Paper

CASE-CONTROL STUDY OF LUNG CANCER RISK FROM RESIDENTIAL RADON EXPOSURE IN WORCESTER COUNTY, MASSACHUSETTS

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Abstract—**A study of lung cancer risk from residential radon exposure and its radioactive progeny was performed with 200 cases (58% male, 42% female) and 397 controls matched on age and sex, all from the same health maintenance organization. Emphasis was placed on accurate and extensive year-long dosimetry with etch-track detectors in conjunction with careful questioning about historic patterns of in-home mobility. Conditional logistic regression was used to model the outcome of cancer on radon exposure, while controlling for years of residency, smoking, education, income, and years of job exposure to known or potential carcinogens. Smoking was accounted for by nine categories: never smokers, four categories of current smokers, and four categories of former smokers. Radon exposure was divided into six categories (model 1) with break points at 25, 50, 75, 150, and 250 Bq m^{-3}, the lowest being the reference. Surprisingly, the adjusted odds ratios (AORs) were, in order, 1.00, 0.53, 0.31, 0.47, 0.22, and 2.50 with the third category significantly below 1.0 ($p < 0.05$), and the second, fourth, and fifth categories approaching statistical significance ($p < 0.1$). An alternate analysis (model 2) using natural cubic splines allowed calculating AORs as a continuous function of radon exposure. That analysis produces AORs that are substantially less than 1.0 with borderline statistical significance ($0.048 \leq p \leq 0.05$) between approximately 85 and 123 Bq m^{-3}. College-educated subjects in comparison to high-school dropouts have a significant reduction in cancer risk after controlling for smoking, years of residency, and job exposures with AOR = 0.30 (95% CI: 0.13, 0.69), $p = 0.005$ (model 1).**
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INTRODUCTION

Exposure to radon gas has been shown to be a significant cause of lung cancer. Radon here means specifically the ^{222}Rn isotope along with its radioactive, alpha-particle-emitting progeny. ^{222}Rn arises as a decay product of ^{226}Ra, which is widely dispersed in rock and soil. Though ^{222}Rn has a half-life of only 3.8 d, its chemical inertness allows it to emerge from the rock and soil into confined spaces where it accumulates. It has been recognized as a significant lung-cancer risk for underground miners for some time. The BEIR VI report (NRC 1999) analyzed the pooled data from 11 cohort studies of the lung-cancer risk from radon exposure of underground miners using a linear, no-threshold (LNT) model of the excess relative risk. The report did recognize that a threshold at well below typical miner exposures could not be ruled out. Because miner exposures were typically 30 times larger than the residential exposures of people, the extrapolation of risk to those lower exposures involves considerable uncertainty. Nevertheless, the U.S. Environmental Protection Agency (U.S. EPA 2003) based a reassessment of lung-cancer risk from radon in homes on the BEIR VI report with only minor revisions in procedure and results.

Well over twenty case-control studies of the lung-cancer risk from radon in homes have now been reported for North American, European, and Chinese locations in order to assess more firmly the risk at lower exposure levels. While many, but not all, report an excess risk, the 95% confidence intervals (CIs) in the great majority of them include the possibility of no excess risk, which would occur if a threshold were to exist. A pooled analysis of the seven North American studies has recently appeared (Krewski et al. 2005, 2006). The data were found to fit an LNT model with "no apparent evidence of nonlinearity throughout the range of radon concentration observed." The slope of the excess odds ratio (OR) was found to be 0.10 per 100 Bq m^{-3} in fine agreement with the BEIR VI slope deduced from the pooled miners data. The 95% CI, −0.01–0.26, however, still includes the possibility of a threshold. A recent pooled analysis of 13 European studies (Darby et al. 2005) has also found agreement with the LNT model with a slope of 0.08 per 100 Bq m^{-3} with a 95% CI,

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0.03–0.16, that excludes a threshold with statistical confidence. Two poolings of Chinese data have been published. The earlier one (Lubin 2003) found an excess OR at 100 Bq m^{-3} of 0.139 with 95% CI of 0.01–0.37. The later study (Lubin et al. 2004) found an excess OR at 100 Bq m^{-3} of 0.33 with 95% CI of 0.01–0.36. Thus, both of the Chinese poolings exclude a threshold. A meta-analysis of seventeen case-control studies also suggested a linear dependence (Pavia et al. 2003).

In view of the unusual and unexpected trend of the adjusted odds ratio (AOR) vs. radon exposure found in this study, to wit, a protective effect, it is worth examining the literature further. First, while a number of the particular case/control studies found individual AOR values below one, that is, protective or hormetic, none found any statistically significant trends in that direction. It is, however, a curious fact (investigated in greater detail in the Discussion section) that the pooled study of Krewski et al. (2005, 2006) has *unadjusted* ORs that are strongly hormetic. Ecologic studies of lung cancer vs. radon exposure have had scattered results and, of course, lack the individual matching of case-control studies. It is interesting, however, that by far the largest and most fully analyzed such studies (Cohen 1995, 1997) found a hormetic result. These have been criticized on a number of grounds and defended. The BEIR VI report (NRC 1999) reviewed these and other ecologic studies and issued a strong judgment: They are not "informative" because of "inherent limitations of the ecologic method."

This paper presents a case-control study of lung cancer incidence vs. residential radon exposure in Worcester County, Massachusetts, carried out between 1990 and 1999 with both cases and controls from a single health maintenance organization. Each case was matched individually by age and sex to two controls. In contrast to previous case-control studies, evidence supporting a hormetic dose-response for radon exposures less than 150 Bq m^{-3} was found. This effect remains marginally statistically significant even after controlling for potentially confounding variables, including age and sex by the matching of the cases and controls, and smoking history, years of residence, income, education, and occupational exposure to suspected carcinogens in multivariable regression analyses. At a time when international consensus is being sought on the lung cancer risk of low radon exposure, it may be regarded as unfortunate to have a nonconforming study appear, but the results were obtained using objective, scientific methods and required peer-reviewed reporting. In addition, many aspects of this study rank it among the most careful ones in both data collection and analysis.

STUDY DESIGN

This study was encouraged as an adjunct study to the Connecticut Study (Sandler et al. 2006) and followed the protocol therein except for a few modifications as required by a lower budget, most significantly testing of only the current home. Approval to recruit cases and controls was obtained by the Institutional Review Board of the St. Vincent Hospital and Fallon Clinic. Both cases and controls were clients of the Fallon Clinic\Fallon Community Health Plan. Subjects of the study were residents of Worcester County, or for a handful of subjects, residents a few miles over its borders. Cases with histologically or cytologically confirmed primary lung cancer were eligible to participate in the study if they were at least 40 y of age, had the permission of their primary care physician, had lived in a radon-testable residence a minimum of 10 y, and were not cigar or pipe smokers (cigarette smoking being accepted). Among never smokers, all cases were histologically confirmed, except for unavailable path specimens in 3 of a total of 15 patients, while smokers with "non-small cell" cancer had cytological confirmation (a total of 8 cases). The pathology was not available for 20 smoking cases. All cases were confirmed by a single, blinded pathologist (Chief of Pathology, St. Vincent Hospital).

