactive decay of radium-226, is a known occupational lung carcinogen /2, 3/. It was discovered in the 1970s that radon gas from subsoils, and to a lesser degree from groundwater sources, can enter a home and accumulate to relatively high concentrations. Radon gas undergoes radioactive decay to a series of decay products called radon progeny or radon daughters. These inhaled solid radon decay products deliver the radiologically significant dose to the lung tissues. The potential adverse health effects from radon progeny exposure prompted the United States Environmental Protection Agency to adopt a 150 Bq m^{-3} (4 pCi L^{-1}) indoor action level for radon. Comparative risk analyses performed in the United States by numerous states and the federal government ranked residential radon exposure as one of the most serious environmental hazards /4/. Lung cancer risk projections, extrapolated from case-control epidemiologic studies of radon-exposed underground miners, attribute around 18,600 lung cancer deaths per year (range 3,000 to 41,000) in the United States population to residential radon exposure /5/.

Because of inherent differences between miners and the general population, in addition to the differences between mine and home environments, extrapolations from miners to the residential population are uncertain /5/. In fact, the validity of even extrapolating from high dose to low dose effects has been questioned /6/. The uncertainty associated with the extrapolations led researchers to investigate directly (without extrapolation) whether residential radon exposure is associated with an increased lung cancer risk in the general population. Since 1981, over 20 ecologic /7–9/ and 12 major case-control studies /10–22/ have been published examining the association between residential radon exposure and lung cancer.

The ecologic studies generally attempted to correlate geographic-based lung cancer rates with the mean radon concentrations from a geographic area. The aggregate measures of radon concentration used in these studies were obtained from a limited number of short-term radon measurements. Because ecologic studies lack information at the level of the individual, the study design is limited to formulating causal hypotheses. Alternatively, case-control studies can establish risk factors for groups of individuals by collecting information at the level of the individual and controlling for potential confounders that may affect the risk estimates.

In the United States, five major case-control studies have been performed (Table 1) to assess the lung cancer risk posed by prolonged residential radon exposure. The New Jersey /19/, Missouri II /21/, Iowa /22/, and the combined states study (Connecticut, Utah, and Southern Idaho) /23/ examined the risk posed to a mixed sample of smokers and non-smokers; the Missouri-I study /20/ examined the lung cancer risk posed by radon only among ex-smokers and never smokers. This paper describes the methodologies and results of these studies when available.

SUMMARY OF RESIDENTIAL RADON CASE-CONTROL STUDIES

New Jersey Residential Radon Study

The New Jersey residential radon study was the first large-scale study that was based on actual

TABLE 1

Attributes of United States residential case-control studies

Study Location	Primary reference	Enrollment Period	Number of subjects	
			Cases	Controls
New Jersey Phases I+II	/19/	1982–1983	480 women	442 women
Missouri-I	/20/	1986–1991	538 women	1,183 women
Missouri-II	/21/	1993–1994	512 women	553 women
Iowa	/22/	1993–1996	413 women	614 women
Multi-State Study	/23/	1989–1993	Total = 1,474	Total = 1,811
Connecticut			963 men and women	949 men and women
Utah, Southern Idaho			511 men and women	862 men and women

radon concentrations in the home and detailed smoking histories for individual subjects. Papers reporting the preliminary /24–26/ and primary /18/ findings on the initial phase I study for the New Jersey Radon Study were published in 1989 and 1990. The phase I radon study was a sub-study of a previous investigation examining the variation in smoking-related cancers /26/. The initial study /26/ included all female residents of New Jersey with lung cancers diagnosed between August 1982 and September 1983. The controls were population-based and selected by random digit dialing from New Jersey women, using either (a) drivers' license files for those under age 65, (b) Health Care Financing Administration files for those 65 years of age old and older, or (c) death certificate files for controls to match deceased cases. Living controls were frequency matched to living cases by race and age. For deceased cases, the controls were individually matched to cases by race, age, and date of death. Potential control death certificates that reported any respiratory disease were not selected. Phase I included 433 cases and 402 controls. Forty-three percent of the case respondents and forty-seven percent of the control respondents were proxies.

Face-to-face interviews collected information on the following information:

- lifetime smoking history by brand of cigarette,
- smoking by other household members,
- lifetime history of towns lived in,
- occupational history, and
- dietary history of foods containing vitamin A.

