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EPIDEMIOLOGICAL EVIDENCE FOR POSSIBLE RADIATION HORMESIS FROM RADON EXPOSURE: A CASE-CONTROL STUDY CONDUCTED IN WORCESTER, MA.

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□ Data from a case-control study of lung cancer and residential radon exposure conducted in Worcester County, Massachusetts, are presented. Lung cancer risk was estimated using conditional logistic regression models that controlled for demographic, smoking, and occupational exposure covariates. Preliminary exploratory analyses using lowess smoothing revealed a non-linear association between exposure and the log odds of lung cancer. Radon exposure was considered by using linear spline terms in order to model this nonlinearity. The best fit of this linear spline model to these data predicted a shift from a positive to a negative slope in the log-odds of lung cancer at a radon concentration of 70 Bq m^{-3}. A statistically significant decrease in cancer risk with increased exposure was found for values ≤ 157 Bq m^{-3} normalized to the reference exposure of 4.4 Bq m^{-3}, the lowest radon concentration measured (adjusted odds ratio (AOR) [95% CI] = 0.42 [0.180, 1.00], p = 0.049). This result is consistent with those reported elsewhere that considered radon exposure with cubic spline terms (Thompson, RE *et al.* 2008). Furthermore, this model predicts an AOR that is numerically less than 1.0 for radon exposures up to 545 Bq m^{-3} versus the above baseline, reference exposure.

Key Words: Radon, Adaptive Response, Hormesis, Lung Cancer

INTRODUCTION

Radon, specifically the ^{222}Rn isotope and its high linear-energy-transfer (LET) alpha emitting progeny, have been shown to be carcinogenic at high doses. This has been confirmed by observed increased rates of lung cancer among miners exposed to excessive amounts of radon gas that becomes trapped and concentrated in the enclosures of underground mines. As far back as the 16th century, it was widely recognized that miners in Central Europe experienced higher mortality rates than the general population from respiratory diseases (Darby *et al.* 2001). Among modern investigators, Samet *et al.* (1991) found a statistically significant standardized mortality ratio [95% CI] for lung cancer = 4.1 [3.1 – 5.1] among a cohort of 3469 male uranium miners in New Mexico. The miners in this study had mean and median radon exposures of 111.4 and 35.0 Working Level Months (WLMs), respectively.

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Because radon is a chemically inert gas, it easily seeps upward from rocks and soil below ground and can accumulate in confined above-ground spaces such as homes. However, the average radiation exposure to the population from radon trapped in homes is much less than that experienced by underground miners. For example, Field *et al.* (2000) found that roughly one-third of the homes measured in the Iowa Radon Lung Cancer Study had radon concentrations that exceeded 11 WLMs (e.g. approximately 4 pCi liter^{-1}) on the first level, suggesting that the mean exposures experienced underground are at least one order of magnitude greater than those seen in the home.

In order to estimate lung cancer risk from residential radon exposure, regulatory and scientific agencies have extrapolated risks seen in the underground miners down to the radon concentrations present in the home. The linear, no-threshold (LNT) model is commonly assumed when making these risk extrapolations. The implication of the LNT model is that there is no threshold level of radiation exposure below which there is no cancer risk, and that a doubling of exposure leads to a doubling of this risk. Based on LNT extrapolations of the miner's data, it has been estimated that there are approximately 18,600 excessive lung cancer deaths in the United States each year due to residential radon exposure (NRC 1999). One justification for LNT is the observed, consistent linearity of the radon-cancer dose-response relationship over the range of exposures seen in the miner studies (Lubin *et al.* 1995). However, the enormous differences in exposure levels seen between underground miners and the general population lead to a great deal of uncertainty in these extrapolation models.