Of 580 cases considered for the study, 113 refused entry, 102 did not meet the residency requirement, 62 were not given physician approval to participate, 89 died before both the case's physician and the case subject had agreed upon participation in the study, 5 were disqualified for cigar/pipe smoking, and 209 were enrolled in the study. Radon detectors were lost for 9 of these, leaving 200 cases in the study. Males comprised 58%, females 42%. The cancer pathology of the cases indicated 59 (29.5%) with adenocarcinoma, 44 (22.0%) with small cell carcinoma, 20 (10.0%) with large cell carcinoma, 44 (22.0%) with squamous cell carcinoma, 10 (5.0%) with other, and 23 (11.5%) with no available pathology.

Controls were randomly selected by computer from the same client population. Two were matched individually to each case on sex and age to within ± 2.5 y using date-of-birth (independent of year-of-participation). Of 939 controls considered for the study, 292 refused entry, 146 did not meet the residency requirement, 87 were not given physician approval to participate, 13 were disqualified for cigar/pipe smoking, and 401 were enrolled in the study. Radon detectors were lost for 4 of these, leaving 397 controls in the study. By default, 99% of the subjects were Caucasian.

A questionnaire was filled out by a trained interviewer during a face-to-face interview for every case and control. Because of illness or recent death, a surrogate (a

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spouse or offspring) was interviewed for 21.5% of cases and 3.3% of controls. A detailed smoking history of the number and type (unfiltered or filtered) of cigarettes smoked per day for each year in the subject's life was obtained. The years of residency of the home and any structural changes made during that time were recorded. Previous radon testing and radon remediation were ascertained. Among cases and controls, 7.5% and 9.8%, respectively, had had the home tested, but only 0.5% of cases and 5.5% of controls could remember the result. Only one home had had any remediation, and that was minimal (crack filling). The subjects were questioned in detail concerning hours per week spent in wakeful living areas and bedroom(s) and any other level of the house, usually the basement, where the subject spent one or more hours per week. Sleep was assigned eight hours per night. This distribution of occupancy time was determined over days of the week and weekends, over seasons of the year, and for each differing lifestyle period (full-time work, part-time work, retirement, child-rearing, etc.). These questions determined the placement of detectors in the house. A job history of each subject was obtained, and corresponding years of occupational exposures to heat welding, asbestos, vinyl chloride, formaldehyde, ethylene oxide, x-rays, radioactivity, insecticides, herbicides, smelter fumes, and foundry fumes were obtained. Finally, stratified family income and years of education were requested. Table 1 summarizes many of these data.

DOSIMETRY

Radon concentrations were measured in yearlong exposures of Radtrack etch-track detectors (Tech/Ops Landauer, Inc., 2 Science Road, Glenwood, IL 60425) in the present, or for a few subjects, the immediate past residence that had been lived in for a minimum of 10 y. Before forwarding each batch of exposed detectors for reading by Tech/Ops Landauer, Inc., the U.S. EPA's National Air and Radiation Environmental Laboratory in Montgomery, Alabama, disguised "blanks" (unexposed detectors) and "spikes" (detectors given a calibrated exposure) in each batch (Smith et al. 1992). The number of spikes and blanks disguised in each batch was determined by the Montgomery EPA testing lab, and typically contained two spikes and one blank per batch. A correction factor of the calibration value divided by the

Table 1. Study population demographics, smoking status, and radon exposure.

Covariate	Controls (N = 397)	Cases (N = 200)	p-value
Mean (SD) radon exposure	66.3 (65.2)	67.5 (118.5)	0.086[a]
Same as above, one outlier removed		60.2 (59.4)	0.047[a]
Median radon exposure	50.1	43.7	0.039[b]
Same as above, one outlier removed		43.6	0.030[b]
Sex			0.966[b]
Men	229 (57.7%)	115 (57.5%)	
Women	168 (42.3%)	85 (42.5%)	
Residency (y)			0.081[d]
<20	90 (22.7%)	62 (31.0%)	
20–39	203 (51.1%)	94 (47.0%)	
≥40	104 (26.2%)	44 (22.0%)	
Mean (SD) time of residency (y)	30.6 (12.1)	28.5 (12.1)	0.049[e]
Mean (SD) time in home (h wk^{-1})	113.6 (18.2)	116.6 (17.9)	0.052[c]
Mean (SD) age (y)	67.7 (10.0)	66.6 (9.7)	0.225[c]
Smoking status			<0.001[d]
Never smoker	162 (40.8%)	15 (7.5%)	
Former smoker	196 (49.4%)	80 (40.0%)	
Current smoker	39 (9.8%)	105 (52.5%)	
Total job exposure (y)			0.112[d]
0	290 (73.0%)	134 (67.0%)	
1–9	52 (13.1%)	25 (12.5%)	
≥10	55 (13.9%)	41 (20.5%)	
Education			<0.001[d]
<High school	77 (19.4%)	67 (33.5%)	
High school	149 (37.5%)	90 (45.0%)	
At least some college	165 (41.6%)	40 (20.0%)	
Refused	6 (1.5%)	3 (1.5%)	
Income ($ y^{-1})			<0.001[d]
<30,000	159 (40.1%)	109 (54.5%)	
≥30,000	190 (47.9%)	58 (29.0%)	
Refused	48 (12.1%)	33 (16.5%)	

[a] T-test of natural logs.
[b] Kruskal-Wallis test.
[c] Two sample t-test.
[d] Chi-squared test.

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Landauer reading was found for each spike, and an average of those correction factors for a particular analysis batch was applied (multiplied) to each Landauer measured value in that batch. Such corrections averaged a 19% increase. Another quality assurance procedure was to place two detectors side by side for exposure in approximately one-tenth of all homes. Sixty-four such tests were conducted. The coefficient of variation for the duplicate readings was 12%, which is thus a measure of the precision of individual radon concentration measurements.

The radon detectors were placed in the house after administering the questionnaire and thus determining the usage of various parts of the house. Detectors were always placed in the living area most often used, in the present bedroom, and in any former bedroom. Also, a detector was placed in any other level of the house that had been used on average for one or more hours per week. Typically this was the basement, but occasionally an upper story of the house when the bedroom was on the ground level.

The exposure rate was then calculated as a doubly weighted average of the various detector measurements: first, an average weighted by the fraction of hours per week usage of the particular area in a given lifestyle period, and second, an average of such averages weighted by the number of years of each lifestyle period during residency in the house (the most recent five years being excluded as a latency period). This is a more elaborate and accurate method than that used in the pooling of data (Krewski et al. 2005, 2006), where a "living area" (sometimes an average of the living area and bedroom) measurement was used. The importance of resident mobility within the house in determining the average exposure has been studied and emphasized by the Iowa group (Field et al. 2000). A sub-analysis presented below supports this thinking. Two extreme examples that occurred in this study illustrate the point. One subject with full-time employment lived in a two-story house but spent 50 h per week in the basement. Another subject lived entirely in the basement for a number of years before building the upper two floors of the house.