TABLE 2

Radon dosimetry type and placement for residential case-control studies performed in the United States

Study location	Ref.	Dosimetry type[1]	Test duration	Location of placement
New Jersey	/18, 19/	ATD	1 year	ATDs placed in living area and basement.
		CC	4 days	Short-term CCs placed in some living areas and basements
Missouri-I	/20/	ATD	1 year	ATDs placed in the kitchen and bedroom
Missouri-II	/21/	ATD	1 year	ATDs placed in kitchen and in subject's bedroom
		RRD	60 days	RRDs placed on selected household glass items.
Iowa	/22/	ATD	1 year	ATDs placed in subject's bedroom, historic bedroom, home work area, and each level of the home and outside the home
		RRD	1 year	RRDs placed in bedrooms and living area
Connecticut, Utah, S. Idaho	/23/	ATD	1 year	ATDs placed in subject's bedroom, lowest living level, and basement.

[1]ATD = Alpha Track Detector; RRD = Retrospective Radon Detector; CC = Charcoal Canister

Information was not collected concerning the percent of time spent in the home. Phase I subjects were included into the study only if they had been living in a single 'index' residence for at least 10 years during the 10 to 30 years before diagnosis for cases or selection for controls. The authors point out that in this study, the overall distribution of radon concentrations in the home was relatively low /24/. Homes of only 36 subjects (24 cases and 12 controls) out of the 835 phase I subjects had living area radon concentrations greater than 73 Bq m^{-3}. An updated version of phase I, called phase II, was published as part of a proceedings /19/ and included additional subjects that were ineligible under the phase I study. Phase II of the New Jersey Study /19/ relaxed the 10-year index residency period requirement and included subjects who had been living in one or more 'index residences' during the 5- to 30-year period before diagnosis or selection. Phase II added both the individuals who had been ineligible for phase I and additional houses for the phase I subjects. Subjects were included in the combined phase I and II analysis only if the radon measurements or the estimates covering at least 9 years of the 25-year index period were available. Thirty-five percent of the subjects had been living at the index residence(s) for the full 25-year period. The median residency in the index homes was 22 years for both cases and controls. The combined phase I and II New Jersey Study included 480 cases and 442 controls (Table 1).

TABLE 3

Basement and Living Area Radon Concentrations for U.S. Residential Radon Studies

Study Location	Geometric Mean (Geometric Standard Deviation) ($Bq\ m^{-3}$)[1]			
	Basement	Level 1	Level 2	Reference
New Jersey		19 (2.3)	26 (2.2)	/24/
Missouri-I	89 (1.9)	44 (2.2)	44 (2.2)	/20/
Missouri-II	89 (2.0)	44 (2.2)	44 (2.2)	/21/
Iowa	170 (2.2)	93 (2.2)	74 (2.1)	/22/
Connecticut, Utah	56 (2.7)	19 (2.8)	15 (2.7)	
Southern Idaho[2]	67 (2.3)	44 (2.2)	37 (2.2)	

[1]Summary data represent those homes that were measured with no imputed values added.

[2] Shore D, Personal Communication

For the combined phase I and II study, year-long alpha-track detector (ATD) measurements for radon were performed for the living area of the home for 77% and 76% percent of the case and control homes, respectively (Table 2). Living-area estimated radon concentrations were made from ATDs placed in the basement for 5% of cases and for 6% of controls. Living-area estimated radon concentrations were also made for 7% of the cases and for 9% of the control homes from short-term charcoal radon-detector tests. For the remaining 11% of cases and 10% of controls who were apartment dwellers living above the second floor, the average radon concentration was assumed to be less than 37 Bq m^{-3}. The geometric mean radon concentrations for the various levels of the home were below 37 Bq m^{-3} (Table 3). For analysis using time-weighted radon concentrations, no imputation for time period gaps for the 25-year interval was used. The analysis using cumulative radon exposures assumed a living-area radon concentration of 22 Bq m^{-3} for missing gaps. Information on the time the subject spent in the home was not collected.