Several case-control studies have been performed over the past two decades with the goal of directly measuring the excess lung cancer risk from residential radon. However, these epidemiological studies are limited by the difficulty in making accurate estimates of cumulative exposures and lack statistical power due to the small study sizes and corresponding low cancer risk (Lubin *et al.* 1995). In an attempt to overcome the issue of low statistical power, two large meta-analyses have been performed that pooled data from case-control studies conducted in North America (Krewski *et al.* 2006) and Europe (Darby *et al.* 2005). Investigators in these studies also assumed LNT and have reported excessive cancer risks under this model directly proportional to increases in radon exposure. Among the North American studies, Krewski *et al.* (2006) reported an excessive odds ratio (EOR) of 0.10 per 100 Bq m^{-3}, a result that trends toward statistical significance (95% CI = [-0.01, 0.26]). However, when the data are restricted to those study participants with ≤ 2 residences and ≥ 20 years with α-track air monitors, these same investigators report a statistically significant EOR [95% CI] per 100 Bq m^{-3} = 0.18 [0.02, 0.43]. Similarly, Darby *et al.* (2005) found a statistically significant EOR [95% CI] per 100 Bq m^{-}

^{3} = 0.08 [0.03, 0.16] in the European pooling study. Under the LNT model used in these pooling studies, the adjusted odds ratio (AOR) is determined by one plus the EOR times the exposure of interest.

Although some investigators have claimed that these large pooling studies confirm once and for all the LNT model for residential radon exposure (e.g. Samet 2006), research in the area of adaptive-protective responses calls into question the scientific validity of the LNT model at the lower doses of radiation exposure. In particular, adaptive-protective responses induced by exposure to low LET ionizing radiation (e.g. x-rays, gamma rays, and beta particles) have been observed that protect against both spontaneous cell damage and cell damage from an initial mutagenic ionizing radiation dose. For example, Redpath *et al.* (2001), showed that exposure of human fibroblast skin cells *in vitro* to gamma radiation doses of up to 10cGy induced an adaptive-protective response among these cells against spontaneous neoplastic transformation. In contrast, Day *et al.* (2007) used a two-dose *in vivo* experiment to demonstrate for the first time that a low follow-on x-ray dose (0.01 – 1 mGy) to mice can induce an adaptive-protective response against a larger, initial whole-body x-ray dose (1000 mGy) given several hours prior.

As an alternative to LNT, Scott *et al.* (2009) have recently proposed a stochastic hormetic relative risk (HRR) model that incorporates both radio-adaptive protection against intermediate doses of high LET ionizing radiation activated by exposure to low LET radiation and the epigenetic silencing of this protective response under the condition of large doses of high LET radiation. This model is stochastic in the sense that the protective thresholds of low LET exposures that activate the adaptive response are assumed to vary from person to person.

This paper presents data from a case-control study of lung cancer and residential radon exposure conducted in Worcester County, Massachusetts, that provides possible epidemiological evidence supporting such a hormetic cancer risk model.

STUDY DESIGN AND DOSIMETRY

The design and dosimetry of the present study have been described in detail elsewhere (Thompson *et al.* 2008). Briefly, a total of 209 cases were recruited into the study, with each case matched to two controls randomly chosen from the same HMO patient population. Case-control matching was based on gender and age to within +/- 2.5 years. Due to loss of radon detectors, the final number of cases and controls in the study was 200 and 397, respectively. No data of radon exposures were imputed in this study. All study participants were clients of the Fallon Clinic \ Fallon Community Health Plan. In addition, all cases and controls were residents of Worcester County, or for a few participants, lived just outside the county line. Extensive face-to-face interviews were given to all study

participants, or in cases of death or illness, to a spouse or offspring. Data obtained included basic demographics, years of residency in the home, a detailed smoking history on the number and type (e.g. filtered or unfiltered) of cigarettes smoked in each decade of life, and occupational exposure to known or suspected carcinogens including heat welding, asbestos, vinyl chloride, formaldehyde, ethylene oxide, x-rays, radioactivity, insecticides, herbicides, and smelter and foundry fumes. Surrogate interviews were given for 3.3% of controls and 21.5% of cases.

In the current study, emphasis was placed on obtaining accurate and extensive within-home radon measurements. Radtrack etch-track detectors (Techs/Ops Landauer, Inc.) were placed in the current homes of all study participants to obtain year-long radon concentration measurements. For a few study participants, detectors were placed in the immediate past residences if they had lived in the home for at least 10 years. Detectors were placed in the current bedroom, living area of the home most often used, and on another level of the home that was occupied for at least one hour per week. Typically, this was in the basement of the residence.