Several yearlong etch-track detector tests of outdoor Worcester County air yielded either below detectable, or barely detectable, concentrations (average $\sim$10 Bq m^{-3}). Thus, only in-house exposure was considered in this study. It is worth mentioning that no exposure contribution was imputed for any of this study's subjects; all contributions were measured. The few subjects for whom exposure measurements were lost (in spite of a written request on the detectors to be notified in case of death, occupancy change, etc.) were dropped from the study. For our study population of 597 subjects, we found the mean (standard deviation, SD) and median radon concentrations for the living area to be 63.5 (79.4) and 44.0, for the bedroom to be 61.6 (77.6) and 43.3, and for the basement (419 subjects) to be 176.8 (185.7) and 133, all in units of Bq m^{-3}.

One detector problem encountered in this study is worth mentioning. The EPA furnished the detectors for this study all at once, and the manufacturer did not list any shelf life for them. Thus, after six years into the study, it was a surprise to find that the "blanks" began to show small non-zero readings. A conversation with the detector maker[§] revealed several things: (1) there is an aging phenomenon in etch-track detectors which causes the background (unexposed) reading to increase with time; and (2) the reading procedure of the detector maker uses a background subtraction procedure determined from samples of the same plastic sheets (typically held for four years) that the exposed detector came from. The conversation thus affirmed a procedure of subtracting the average reading of the "blank" detectors from the readings of exposed detectors in that batch. Many "blanks" were then placed in the following batches to better evaluate the effect until new detectors were furnished. A plot of all the corrected measurements vs. the time of measurement showed no secular variation, thus supporting the subtraction procedure.

STATISTICAL ANALYSIS

All analyses were performed using the statistical software package Stata Release 8.0 (Stata Corp. 2003). As an initial step, exploratory analyses were performed on the data to summarize and quantify data spread and to look for important trends. Initial confirmatory analyses were used to investigate the statistical associations between the outcome of lung cancer (case or control) and several explanatory variables. In order to test for statistical associations, the chi-squared goodness-of-fit test was used on the categorical data, while the two-sampled t test was used for continuous outcomes. The non-parametric Kruskal-Wallis test for differences in the medians was also used. Potential outlier observations were identified using the Extreme Studentized Deviate (ESD) statistic method as described by Rosner (2000).

Conditional logistic regression was used to model the binary outcome of cancer status on radon exposure rate (in Bq m^{-3}) while controlling for potential confounders including years of residency, smoking status, education ($<$high school, high school graduate, and at least some college), household income ($\leq$\$30,000 vs.

[§] Private communication, Mark Salasky, Tech/Ops Landauer; 1996.

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>$30,000), and total years of job exposure to known or potential carcinogens (0 y, 1–9 y, and ≥10 y). Due to the large number of respondents who refused to give their household incomes or, to a lesser extent, education level, refusals for these two variables were considered as separate categories in the regression models.

Persons were considered former smokers if they had not smoked within two years of their interview date. Current smokers were classified into categories of pack-years smoked, while former smokers were categorized by the time since last smoked. The number of filtered cigarettes smoked was multiplied by a weight factor of 0.8 compared to unfiltered cigarettes. "Filtered" cigarettes have changed with time over the decades of this retrospective study, and smokers' response to them has been found to change also, making any such factor rather speculative. The assumption of a modest reduction of inhaled carcinogens of 20% seems to be reasonable, and was used in calculating smoking intensity. Pack-years of smoking were calculated as the lifetime-averaged number of packs smoked per day multiplied by the total number of years of smoking. The number of years smoked was given to the nearest year.

Because of the importance of smoking as a potential confounder, several alternative ways of modeling smoking into the multivariable regression models were considered. Preliminary univariate analyses and log-odds plots revealed a strong positive relationship between pack-years smoked and cancer among current smokers, and an inverse, non-linear relationship between time since last smoked and cancer among former smokers. Among former smokers, initial analyses revealed no statistical correlations between pack-years and cancer. Neither age when first smoked nor age at quitting for former smokers was found to be statistically associated with cancer. In addition, no statistically significant multiplicative interaction terms between smoking and radon were found. Based on these preliminary results, it was determined that the smoking data were best modeled with categories of pack-years for current smokers, and categories of time since last smoked for former smokers.

The total job-related exposure in years to all the known and potential carcinogens, listed above, was taken as a covariate. No data were available on the intensity of the exposure. Preliminary univariate analyses on individual compounds revealed some marginal statistical associations with lung cancer; however, these results became statistically non-significant once smoking was controlled for. Nevertheless, since it is important to control for exposure to other carcinogens when looking at the effects of radon on lung cancer, it was decided that this exposure could be best quantified as an index of total, cumulative years exposed to all the compounds considered.

Log-odds plots of the data suggested that there was a non-linear dose-response relationship between radon exposure and lung cancer. Therefore, radon exposure was considered as a categorical variable to allow for this potential non-linearity. In addition, radon exposure was modeled with a smooth function using natural cubic spline terms with two degrees of freedom (Hastie and Tibshirani 1990). Natural spline terms for radon exposure were obtained from the data set using the 'ns' function from the statistical package R (R Development Core Team 2005). Since neither analysis imposed a theoretical risk-vs.-exposure functional dependence, the data thus determined their own functional shape. For comparison, a fit to the LNT model was also calculated.

RESULTS

Summaries of demographics and radon-exposure for the 200 cases and 397 controls in the study are presented in Table 1. Controls had a mean (SD) radon exposure rate of 66.3 (65.2) Bq m^{-3} and a median exposure of 50.1 Bq m^{-3}. In contrast, cases had a mean (SD) and median radon exposure of 67.5 (118.5) Bq m^{-3} and 43.7 Bq m^{-3}, respectively. However, one outlier among the cases was identified at 1,511 Bq m^{-3}. With this outlier removed, the mean (SD) and median for cases dropped to 60.2 (59.4) and 43.6 Bq m^{-3}, respectively, a difference that is statistically lower than that of the controls ($p = 0.047$ for means and $p = 0.030$ for medians via the Kruskal-Wallis test). This comparison of the simplest measure of exposure of cases and controls makes the possibility highly unlikely that these data are consistent with a linear increase in the risk of lung cancer with increasing radon exposure over the low dose region covered. Fig. 1 shows

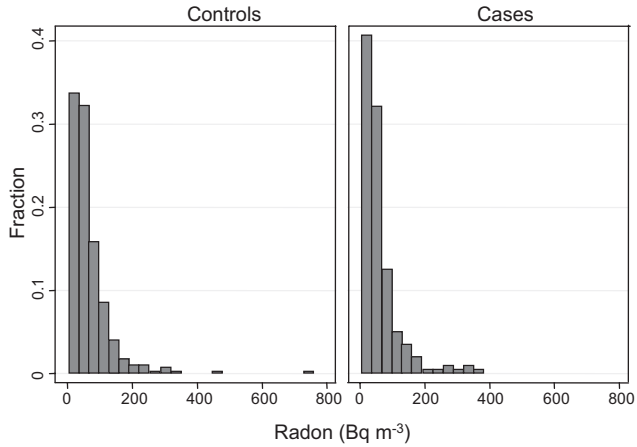

Fig. 1. Distribution of radon exposures (Bq m^{-3}) by cases and controls. One outlier at 1,511 Bq m^{-3} among the cases is not shown.

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the distribution of radon exposure for both cases and controls.