Based on the combined phase I and II data, the respective adjusted odds ratios (ORs) for the 4 time-weighted average exposure categories <37, 37–73, 74–147, and 148–418 Bq m^{-3} were 1.0, 1.2, 1.1, and 8.7. The OR for the highest exposure category was statistically significant, based on the 90% confidence interval (Table 4). A statistically significant test for trend (1-sided $p = 0.04$) in ORs with increasing radon exposure was also noted. The findings were adjusted for lifetime average cigarettes/day, years since smoking cessation, age, occupation, respondent type, and interaction terms between respondent type and cigarettes per day. The authors point out that these findings should be

TABLE 4

General results for U.S. residential radon studies[1]

Study	Ref..	General Results		
		Highest Exposure Group	Odds Ratio (CI)	Comments
New Jersey Phase 1 + II	/19/	148–418 Bq m^{-3}	8.7 (1.3–57.8)*	Exposure based on time-weighted average radon concentration. Test for trend in odds ratios with increasing radon concentration (p = 0.04).
Missouri-I	/20/	91.0–566.1 Bq m^{-3}	1.2 (0.9–1.7)**	Exposure based on time-weighted average radon concentration. Test for trend in odds ratios with increasing radon concentration (continuous p = 0.99; categorical p = 0.19).
Missouri-II	/21/	$\geq$148 Bq m^{-3}	0.71 (0.3–1.3)**	Exposure based on time-weighted indoor air track-etch radon detectors. Test for trend in odds ratios with increasing radon concentration (continuous p = 0.79)
		and		
		$\geq$148 Bq m^{-3}	3.33 (1.5–7.5)**	Exposure based on time-weighted-average indoor exposure CR-39 surface measurements. Test for trend in odds ratios with increasing radon concentration (continuous p = 0.02)
Iowa	/22/	$\geq$16.95 $WLM_{5\text{-}19}$	1.79 (0.99–3.26) **	Exposure for all cases and controls based on cumulative radon exposures using a complex retrospective exposure algorithm Test for trend in odds ratios with increasing radon concentration (continuous p = 0.14; categorical p = 0.05).
		and		
		$\geq$16.95 $WLM_{5\text{-}19}$	2.14 (1.12–4.15)**	Exposure for all live cases and controls based on cumulative radon exposures using a complex retrospective exposure algorithm Test for trend in odds ratios with increasing radon concentration (continuous p = 0.03; categorical p = 0.01).

[1]Results have not yet been reported for the joint study performed in Connecticut, Utah and Southern Idaho.
*90% Confidence Interval; **95% Confidence Interval

cautiously interpreted because the upper exposure category contained only five cases and one control. Again using the combined phase I and II data, the respective adjusted ORs for the 4 cumulative radon exposure categories <463, 463–924, 925–1849, 1850–2868 Bq m^{-3} were 1.0, 1.3, 0.91, and 8.0. The OR for the highest exposure category for cumulative exposure was also statistically significant, based on the 90% confidence interval (Table 4), using only 4 cases and 1 control. The trend in ORs with increasing cumulative radon was not statistically significant (1-sided p=0.06). The general study findings for the combined phase I and II are presented in Table 4. A supplementary paper concerning the New Jersey Study is available elsewhere /27/.

Missouri-I Residential Radon Study

Alavanja et al. /20/ published the major findings paper for the Missouri-I Radon Study in 1994. The lung cancer cases comprised nonsmoking white females, aged 30 to 84 years that had been reported to the Missouri Cancer Registry between June 1986 and June 1991. In addition to the registry-reported primary lung cancer diagnosis, for 76% of the cases tissue slides were reviewed for histologic verification. The controls were population based and randomly selected using Missouri driver's license files for women 30 and 64 years old. Women between 65 and 84 years of age were randomly selected from Health Care Finance Administration files. The controls were matched in 5-year age strata to the number of case subjects that been reported in previous years. Both lifetime nonsmokers and former smokers were enrolled in the study. 'Lifetime nonsmokers' were identified as women who had smoked less than 100 cigarettes in their lifetime or had not used any tobacco products for more than 6 months. Women who had ceased using all tobacco products 15 or more years before the interview were classified as 'former smokers'. Of the 538 cases and 1,183 controls (Table 1), 30% of the cases and 17% of the control respondents were classified as former smokers. Sixty-three percent of the case respondents and zero percent of the control respondents were proxy respondents.

Telephone interviews with either subjects or proxy respondents collected information on lifetime smoking history, environmental tobacco exposure, education, and previous lung disease. A follow-up face-to-face interview collected information on dietary factors and housing characteristics. Radon measurements were made to estimate the subjects' exposure for the period 5 to 30 years before enrollment. The authors indicate that they chose the 5-year period because it was the minimal latency period noted for radiogenic lung cancer in underground miners. The authors choose a 30-year upper boundary both because miner studies indicate risk decreases with time since exposure and because prior radon exposure estimates become increasingly inaccurate with time.