A number of 'blanks' (e.g. unexposed detectors) and 'spikes' (e.g. detectors with known, calibrated exposures) were placed in each batch of detectors. The number of these blanks and spikes in each batch was determined by the U.S. EPA's National Air and Radiation Environmental Laboratory in Montgomery, Alabama. An average correction factor obtained from the calibrated radon exposure of the spikes in each batch was then applied to all the detectors in that batch. Two radon detectors were placed side-by-side in about one-tenth of all homes. These duplicate readings gave a coefficient of variation of 12%.

In order to obtain an accurate assessment of within-home mobility, study participants were asked about the 'wakeful' time spent in various living areas of the home over all lifestyle periods that included full-time and part-time employment outside of the home, child rearing, and retirement. These distributions of weekly in-home usage averaged over all lifestyle periods were used to obtain weighted averages of radon exposure. The importance of using residence mobility to obtain more accurate estimates of radon exposure has been emphasized in the Iowa Radon and Cancer Study (Field *et al.* 2000).

STATISTICAL ANALYSES

All analyses presented here were performed using the statistical software package Stata Release 10.0 (Stata Corp. 2009). Summary statistics were initially obtained from the data and detailed in the results section below. Initial confirmatory analyses were used to test for statistical associations between lung cancer status and the covariates of interest. The chi-square goodness-of-fit test was used for categorical data, while the two

sample t-test, or when the data were not normally distributed the non-parametric Kruskal-Wallis test, was used for continuous variables. More extensive analyses on the binary outcome of cancer status were conducted by the use of univariate and multivariable conditional logistic regression models, producing measures of association in terms of unadjusted odds ratios (OR) and adjusted odds ratios (AOR) and corresponding 95% confidence intervals (CI). The Stata function 'fracpoly' was used to determine the best fit to the data when modeling the dose-response relationship via polynomial functions. Potential confounders controlled for in these regression models include categories of income, education, job exposure, and smoking status, as well as the continuous measure of residency in years. Refusal responses for income and education were considered as separate categories in these models due to the large number of participants who refused to answer these two questions. Based on extensive initial investigations of these data on the relationship of smoking and cancer, it was decided to categorize smoking into never smokers, four groups of former smokers based on years since last smoked, and four groups of current smokers based on pack-years.

Initial log-odds plots and lowess smoothing of the data showed a clear non-linear relationship between case-control status and radon exposure. Several analytical methods were considered to model this non-linear dose-response relationship, including categories of radon exposure, natural or cubic spline terms, linear spline terms, and polynomial functions. Results of regression models that quantified radon exposure with a categorical variable and models that considered natural spline terms have been previously reported (Thompson *et al.* 2008). In the current paper, additional results that include those based on the linear spline model and polynomial functions are presented.

RESULTS

A detailed description of differences in radon exposure and other covariates between the cases and controls has been previously reported in Thompson *et al.* (2008). In summary, cases had a mean (sd) exposure equal to 67.5 (118.5) Bq m^{-3}, slightly higher than that of controls who had a mean (sd) radon exposure of 66.3 (65.2) Bq m^{-3}. However, when one outlier at 1511 Bq m^{-3} was removed, the cases were found to have a marginally statistically significant lower mean exposure than controls: 66.3 Bq m^{-3} for controls versus 60.2 Bq m^{-3} for cases ($p = 0.047$ based on the two-sample t-test of the natural log of exposure). The median exposure for controls (= 50.1 Bq m^{-3}) was also statistically higher than the median for cases (= 43.7 Bq m^{-3}, $p = 0.039$ based on the Kruskal-Wallis test). The lowest radon exposure seen at the study site was 4.4 Bq m^{-3}.

Given the matched design of the study, no differences between cases and controls were seen in terms of gender or age. However, statistically

significant differences were found for the other measured covariates (see Table 1). In general, cases tended to spend fewer years in the current home, be less educated, have less household income, and have more occupational exposure to known or potential carcinogens than controls. Cases had a mean (sd) years of residency equal to 28.5 (12.1) versus a mean (sd) of 30.6 (12.1) years for controls, a difference that is marginally significant ($p = 0.049$). Twenty percent of cases had at least some college education, nearly half that of controls (41.6% obtaining this educational level). In contrast, 33.5% and 19.4% of cases and controls, respectively, had less than a high school education (unadjusted OR [95% CI] = 0.22 [0.13, 0.38] with < H.S. as the reference group and $p < 0.001$). Similarly, about 48% of controls and 29% of cases had household incomes ≥ $30,000 per year, giving an unadjusted OR [95% CI] = 0.37 [0.23, 0.60] (income < $30,000 per year as the reference group and $p < 0.001$). Finally, there was nearly a two-fold increase in cancer risk among

TABLE 1: Statistical associations between lung cancer risk with radon exposure, smoking status, and demographic variables based on the unvariate conditional logistic regression model.