Among the sample population, cases tended to have a marginally statistically shorter mean number of years of residency in their homes than controls [28.5 (12.1) vs. 30.6 (12.1) y, $p = 0.049$]. Almost 42% of controls reported having at least some college as compared to 20% of cases, a difference that is highly significant ($p < 0.001$). Controls had statistically significantly higher family incomes than cases, with almost 48% of controls reporting household incomes greater than \$30,000 y^{-1} as opposed to 29% of cases in this income category ($p < 0.001$). The percent of those who refused to give a household income was high for both groups (12% for controls and almost 17% for cases). A higher proportion of cases than controls also tended to have at least 10 y of occupational exposure to potential carcinogens (21% vs. 14%), an increase that is not statistically significant ($p = 0.112$).

Not surprisingly, cases were much more likely to be current smokers than controls. Approximately 53% of cases reported that they were smokers at the time of interview, as compared to only 10% among the controls ($p < 0.001$). Similarly, only 7.5% of cases reported being never smokers as compared to almost 41% among the controls ($p < 0.001$). The proportion of former smokers was about equal between both groups (40% for cases and 49% for controls).

Table 2 shows the unadjusted ORs and corresponding 95% CIs for lung cancer and several predictor variables based on conditional logistic regression models. In this analysis, the radon variable was categorized into 6 exposure rate variables with the base category ranging from 0–<25 Bq m^{-3}. Other break points, 50, 75, 150, and 250 Bq m^{-3}, were chosen to roughly equalize category populations. This univariate regression analysis revealed a significant decrease in cancer rates as radon exposure increased to about 150 Bq m^{-3}. In comparison to the lowest radon category, those with radon exposures in the 25–<50, 50–<75, and 75–<150 Bq m^{-3} categories have a statistically significant lower odds of cancer with deduced ORs (95% CI) equal to 0.53 (0.32, 0.87), $p = 0.012$; 0.45 (0.26, 0.77), $p = 0.004$; and 0.44 (0.25, 0.77), $p = 0.004$, respectively. Study participants in the 150–<250 Bq m^{-3} exposure category were half as likely to be cases as controls; however, this result is not

Table 2. Unadjusted ORs (95% CI) of cancer by radon exposure (as a categorical variable), smoking status, income, education, and total job exposure.

Variable	Cases/Controls	Odds ratio[a]	95% CI
Radon exposure (Bq m^{-3})			
<25	57/70	1.00	Reference
25–<50	60/127	0.53	(0.32, 0.87)[d]
50–<75	34/89	0.45	(0.26, 0.77)[d]
75–<150	34/86	0.44	(0.25, 0.77)[d]
150–<250	8/18	0.49	(0.19, 1.28)
≥250	7/7	1.20	(0.40, 3.59)
Smoking			
Never smoked	15/162	1.00	Reference
Last smoked 3–5 y	20/13	17.66	(6.25, 49.87)[e]
Last smoked 6–10 y	22/16	19.50	(6.83, 55.69)[e]
Last smoked 11–15 y	15/31	6.12	(2.33, 16.11)[e]
Last smoked >15 y	23/136	2.09	(0.92, 4.75)[c]
Smoker 5–30 pack-y	15/12	10.75	(3.53, 32.69)[e]
Smoker 30–50 pack-y	40/12	50.23	(17.83, 141.49)[e]
Smoker 50–60 pack-y	16/7	49.26	(13.50, 179.75)[c]
Smoker >60 pack-y	34/8	68.39	(21.80, 214.56)[e]
Income[b] (\$ y^{-1})			
<30,000	109/159	1.00	Reference
≥30,000	58/190	0.37	(0.23, 0.60)[e]
Education[b]			
<High school	67/77	1.00	Reference
High school graduate	90/149	0.66	(0.43, 1.01)[c]
At least some college	40/165	0.22	(0.13, 0.38)[e]
Total job exposure (y)			
0	134/290	1.00	Reference
1–9	25/52	1.07	(0.63, 1.81)
≥10	41/55	1.74	(1.07, 2.82)[d]

[a] ORs and 95% CIs obtained from univariate conditional logistic regression.
[b] Refusals removed.
[c] $p \leq 0.1$.
[d] $p \leq 0.05$.
[e] $p \leq 0.001$.

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statistically significant [OR (95% CI) = 0.49 (0.19, 1.28), $p = 0.143$]. The highest category of radon exposure (≥250 Bq m^{-3}) predicts an increase in the odds of cancer as compared to those in the base category, but the OR is not statistically significant [OR (95% CI) = 1.20 (0.40, 3.59), $p = 0.746$].

Initial regression analyses also revealed a decrease in the odds of cancer among former smokers as the time since cessation of smoking increased. Former smokers with 3 to 5 y and with 6 to 10 y since quitting were 17.7 and 19.5, respectively, times more likely to develop lung cancer as compared to the base group of never smokers, an increase that is highly statistically significant ($p < 0.001$ for both groups). Those who last smoked 11 to 15 y prior to interview were only 6 times more likely to be cases compared to never smokers, a result that is also highly significant [OR (95% CI) = 6.12 (2.33, 16.11), $p < 0.001$]. Former smokers who had not smoked for at least 15 y had an estimated increase in cancer risk that is not statistically greater than for never smokers [OR (95% CI) = 2.09 (0.92, 4.75), $p = 0.078$].

Among current smokers, there was clearly a trend toward increasing risk as the number of pack-years of smoking increased. For example, those with 5 to 30 pack-years of smoking had an estimated 11-fold risk in cancer compared to never smokers [OR (95% CI) = 10.75 (3.53, 32.69), $p < 0.001$] while those with more than 60 pack-years of smoking had a cancer risk about 68 times greater than the never smokers [OR (95% CI) = 68.39 (21.80, 214.56), $p < 0.001$]. In fact, 34 of the 42 participants with greater than 60 pack-years of smoking were cases, as compared to only 15 cases among the 177 never smokers in the study. No current smokers reported less than 5 pack-years of smoking.

Other factors that were statistically associated with cancer risk include education level, household income, and total years of job exposure to known or potential carcinogens. Those study participants who were high school graduates had two-thirds the risk of cancer as compared to those with less than a high school education, a difference that approaches statistical significance [OR (95% CI) = 0.66 (0.43, 1.01), $p = 0.057$]. Participants with at least some college had an OR of 0.22 (0.13, 0.38) of cancer, a decrease in risk that is highly significant ($p < 0.001$). Similarly, those with family incomes greater than \$30,000 y^{-1} had a highly statistically significant reduced cancer risk as compared to those making less than \$30,000 y^{-1} [OR (95% CI) = 0.37 (0.23, 0.60), $p < 0.001$]. In terms of occupational exposure, there was an almost two-fold cancer risk among those who were exposed to known or potential carcinogens for 10 or more years on the job as compared to those with no job-related exposure, an increase that is statistically significant [OR (95% CI) = 1.74 (1.07, 2.82), $p = 0.027$]. Those with one to nine years of job-related exposure had no significant increased cancer risk when compared to those with no occupational exposure.