Alpha track detectors were placed in the kitchen and the bedroom of each dwelling studied in Missouri that had been occupied for at least 1 year during the 30 years before subject enrollment (Table 2). The ATD measurement results were available for 74% of the dwellings and included 78% coverage for the 5- to 30-year period window. Information on residential occupancy was collected to account for the time that the subject spent outside the home. The mean occupancy factor for cases and controls was approximately 84%. The respective geometric mean radon concentrations for the kitchen and bedroom measurements were 44 and 43 Bq m^{-3} (Table 3). Time-weighted average radon concentrations were estimated with weighting by the available years of residence in each home without consideration of individual home occupancy factors. Cumulative radon exposure estimates were also calculated for the exposure window. The respective mean radon concentrations for cases and controls were used to fill in the missing exposure periods for cases and controls.

The ORs for the quintiles of radon exposure categories 3.7–29.4, 29.5–44.0, 44.1–62.7, 62.8–90.9, and 91.0–566 Bq m^{-3}, adjusted for age, were 1.00, 1.01, 0.84, 0.90, and 1.2, respectively. The OR for the highest time-weighted radon exposure was not statistically significant, based on the 95% confidence interval (Table 4). The trend in ORs with increasing radon exposure was not statistically significant for either the continuous (p=0.99) or the categorical analyses (0.19). Adjustments for cancer risk factors had minimal effects on the dose-response patterns. No differences in OR trends were noted for the categories never-smokers or former smokers.

When the histologic type was limited to adenocarcinoma (p=0.04 for categorical analyses), a positive dose-response trend was suggested. In addition, the highest quintile of radon concentration was statistically significant for the adenocarcinoma subgroup (OR=1.66; 95% CI= 1.0–2.6). When the analyses were adjusted for saturated fat intake, both the categorical and the continuous trend tests for adenocarcinoma were statistically significant ($p< 0.05$). A suggestive positive dose-response trend was also noted in the analyses that were restricted to the live-case and live-control subset (p=0.06). Similar dose-response patterns were noted when cumulative dose estimates in the form of Working Level Months (WLM) were used in the analyses. Supplementary-related papers concerning the Missouri-I study are available elsewhere /28–34/.

Missouri-II Residential Radon Study

Alavanja et al. /21/ published the major findings from the Missouri-II Radon Study in 1999. The lung cancer cases comprised females between the ages of 30 and 84 years with primary lung cancer that were reported to the Missouri Cancer Registry between January 1993 and January 1994. In addition to the registry-reported primary lung cancer diagnosis, tissue slides were independently reviewed for all of the available cases. The controls were population-based and randomly selected from Missouri driver's license files for women 30 and 64 old. Women between 65 and 84 years of age were randomly selected from Health Care Finance Administration files. The controls were matched by 5-year age groups to the case subjects. A 2-stage randomized recruitment method was used for controls to help increase the percent of smokers in the control group. All heavy smokers in the pool of potential controls were invited to participate. Sixty-two percent of the light smoking white women and twenty six percent of the former light smoking white women were invited to complete the entire interview. The corresponding percentages of non-white controls who were invited to complete the entire interview were 75% and 34%, respectively.

Telephone interviews with subjects or proxy respondents collected information on residential history, lifetime smoking history, environmental tobacco exposure, education, and previous lung disease. A follow-up, face-to-face interview collected information on dietary factors, housing characteristics, and location of glass surfaces that were appropriate for placing retrospective radon detectors (also called RRDs or CR-39 surface monitors). Radon measurements were made to estimate the subjects' exposures for the period 5 to 25 years before diagnosis for cases or for the period 5 to 25 years before interview for controls. Subjects who did not have at least 70% of the previous 25 years accounted for by either of two types of radon measurements (see below) were excluded from the study. In total, 512 case and 553 control subjects (Table 1) were included in the study. Thirty-two percent of the case respondents and zero percent of the control respondents were proxy respondents.