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^{-1}	20/13	17.66	[6.25, 49.87][e]
Last Smoked 6–10 y^{-1}	22/16	19.50	[6.83, 55.69] [e]
Last Smoked 11–15 y^{-1}	15/31	6.12	[2.33, 16.11] [e]
Last Smoked > 15 y^{-1}	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] [e]
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, 2.85][d]

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

study participants with ten or more years of occupational exposure to harmful compounds as compared to those subjects with no such exposure, a result that is statistically significant (unadjusted OR [95% CI] = 1.74 [1.07, 2.82], p = 0.027). Of the covariates listed above, only education level remained a statistically significant risk factor for cancer in the multivariable model.

Not surprisingly, current and former smokers in the study were at a much higher risk for lung cancer as compared to never smokers. Only 15 out of 200 lung cancer cases in the study were never smokers. A highly statistically significant trend, as determined by the STATA command 'tabodds', towards increased lung cancer risk was seen among current smokers as the number of pack-years of smoking increased (see Table 1, $p< 0.001$). Current smokers with a smoking history of between 5 and 30 pack-years had an almost 11-fold increase in cancer risk as compared to never smokers, while those smokers with more than 60 pack-years showed a 68-fold increase in cancer risk as compared to never smokers. Among former smokers, an increased risk of cancer was detected as the number of years since last smoked decreased. Those with between 3 to 5 years since last smoked were found to have an 18 fold increase in cancer risk, while former smokers with more than 15 years since last smoked exhibited a two-fold increase in risk when the odds of cancer for both groups were normalized by the never smokers category. However, the unadjusted odds ratio for former smokers with more than 15 years since last smoked was not statistically different from one, demonstrating no significant increase in cancer risk for this group when compared to never smokers (unadjusted OR [95% CI] = 2.09 [0.92, 4.75]).

In terms of the association between cancer status and radon exposure, exploratory lowess smoothing plots using locally weighted regression models on the log-odds of cancer against radon exposure demonstrated a strong non-linear dose-response relationship (see Figure 1). Initially, this non-linearity was modeled by considering radon exposure as a categorical variable and through the use of natural, cubic spline terms–methods that are described in detail elsewhere (Thompson *et al.* 2008). The use of linear spline terms in the regression analysis (e.g. the 'broken arrow' regression) allows for modeling the dose-response relationship with linear slopes that can shift in value at given 'knots' or inflection points. Modeling the data with a polynomial function has the advantage over the cubic spline model in that it allows for easier calculations of the adjusted odds ratios, and gives a dose-response curve as an easy-to-interpret mathematical function of exposure.

As shown in Figure 1, an investigation of the lowess smoothing suggests that a shift in the dose-response relationship between lung cancer risk and radon exposure exists between approximately 50 and 150 Bq m^{-3}. In order to find the optimal knot, several regression analyses were per-

formed that allowed the inflection point to shift in unit increments from 50 to 200 Bq m^{-3}. The model that maximized the log-likelihood function then determined the optimal knot location. The result of this method suggested a linear spline model with an inflection point at a radon exposure of 70 Bq m^{-3} would best fit the data (see Figure 2). Mathematically, this model is of the form:

$$\text{logit} = \beta_0 + \beta_1 X + \beta_2 (X - 70)^+ + \sum_{j=3}^{p} \beta_j Z_j \qquad \text{[Eq. 1]}$$

where X is the radon concentration (exposure) in Bq m^{-3}, $(X - 70)^+ = 0$ for $X \leq 70$ Bq m^{-3} and $= X - 70$ for $X > 70$ Bq m^{-3}, while the Z_j terms represent addition variables controlled for in the model. Note that for logistic models conditioned on case-control clusters used in this analysis, the coefficient term β_0 in Equation 1 is not estimated by the regression algorithm. Further considerations of a possible second inflection point at between 150 and 200 Bq m^{-3} did not produce a better fit to the data based on adjusted R^2 values of these extended models.