Unadjusted ORs were calculated for the three cell types that together account for about three-quarters of the cases: adenocarcinoma (59 cases, 117 controls), small cell undifferentiated (44 cases, 87 controls), and squamous cell carcinoma (44 cases, 88 controls). The unadjusted ORs for adenocarcinoma were below unity with statistical significance between 50 and 150 Bq m^{-3}. For the five increasing exposure categories enumerated above, the ORs (95% CI) were 0.53 (0.22, 1.25), $p = 0.147$; 0.28 (0.097, 0.82), $p = 0.020$; 0.31 (0.11, 0.91), $p = 0.032$; 0.38 (0.059, 2.39), $p = 0.30$; 2.72 (0.23, 31.5), $p = 0.43$. The unadjusted ORs for squamous cell carcinoma and small cell undifferentiated were without statistical significance.

Results from multivariable regression analyses are presented in Table 3. Two logistic multivariable models were considered: model 1 which categorized radon exposure into the six separate categories considered in the univariate logistic analyses, and model 2 in which radon exposure was fitted by natural cubic spline terms. Natural spline terms with between 2 and 4 degrees of freedom were considered (e.g., 1 to 3 knots) in order to give the regression model maximum flexibility to fit the data. Preliminary results revealed that varying the degrees of freedom produced overlapping curves and approximately equal fits to the data. Since spline terms with 2 degrees of freedom give a more parsimonious model than models incorporating terms with higher degrees of freedom,

Table 3. AORs (95% CI) by radon categories controlling for smoking, residency, job exposure, income, and education (model 1). Model 2 gives AORs for continuous radon exposure modeled with natural cubic spline terms with 2 degrees of freedom.[a]

	Model 1 AOR (95% CI)	Model 2 AOR (95% CI)
Radon exposure (Bq m^{-3})		
<25	1.00 (Reference)	0.75 (0.55, 1.03)[b]
25–<50	0.53 (0.24, 1.13)[h]	0.39 (0.14, 1.07)[h,c]
50–<75	0.31 (0.13, 0.73)[i]	0.35 (0.12, 1.04)[h,d]
75–<150	0.47 (0.20, 1.10)[h]	0.35 (0.13, 0.99)[i,e]
150–<250	0.22 (0.04, 1.13)[h]	0.36 (0.12, 1.10)[h,f]
≥250	2.50 (0.47, 13.46)	0.47 (0.11, 2.04)[g]

[a] Reference = 4.4 Bq m^{-3}.
[b] 12.5 Bq m^{-3} v. 4.4 Bq m^{-3}.
[c] 37.5 Bq m^{-3} v. 4.4 Bq m^{-3}.
[d] 62.5 Bq m^{-3} v. 4.4 Bq m^{-3}.
[e] 112.5 Bq m^{-3} v. 4.4 Bq m^{-3}.
[f] 200 Bq m^{-3} v. 4.4 Bq m^{-3}.
[g] 880.5 Bq m^{-3} v. 4.4 Bq m^{-3}.
[h] $p \leq 0.1$.
[i] $p \leq 0.05$.

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results using this fit are presented under model 2 in Table 3. The AORs for radon exposure under model 1 were calculated with <25 Bq m^{-3} as the base category of comparison, while under model 2, 4.4 Bq m^{-3} was used as the base of comparison to calculate the AORs at the midpoints of the model 1 radon categories. The value at 4.4 Bq m^{-3} was chosen as the base group in model 2 since this was the lowest radon reading observed in this study. Under model 1, those in the 50–<75 Bq m^{-3} category of radon exposure had roughly one-third the cancer risk of those in the under 25 Bq m^{-3} category, a result that is statistically significant [AOR (95% CI) = 0.31 (0.13, 0.73), $p = 0.008$]. However, three other categories, 25–<50, 75–<150, and 150–<250 Bq m^{-3}, demonstrate a statistical trend toward a decreased risk, giving deduced AORs (95% CI) of 0.53 (0.24, 1.13), $p = 0.099$; 0.47 (0.20, 1.10), $p = 0.083$; and 0.22 (0.04, 1.13), $p = 0.069$, respectively. Those in the ≥250 Bq m^{-3} category had a 2.5-fold increase in cancer risk compared to the base group, but this increase is not statistically significant [AOR (95% CI) = 2.50 (0.47, 13.46), $p = 0.285$]. There was less precision and hence a larger CI in the ≥250 Bq m^{-3} exposure category because of a lack of cases and controls with high exposure values. Within the study population, only 14 (2.4%) participants were in the ≥250 Bq m^{-3} category.

Modeling radon exposure as a smooth function using natural cubic splines (model 2) produces ORs as a continuous function of exposure. Model 2 results presented in Table 3 are the values of the continuous function at the centers of the exposure categories. These results indicate a decreased cancer risk for those in the 75–<150 Bq m^{-3} category as compared to the reference category that is marginally significant ($p = 0.048$). In addition, those in the 25–<50, 50–<75, and 150–<250 Bq m^{-3} categories have a decreased cancer risk that approaches statistical significance compared to the reference category with AORs that have associated p-values equal to 0.068, 0.058, and 0.078, respectively. Model 2 deduced an AOR for subjects in the exposure category ≥250 Bq m^{-3} that was less than one also, but with no significance [AOR (95% CI) = 0.47 (0.11, 2.04), $p = 0.312$]. Fig. 2 shows the AORs, on the natural log scale, and associated 95% CIs for the discrete radon categories under model 1 as well as the continuous AORs (again on the natural log scale) obtained from model 2. A model 2 curve using 3 degrees of freedom (not shown) closely follows the plotted 2 degrees of freedom curve below 300 Bq m^{-3} and then rises somewhat faster, being above 1.0 at the last plotted discrete point [e.g., deduced AOR = 1.41 (0.06, 34.23) at 880.5 Bq m^{-3}]. Model 2 gives deduced AORs that are marginally statistically significant ($0.048 \leq p \leq 0.05$) in the region of radon exposure from about 85 to 123 Bq m^{-3}. Fig. 3 shows the continuous AORs and associated 95% CIs (dashed lines) obtained from model 2 for exposures below 250 Bq m^{-3} on a linear scale.

Multivariable regression analyses also revealed that income and occupational exposure are no longer significantly associated with cancer risk after controlling for education, smoking, and years of residency. However, there is a statistical trend towards an increased risk for those with 10 y or more of job-related exposure ($p \leq 0.13$) from both models 1 and 2. Education remains

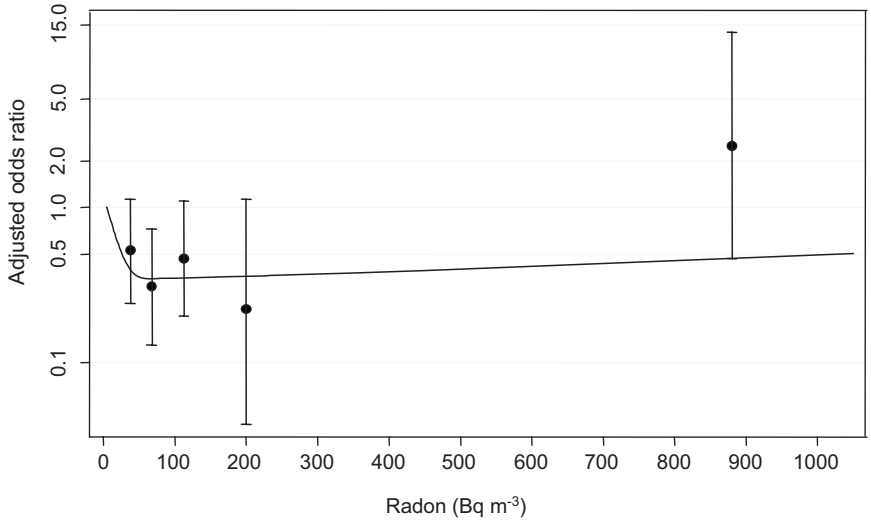

Fig. 2. Plot of AORs and corresponding 95% CIs obtained from model 1 at the midpoint of exposure and continuous AORs obtained from model 2. Odds ratios for model 2 are normalized to 1.0 at 4.4 Bq m^{-3}, the lowest observed radon exposure.