The study incorporated two different radon dosimetry techniques. The first technique used ATDs similar to those used in Missouri I. Yearlong ATD measurements were made in the kitchen and bedroom of the home that was currently occupied by the study subject (Table 2). The other dosimetry technique used glass-based RRDs (retrospective radon detectors) /35–37/. The RRD utilizes the accumulation of a long-lived radon decay product, ^{210}Pb, in glass. As radon gas goes through its radioactive decay chain, it produces a decay product, ^{210}Pb, which has a very long half-life (around 22 years). A fraction of the ^{210}Pb implants in glass surfaces in a room, providing a long-lasting marker for retrospective radon concentrations. Lead-210, in turn, produces a shorter-lived decay product, ^{210}Po. The ^{210}Po

decay can be measured by the tracks it creates in a suitable piece of plastic by the emitted alpha particles.

Over 70% of the homes had results of either the ATD or RRD measurement, which resulted in a 91% coverage for the 5- to 25-year period window. Information was not provided concerning the percent coverage by detector type or the percent of time that the subjects spent in the home. The respective mean radon gas ATD measurements for the current kitchen and bedroom were 58 and 56 m^{-3}. The geometric radon concentrations by level of the home are presented in Table 3. The respective mean RRD measurements for the kitchen and the bedroom were 65 and 65 Bq m^{-3}. Neither dosimetry technique produced a significant difference between the two rooms, so the authors used the mean radon concentration for the two rooms as their measure of radon exposure for each of the two procedures. The RRD measurements were performed on objects with average ages of 32 and 31 years for controls and cases, respectively. Time-weighted average radon gas exposures were estimated for the current home and assumed to be representative of the radon concentration existing in all homes during the period of interest. Annual time-weighted average radon exposures were also calculated by dividing the cumulative radon measurement results, obtained by RRDs, by the number of years the subject had owned the glass object. The respective mean radon gas measurements (obtained from ATDs) and glass-based measurements (obtained from RRDs) from controls were used to impute missing data for the air gas measurement and glass measurement techniques.

The respective ORs for air measurements using ATDs, adjusted for age, education, previous lung disease, pack-years of smoking, and mean servings of vegetables per week for four categories of radon exposure (<37, 37–73, 74–147, and $\geq$148 Bq m^{-3}) were 1.00, 0.87, 0.91, and 0.71 (Table 4). The continuous trend in ORs with increasing radon concentration was not statistically significant (p=0.79). Alternatively, a significant lung cancer risk was noted for the analyses that were based on RRD glass-based measurements. The respective ORs based on 471 controls and 372 cases using RRD glass-based measurements, adjusted for age, education, previous lung disease, pack-years of smoking, and mean servings of vegetables per week, for the four categories of radon exposure (<37, 37–73, 74–147, and $\geq$148 Bq m^{-3}) were 1.00, 1.11, 1.32, and 3.33. The OR for the highest exposure category was also significant at the 95% confidence interval (Table 4). The continuous trend in ORs with increasing radon concentration was statistically significant (p=0.02). The dose-response trend was similar for each histologic type. The authors performed an error analysis indicating that the discrepancy between air measurements and RRDs may have been due to increased random error for the indoor measurements relative to RRDs. Supplementary papers concerning the Missouri-II study are available elsewhere /38–41/.

Iowa Residential Radon Study

Field et al. /22/ published the major findings paper from the Iowa Radon Lung Cancer Study in 2000. The lung cancer cases were females aged 40 to 84 years having newly diagnosed, microscopically confirmed, primary lung cancer with no prior lung cancer. The cases were restricted to residents of Iowa who had been living in their current home for at least 20 years. The cases were identified (over 90% rapid reported) by the Iowa Cancer Registry between May 1993 and October 1996. In addition to the registry reported primary lung cancer diagnosis, 98% of the cases tissue slides were independently reviewed for histologic verification. The controls were population based and randomly selected from Iowa driver's license files for women 30 and 64 years old. Women between 65 and 84 years of age were randomly

selected from Health Care Finance Administration files. The controls were matched in 5-year age strata to the case subjects. Both lifetime nonsmokers, former, and current smokers were enrolled in the study. 'Ever smokers' were identified as women who had smoked at least 100 cigarettes in their lifetime or had used any tobacco product for more than 6 months. Women who had ceased using all tobacco products 15 or more years before the interview were classified as former smokers. Of the 413 cases and 614 controls (Table 1), 86% of the cases and 33% of the control respondents were classified as ever smokers. All the controls were alive at time of the interview. In addition, rapid reporting of cases led to a high percentage (69%) of living cases at time of interview.

Study questionnaires were mailed to subjects or to proxy respondents (generally next-of-kin), with a follow-up, face-to-face facilitation and interview. The questionnaires provided information on family health history, demographics, personal health history, occupational exposures, dietary factors, retrospective personal mobility, and housing characteristics.

A radon dosimetry assessment included the following:

- an on-site residential assessment,
- on-site radon measurements (both ATD and RRD),
- regional outdoor radon measurements,
- assessment of subject's exposure while in another building, and
- linkage of historical subject mobility with residential, outdoor, and other building radon concentrations.

Yearlong ATD measurements were performed on each level of the home and in the current and historical master bedroom. Overall, 97% of all alpha track detectors were retrieved 1 year later. Cumulative radon exposures, accounting for all time spent in and out of the house with linkage to radon concentration, were expressed in working level months for exposures occurring during the 15-year time window 5 to 19 years ($WLM_{5\text{-}19}$) before diagnosis for cases or interview for controls. Because of the 20-year inclusion criteria, there was 100% coverage of the time window of interest. Cases and controls spent an average of 73% and 72% of their time at home, respectively. The geometric mean radon concentrations for the various levels of the home are higher than those reported in the other residential studies (Table 3).

Risk analyses were performed for all subjects, with a sub-analysis of the living subjects. The respective ORs, adjusted for age, education, and active smoking, for the 5, a priori selected cumulative radon exposure categories of 0–4.23, 4.24–8.47, 8.48–12.7, 12.71–16.94, >16.95 $WLM_{5\text{-}19}$ were 1.00, 1.34, 1.73, 1.62, and 1.79. The OR for the highest exposure category for cumulative exposure was nearly statistically significant, based on the 95% confidence interval (Table 4). The trend in ORs with increasing cumulative radon was not statistically significant for continuous trend (p=0.14), but was statistically significant for the categorical analyses (0.05).

The Iowa authors presented separate findings excluding deceased subjects to minimize possible biases or exposure misclassification that might be associated with the second-hand information from relatives. When the analysis focused on the living cases, the OR for the highest exposure category was statistically significant (Table 4). In addition, the tests for trend were statistically significant for both the continuous (p=0.03) and the categorical analyses (p=0.01). Excess odds were calculated for an average exposure of 11 $WLM_{5\text{-}19}$ (approximately equal to a 15-year residential exposure at 148 Bq m^{-3}). After adjustment for age, smoking, and education, statistically significant excess odds of 50% and 83% were found using categorical radon exposure estimates for all cases and live

cases, respectively. Slightly lower excess odds of 24% and 49% were noted for all subjects and live subjects, respectively, using a continuous analysis. Among the different histologic types, large-cell carcinoma exhibited both a statistically significant continuous and categorical trend. The differences in the linear excess odds between histologic types were not statistically significant, however. A reanalysis of the Iowa data, incorporating glass-based retrospective reconstruction detectors, is planned /42–44/. Supplementary papers concerning the Iowa study are available elsewhere /45–51/.

Connecticut/Utah/Southern Idaho Combined Residential Radon Study

Sandler et al. /23/ performed a combined case-control study of subjects residing in Connecticut, Utah, and Southern Idaho. The findings of the paper have not yet been published, but the study methodology has been described /23/. The lung cancer cases were male and females aged 40 to 69 years and diagnosed between 1989 and 1993 from the cancer registries and medical records located in their respective states. A screening telephone interview was used to select subjects according to current and past tobacco usage (never smokers, non smokers, and current smokers). In addition to the reported primary lung cancer diagnosis, for the majority of cases, tissue slides were reviewed for histologic verification. Controls were identified by random telephone screening. For Utah and Idaho, controls over the age of 64 years were also identified from Health Care Finance Administration files. Randomized recruitment was used to select controls matched on smoking status 10 years before interview, age, and gender. In most instances, one control was chosen for each case, except in Utah where two controls were selected for never and non-smokers. Additional selection criteria were also imposed, including (a) the duration of adult residence in study states, (b) the number of lifetime residences, (c) employment in mining, and (b) the ability to complete the interview.

Of the 1,474 cases and 1,811 controls (Table 1), 8% of the cases and 14% of the controls never smoked. Telephone and in-home interviews collected information on residential history, education, medical history, and lung cancer risk factors. As part of the residential history, subjects provided information about each home that had been occupied for one year. The information included the number of hours spent on each floor of the home, the location of bedroom where they slept, and whether they worked outside the home. Forty-nine percent of the case respondents and one percent of the control respondents were proxy respondents. Radon measurements were attempted in each home where the subject had lived since the age of 25, as well as the longest childhood residence. In all homes measured, yearlong alpha track measurements were placed in the subject's bedroom, in another room on the lowest living level where significant time was spent, and in most basements (Table 2). In a sub-sample of multi-level homes, a detector was placed on each level.