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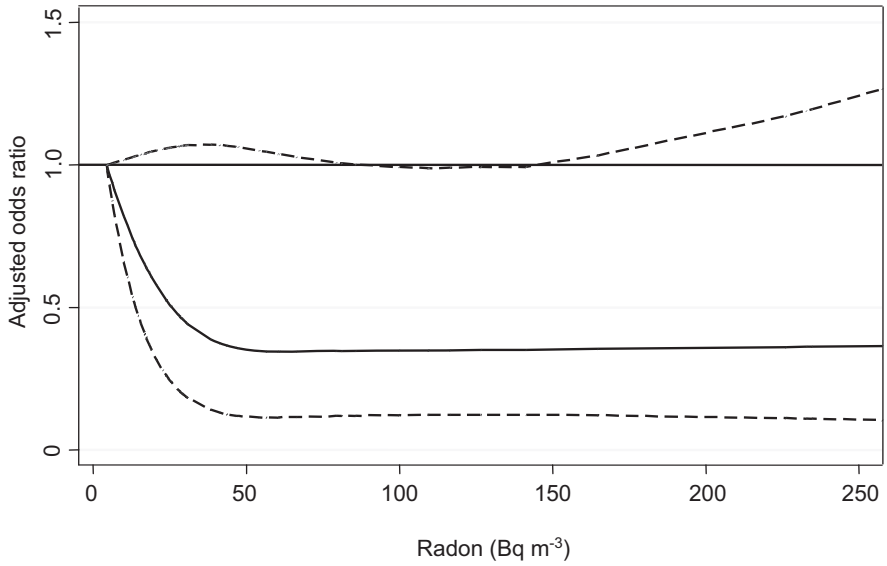

Fig. 3. Plot of AORs and corresponding 95% CIs (dash lines) obtained from model 2 for radon exposures less than 250 Bq m^{-3}. Odds ratios are normalized to 1.0 at 4.4 Bq m^{-3}.

statistically associated with cancer risk even after adjusting for the other covariates, with college-educated participants having approximately one-third the risk as compared to those with less than a high school education [AOR (95% CI) = 0.30 (0.13, 0.69), $p = 0.005$, model 1, and AOR (95% CI) = 0.31 (0.14, 0.69), $p = 0.004$, model 2]. Those who refused to give their education status and those with a high school degree had no statistically different cancer risk when compared to those with less than high school. AORs for the each of the three cell types discussed above were completely lacking in significance under either model 1 or 2.

Because other studies of lung cancer risk vs. residential radon exposure, including the pooling study, have compared their data to the LNT model, a fit to that imposed model was calculated here. A positive slope (95% CI), albeit statistically insignificant, of +0.04 (−0.20, 0.35) per 100 Bq m^{-3}, was found. The positive risk values at the higher exposure values pull the best-fit linear function upward in spite of the large hormetic dip at the lower values. The likelihood ratio test was used to determine if the regression model 2 with natural spline terms gives a superior fit to the data as compared to the linear model. This test resulted in a marginally significant result ($p = 0.0496$) that corresponds in magnitude to the p-values associated with the AORs deduced from model 2.

According to both models 1 and 2, the AOR per year of residency was very close to unity (0.99). This indicates that years of residency had little statistical effect on this study's deduced cancer risk. Nevertheless, admission of subjects with as little as 10 y of residency is a weakness of this study. To address this weakness, a sub-analysis of model 1 that included only subjects with at least 20 y of residency was performed. Because conditional logistic analysis was used, case-and-two-control triads were eliminated from the analyses if the case or both controls of the triad had a residency of less than 20 y. This cutoff at 20 y reduced the sample size from 597 to 348 subjects. Recalculating the univariate analysis of Table 2 with this data subset did not change the unadjusted ORs substantially but did, of course, expand the CIs because of the reduced statistical power. For comparison to Table 2, the new ORs and 95% CIs for the categories of increasing radon exposure were: 0.57 (0.31, 1.04), $p = 0.067$; 0.41 (0.20, 0.83), $p = 0.013$; 0.54 (0.28, 1.05), $p = 0.071$; 0.53 (0.13, 2.19), $p = 0.376$; and 1.08 (0.21, 5.68), $p = 0.926$.

When radon as a categorical variable was considered and covariates listed under model 1 controlled for in this sub-analysis, the AORs were greatly reduced for the 25–<50 and 50–<75 Bq m^{-3} categories of radon exposure as compared to the results presented in Table 3. Despite the reduced sample size, AORs for both categories were statistically less than one. Those in the 25–<50 Bq m^{-3} category gave an AOR (95% CI) = 0.24 (0.07, 0.85), $p = 0.027$, while those in the 50–<75 Bq m^{-3} had an AOR (95% CI) = 0.11 (0.02, 0.60), $p = 0.011$. The results for the 75–<150, 150–<250, and ≥250 Bq m^{-3} radon categories also differ from the results presented in Table 3, with those in the 75–<150 and 150–<250 Bq m^{-3} exposure categories having an increased risk, and those in the ≥250 Bq m^{-3} radon category having a decreased risk of cancer compared to the results using the

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full data set. However, the AORs were not statistically different from one for any of these three categories in the sub-analysis, reflecting its loss of statistical power [AOR (95% CI) = 0.70 (0.21, 2.31), $p = 0.564$; AOR (95% CI) = 1.13 (0.06, 21.62), $p = 0.934$; and AOR (95% CI) = 0.73 (0.06, 8.99), $p = 0.804$ for the 75–<150, 150–<250, and ≥250 Bq m^{-3} radon categories, respectively]. While the complete loss of statistical significance in the three highest exposure categories is not surprising in view of the loss of 42% of the subjects in this sub-analysis, the lowering of the AORs in the lower two exposure categories and their increased statistical significance at being less than one is quite remarkable. These changes in AORs are difficult to explain given the nature of multivariable regression analyses. However, these results suggest the possibility that a greater nonlinear association between radon and cancer risk would have been seen if available resources had allowed for enrolling only subjects with a residency of ≥20 y, as the Iowa study (Field et al. 2000) was able to do.