An average of 4 homes were reported for the time window of interest (age 25 up to 5 years before diagnosis for cases or before interview for controls). Yearlong radon measurements were available for 57% of the eligible dwellings in Connecticut and 60% in Utah/S. Idaho (Table 3). Seventy-nine percent and eighty-three percent of the subjects in Connecticut and Utah/S. Idaho, respectively, had dosimetry coverage (one or more radon measurements) in at least 50% of their homes for the time window of interest. Overall, 62% of subjects had complete exposure information for the period from 5 to 25 years before diagnosis for cases or interviewed controls.

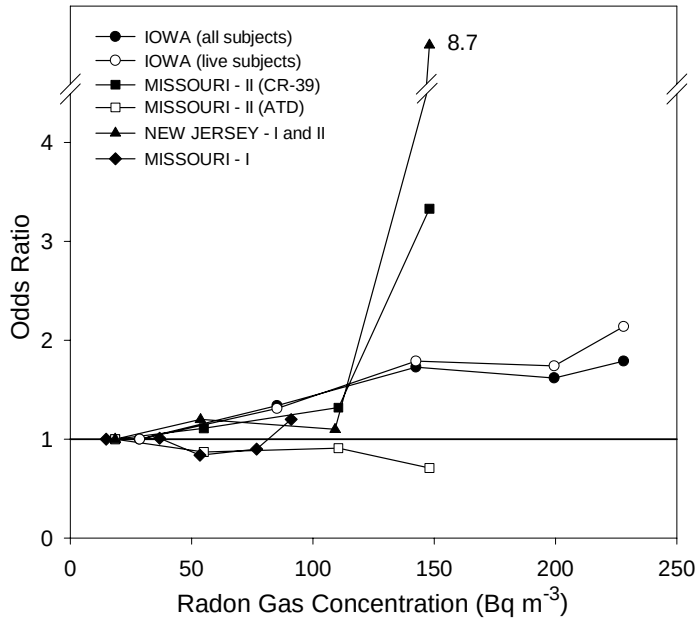

Fig. 1: Plot of odds ratios versus estimated radon concentrations for the various exposure categories for each study. The radon gas concentration point estimates were constructed by using the midpoint of the exposure category or the lower limit in the case of the highest exposure category from each of the study's publications. Confidence intervals for the point estimates are not presented on the plot. The reference line represents an odds ratio of 1.0 or no increased risk. Odds ratios are presented for both types of radon measurements used in the Missouri-II Study. Findings for both all cases and controls and the live cases and controls are presented for the Iowa Study.

Average exposures to radon from age 25 to 5 years before diagnosis or interview were calculated as a time-weighted average of both the amount of time in each residence and the proportion of time spent on each level of the home. Mean radon concentrations from measured homes were used to impute radon concentrations for similar homes that could not be measured. Similar residences were identified by use of regression trees that included categories like the level of home, housing characteristics, geological characteristics, and others /52/. The authors indicate /23/ that they will estimate lung cancer risk associated with cumulative radon exposure for specific time windows.

DISCUSSION

The residential radon case-control studies performed in the United States had not only many similarities in study design but also numerous factors that varied among the studies, including differences in state residential radon concentration distributions (Fig. 1; Table 3) and study designs. The studies designs varied by case selection method, subject residency requirements, exposure windows of interest, dosimetry methods, and analytical analyses. For example, the first exposure category for the combined New Jersey study ended at 37 Bq m^{-3}, whereas the first exposure category for the Missouri-I Study ended at 29 Bq m^{-3}.

Because the first category is the referent category for the calculation of the ORs for the remaining categories, comparisons among the studies become more involved. Therefore, cautiously interpreting the comparative findings between the studies and carefully weighing the strengths and weaknesses of each study is prudent, while considering the following observations.