A second alternative analysis based on model 1 was considered where radon exposure was calculated as a simple average of the living room and bedroom exposures, the "living area" exposure of the pooling study (Krewski et al. 2005, 2006), in contrast to the mobility-weighted average approach. Interestingly, with the exception of the highest radon exposure category of ≥250 Bq m^{-3}, this alternative model produced ORs adjusted for the covariates listed in Table 3 that were 26 to 38% larger than those obtained using the weighted average method. In addition, the *p*-values for the alternative AORs increased substantially in every category, with only the 50–<75 Bq m^{-3} category retaining statistical significance [e.g., AOR (95% CI) = 0.73 (0.35, 1.52), $p = 0.396$; AOR (95% CI) = 0.39 (0.17, 0.91), $p = 0.029$; AOR (95% CI) = 0.59 (0.25, 1.38), $p = 0.222$; AOR (95% CI) = 0.30 (0.06, 1.59), $p = 0.157$; and AOR (95% CI) = 2.20 (0.38, 12.77), $p = 0.381$ for the 25–<50, 50–<75, 75–<150, 150–<250, and ≥250 Bq m^{-3} radon categories, respectively]. Note that in every category this less accurate measure of exposure caused the AORs to move closer to unity, that is, to blur out the functional dependence. Also, note that in all but the highest (and least significant) exposure category the 95% CIs increased from 23 to 40%, demonstrating that the pooling study measure of exposure produces a greater randomness or misspecification in the exposure values compared to the weighted average used in this study.

Because of the substantial number of cases and controls that were interviewed by proxy (21.5% for cases, 3.3% for controls), a third sub-analysis was performed using only those data obtained from the participant interviews. The statistical results in the unadjusted case were unaffected by this analysis. However, in the multivariable model, the trends towards significance disappeared for radon categories less than 250 Bq m^{-3}, but the deduced AORs for these categories were still less than unity. A trend towards significance persisted in the ≥250 Bq m^{-3} category, giving an AOR of 9.35 ($p = 0.067$) as compared to the reference category (model 1). An investigation to understand this found only one thing: smokers interviewed by proxy had a statistically higher number of pack-years as compared to smokers interviewed in person. Whether this is proxy recall bias is unclear, and whether it alone could account for the loss of significance is also unclear. Of course, a lower statistical power from the loss of a quarter of the subjects could also contribute to the loss of statistical significance in the regression model.

DISCUSSION

The results of this study differ strongly from previous case-control studies concerning the risk of lung cancer from residential exposure to radon. The data here exhibit a striking protective or hormetic dip in the low dose rate region for both models 1 and 2. The four exposure categories between 25 and 250 Bq m^{-3} have an average AOR of 0.38 for model 1 and 0.36 for model 2. The AOR is less than 1.0 with statistical significance for model 1 between 50 and 75 Bq m^{-3} and with marginal statistical significance for model 2 between approximately 85 and 123 Bq m^{-3} (ranges below the EPA action level of 4 pCi L^{-1} = 148 Bq m^{-3}). This result was entirely unexpected. There have been many other reports in case-control studies of ORs below one in the low dose region but in all cases without statistical significance (Blot et al. 1990; Letourneau et al. 1994; Alavanja et al. 1994, 1999; Auvinen et al. 1996; Kreuzer et al. 2003; Baysson et al. 2004; Wichmann et al. 2005; Sandler et al. 2006). What reasons can be offered for this difference?

One important aspect of any radon study is careful dosimetry. Year-long measurements of radon with constant calibration of detectors using spikes, blanks, and duplicates are necessary. Equally important is the use of detectors in multiple house locations to account adequately for the subjects' mobility in the house. It is of great importance to determine this mobility, not just for the subjects' present lifestyle (full-time work, part-time work, retirement, child-rearing, etc.) but for all previous lifestyle periods in that house. This requires careful questioning of subjects and forming of doubly weighted averages. While this study was begun with this approach in 1990, more than a few studies performed since have not held to this standard. However, the Iowa study, the most elaborate one to date, did emphasize the importance

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of this standard, but it did not find an OR dip below one (Fisher et al. 1998; Field et al. 1998a and b, 2000). As a test of this measurement standard, the data were reanalyzed using simply the average of living area and bedroom detector readings as the measure of exposure, as in Krewski et al.'s pooling studies (Krewski et al. 2005, 2006). There was a significant tendency for all OR values to move toward unity (from both above and below) and for CIs to enlarge and so remove statistical significance. One dosimetry difference of this study compared to the Iowa study should be noted. The high outdoor radon concentration in Iowa required assuming an exposure (35 Bq m^{-3}) of subjects outside their houses, while, as discussed above, radon concentrations in outdoor Worcester County air were sufficiently low ($\sim$10 Bq m^{-3}) as to be ignored.

Since cigarette smoking is known to be the dominant cause of lung cancer, at least ten times as lethal as radon as a national mortality cause, it is essential to account for it carefully. The year-by-year smoking histories of the subjects in this study (number and type smoked) were obtained from the interviews. This allowed exploring smoking in many statistical ways, leading to the use of nine smoking categories (Table 3) in our final analysis. Handling of this important confounder by considering both the duration and intensity of smoking among current smokers and length of time since last smoked among former smokers is in line with previously published radon studies (e.g., Wichmann et al. 2005; Krewski et al. 2005, 2006).

Under all the models that were considered, both former and current smoking greatly increased the risk of cancer with a single exception: former smokers who reported not smoking for at least 15 y prior to entering into the study had only a slightly elevated risk of cancer compared to never smokers that was not statistically greater than one (Table 3). Another major finding that was consistent across all the models considered was that those with at least some college had approximately one-third the risk of cancer as compared to those with less than a high school education. Whether this results from nature (genes) or nurture (healthier behavior) is unclear, but there is some indication of the latter. More highly educated people may have a healthier diet containing more anticarcinogens. This hypothesis is supported by findings in Italy which showed a marginally statistically significant reduced lung cancer risk of approximately one-third for those with a high consumption of carrots and tomatoes compared those with a low consumption of these vegetables (Bochicchio et al. 2005). A suggestion of reduced lung cancer risk with increased intake of vegetables, fruits, and juices was also reported for Missouri women (Wright et al. 2002). No significant protective benefit for those with a high school degree, as compared to those with less education, was found.

A rather unique aspect of this radon study design was use of the same health maintenance organization client pool (but not a hospital-based pool as in Baysson et al. 2004) for randomly choosing controls to be matched individually by age and sex to the cases. Because a control should be as identical as possible to its matched case (except, of course, for the presence of primary lung cancer), such a procedure should be superior to choosing the controls from the general population. This closer matching of cases and controls can potentially adjust for confounders that are not easily quantified or adjusted for in a regression analysis. Compared to population-based recruiting, controls in this study came from a more similar socio-economic, geographic, and medical-care stratum of the population. How much difference can that make? The only way to answer that would be to recruit a new set of 400 controls matched to the 200 cases from the general population in Massachusetts and re-analyze the data. Unfortunately, resources are not currently available for such a study.