Elevated risks (ORs) were noted for the highest exposure categories for all of the published studies, except for the Missouri-II analysis that relied on current home contemporary radon gas measurements (Table 4, Fig. 1). The combined phase I and II New Jersey Study produced the highest categorical OR (OR=8.7), which was also statistically significant at the 90% confidence level. This result requires a cautious interpretation, however, because that category contained a very limited number of subjects. In the Missouri-II study, statistically significant upper exposure categories were also found for the glass-based CR-39 detector analysis (OR=3.3) and for the live case subset analysis of the Iowa study (OR=2.1). A nearly statistically significant odds ratio of 1.8 was also noted for the upper category of the overall analysis for the Iowa study. Statistically significant tests for trend in ORs with increasing cumulative radon were noted for both the Iowa Study and the Missouri-II Study (glass-based CR-39).

In reviewing the findings from the residential radon case-control studies performed in the U.S., the studies with the more advanced dosimetric approaches have indicated a statistically significant association (95% confidence level) between prolonged residential radon exposure and lung cancer. In fact, Field et al. /22/ and Alavanja et al. /53/ suggested that the inability to detect an association in certain studies may have been due to poor retrospective radon exposure assessment /53/. One of the major challenges in performing a case-control study is the ability to assess retrospectively the exposure to an agent accurately over a person's lifetime. Although studies of radon-exposed underground miners report that the 15 to 20 years before the development of lung cancer is the biologically important period to assess exposure, radiation exposures occurring at younger ages may also carry increased risk. Attempts to find an in vivo marker, such as measurement of polonium-210 in bone, to predict the lifetime cumulative radon exposure have been somewhat limited for residential studies by their limited level of sensitivity and the confounding by other sources (such as cigarettes) of polonium-210 deposition /54, 55/.

Residential radon case-control studies have some advantages over other types of case-control studies in determining retrospective exposure because a significant proportion of the radon exposure occurs in the home and the radon concentrations can be measured at some later date. Uncertainty in the estimating retrospective radon exposures increases, however, when certain time periods in the 15 to 20-year time period before study enrollment are missing. For example, consider the conflicting results from the Missouri-II study, which used two methods to estimate past radon residential radon concentrations. The first technique used by the Missouri-II study relied on current radon gas concentrations in the current home to predict past exposures. In some cases, the current home was occupied for only a few years, which likely resulted in poor overall retrospective radon concentration estimates. The inability to account for missing time periods increases the likelihood of exposure misclassification in a study, which in turn decreases a study's power to detect an association if one exists. To capture an average integrated radon exposure over a longer period, the Missouri-II study used CR-39 (RRD) measurements from glass items that were located for many years in the current home and in previous homes. The first technique did not find any association between the radon gas measurement and risk of

lung cancer, whereas the second technique found a statistically significant association. The positive findings using the more advanced measurement technique are attributable either to decreased exposure misclassification or to some unknown systematic bias. Additional work to determine the validity of this new dosimetry method is currently underway /56/.

The findings of the Iowa Radon Lung Cancer Study also suggest that improved retrospective radon measurement enhances the ability of a study to detect an association between radon exposure and lung cancer. The Iowa study limited the enrollment only to subjects who had been living in their current home for at least the previous 20 years. This feature of the study prevented gaps in the radon measurement data and allowed the investigators to focus their radon measurements on a single home per subject. The Iowa study also collected information on where the subject spent time within the home, as well as the time spent outside the home and in another building. This information on personal mobility was linked to the estimated radon concentrations for each area to determine a cumulative retrospective exposure estimate for the 20-year period before study enrollment. The Iowa authors also performed an error analysis suggesting that alternative, less rigorous methods, which failed to link either mobility or all the radon measurements in the home, produce lower risk estimates. Several of the studies (New Jersey and Connecticut) had relatively low residential radon concentra-tions, which reduced the overall power of the studies to detect an association. Other methodologic challenges associated with residential radon studies are presented elsewhere /45/.

Additional research in the area of residential radon epidemiology is currently underway in the U.S. Investigators from the Iowa and Missouri studies are calibrating the glass-based detectors (RRDs) that were used in both the Iowa and the Missouri studies. Following the intercalibration of the detector, the Iowa researchers will be analyzing the results of the glass-based retrospective radon detector measurements that have already been performed in the Iowa study homes. A pooling of the glass-based results from the Iowa and Missouri studies is planned /56/. In addition, the data from all the residential radon studies that have been performed in North America are being pooled. Once the North American pooling is complete, the data will be pooled with the data from the on-going European pooling.

In summary, the general findings from the United States studies, along with extrapolations from radon-exposed underground miners, support the conclusion that prolonged exposure to residential radon may contribute to a significant increase in lung cancer risk.

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