Because our results conflict with the LNT hypothesis, it is worth reconsidering that issue. Its appeal originally stemmed from two ideas. First, a linear increase without a threshold requires but one parameter, a slope, and so is the simplest, nontrivial mathematical model. In the absence of further scientific information, this is naturally the preferred starting point. In time, a theoretical basis for the LNT hypothesis emerged: most cancers are monoclonal, and at typical residential exposures it is exceedingly unlikely that a lung cell will be struck twice by an alpha particle from radon and its progeny even in a person's lifetime. Doubling the exposure doubles the number of cells struck, and so doubles the chances of cancer. There is thus no basis for nonlinearity, and hence LNT is the logical conclusion (NRC 1999). Such reasoning assumes that cells do not communicate with each other. However, the "bystander effect," where nearby cells "know" that a cell has been damaged, is well established for in vitro cellular systems (Morgan and Sowa 2007). It undermines the theoretical reasoning for the linearity supporting LNT since nearby nontargeted cells could potentially experience either detrimental effects such as genetic damage (Morgan 2003) or non-detrimental effects such as a radio-adaptive response (Iyer and Lehnert 2002). Nevertheless, the importance of the bystander effect as a modifier on radiation responses at the tissue and organ level and, by extrapolation, on human health is unclear (Morgan and Sowa 2007). In opposition to evidence supporting nonlinearity, however, a third support for LNT has now appeared: the pooling of seven studies (Krewski et al. 2005, 2006) finds a linear

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dependence of excess odds ratios [EOR (95% CI) = 0.10 (−0.01, 0.26) at 100 Bq m^{-3}, $p = 0.10$].

So what can be made of this? First, it should be said that, although BEIR VI backs the LNT hypothesis, it acknowledges the bystander effect and states, "The committee acknowledged that other relationships [than LNT], including threshold and curvilinear relationships, cannot be excluded with complete confidence, particularly at the lowest levels of exposure" (NRC 1999). The Phase I study of BEIR VII (NRC 1998) states, "Enhanced expression of p53 [gene] has also been reported in bystander cells in cultures exposed to alpha rays" (Hickman et al. 1994), and then goes on to state, "The existence of inducible repair systems that improve the efficiency of DNA repair has fueled speculative proposals that low levels of ionizing radiation actually have beneficial, rather than deleterious, effects. These suggestions of hormesis in the radiation response must be considered seriously but critically."

How could such nonlinear dependences—a hormetic dip, in this study—be missed in other case-control studies? One possible contributing effect would be that the reference category includes a substantial portion of those subjects that experience the protective effect. In that case, the reference category, normalized to OR = 1, would really contain a sizable population that properly belongs to OR < 1. An increase from such a reference category would be expected. For example, the high outdoor radon concentration in the Iowa study required using a reference category whose upper limit (corresponding to an average exposure *rate* of 58 Bq m^{-3}) covers all of the radon exposure category used here that gave an AOR = 0.53 (model 1) or 0.39 (model 2) and one-third of the next category used here that gave an AOR = 0.31 (model 1) or 0.35 (model 2). The need for a substantial number of low-exposed subjects in order to detect hormesis has been emphasized in a recent review (Calabrese 2005). A second possible contributing effect is inadequate dosimetry, particularly in not accounting properly for in-house mobility and for its differences during earlier lifestyle periods. This could cause a blurring out of an OR dip before its inevitable rise. The sub-analysis of this study using the simpler, pooled-analysis (Krewski et al. 2005, 2006) measure of radon exposure, discussed earlier, gives strong support to this conjecture.

Though the Iowa study is the most rigorous and elaborate study reported to date, the recent pooled analysis of Krewski et al. (2006) should probably be regarded now as the standard of comparison. The present study has both similarities and differences with that pooling. Some basic measures of the studies' data are surprisingly similar: from tables 3 and 5 of Krewski et al. (2006), the mean of the mean values of radon exposures reported (SD) for all cases was found to be 69.8 (46.5) Bq m^{-3} while that of controls was higher at 71.1 (43.0) Bq m^{-3}. In the present study, the mean radon exposure of all cases was 60.2 Bq m^{-3} (one outlier removed) while that of controls was higher at 66.3 Bq m^{-3}. Also, the *unadjusted* ORs (95% CI) calculated using 2-by-2 tables from data presented in table 9 of Krewski et al. (2006) yield: 0.80 (0.71, 0.90), $p < 0.001$; 0.69 (0.60, 0.78), $p < 0.001$; 0.75 (0.63, 0.88), $p < 0.001$; 0.90 (0.78, 1.05), $p = 0.178$; 0.77 (0.62, 0.96), $p = 0.02$; and 0.75 (0.61, 0.93), $p = 0.008$ for the categories 25–<50, 50–<75, 75–<100, 100–<150, 150–<200, and ≥200, respectively, all in Bq m^{-3}. With the exception of the 100–<150 category, all the unadjusted ORs were statistically less than 1.0. These values have their counterpart in the present study. For comparison on an equal footing [individual matching of cases and controls is not considered and radon exposure was determined *using the simple average living area measure* as used in Krewski et al. (2006)], the unadjusted ORs (95% CI) of the present study were: 0.70 (0.45, 1.09), $p = 0.113$; 0.54 (0.32, 0.92), $p = 0.024$; 0.52 (0.31, 0.88), $p = 0.015$; 0.59 (0.22, 1.63), $p = 0.311$; and 1.19 (0.38, 3.71), $p = 0.770$ for the categories 25–<50, 50–<75, 75–<150, 150–<250, and ≥250, respectively, all in Bq m^{-3}.

In spite of these similarities, after adjustment for confounders, this study and the pooling study arrive at strikingly different conclusions: this study finds a hormetic dip (AOR <1.0) persists over a substantial range before a positive cancer risk begins to emerge at higher radon exposure levels; in contrast, the pooling study finds a positive cancer risk throughout the range. The methods used for calculating the risk differ markedly: the present study fits cubic splines to the AOR data, letting the data determine the functional form; the pooling study fits only to chosen functional dependences with the main emphasis on the LNT function. (A forced fit of the present study data to the LNT model also gives a positive slope, albeit statistically insignificant.)

The confounders adjusted for in the final analyses of the two studies differ: the pooling study used age at diagnosis/enrollment, smoking categories, number of residences, and years of residence covered by alpha-track detector measurements; this study used smoking categories, education, and exposure to known or suspected carcinogens. The puzzle that needs to be answered then is how these differing adjustments lead to such different results for data sets that share similar simple hormetic measures of exposure.

In addition, aspects of the study designs may be important. The pooling study is hindered somewhat by having to find a "lowest common denominator" for the

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data of the seven studies, while the present study is not so affected. The present study used controls individually matched to cases, not frequency matching as most of the seven studies used. The present study imputed no data while several of the seven studies used imputed exposure data. The present study used historic-mobility-weighted averages of exposure while the pooling was able to use only a "living area" measurement. The present study matched controls to within ±2.5 y while the pooling study used ±5 y. All the seven pooled studies used population-based controls while the present study used controls from the clients of same health maintenance organization as the cases were from, giving presumably a better socio-economic, geographical, and medical-care stratum match to the cases. Lastly, the present study used only face-to-face interviews for which 21.5% of case interviews were surrogates, while the pooled study included a wider range of interview techniques and had 44.1% surrogates for case interviews. It is hoped that this juxtaposition of both similarities and differences will help to resolve the puzzle posed above.

This paper's final conclusion: the possibility of a hormetic effect on lung cancer at low radiation doses cannot be excluded.

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