From Equation 1 above, the adjusted odds ratio for radon concentrations ≤ 70 Bq m^{-3} (X) as compared to a given reference value (X_0) can be estimated by

$$\text{AOR} = \exp[\hat{b}_1 (X - X_0)], \qquad \text{[Eq. 2]}$$

while for $X > 70$ Bq m^{-3} and $X_0 \leq 70$, the AOR is given as

$$\text{AOR} = \exp[\hat{b}_1 (X - X_0) + \hat{b}_2 (X - 70)]. \qquad \text{[Eq. 3]}$$

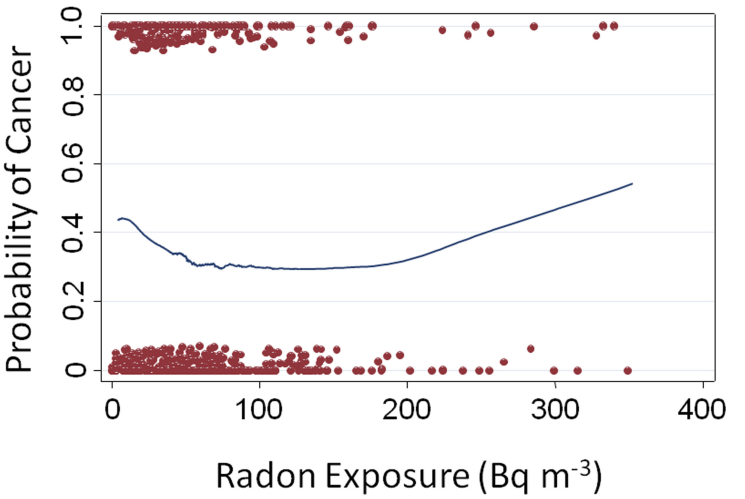

FIGURE 1: Lowess smoothing average of cases and controls. Points near the top of the plot represent cases while those at the bottom represent the controls. These points have been jittered to better show the distribution of cases and controls as a function of radon exposure.

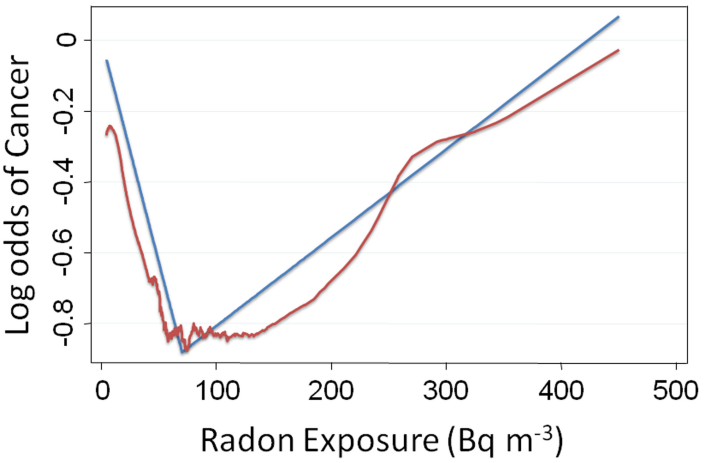

FIGURE 2: Linear spline model superimposed on lowess smoothing of the data. Data are given on the logit (e.g. log odds) scale.

In Equations 2 and 3, $\hat{b}_1$ and $\hat{b}_2$ are the estimated values for the parameters β_1 and β_2 in Equation 1. The values for $\hat{b}_1$ and $\hat{b}_2$, along with their corresponding standard errors (SE), were found to be -0.016 (0.0070) and 0.018 (0.0077), respectively, in the conditional logistic regression model that controlled for smoking status, years of residence in the home, years of occupational exposure to possible carcinogens, and education and income status.

Given the negative value of -0.016 for $\hat{b}_1$ and setting X_0= 4.4 Bq m^{-3}, the lowest radon concentration measured in the study, Equation 2 predicts an approximate 65% reduction in the odds of cancer for a hypothetical exposure at 70 Bq m^{-3} as compared to a hypothetical exposure at this baseline value, a result that is statistically significant (AOR [95% CI] = 0.35 [0.14, 0.85], p = 0.021). Furthermore, even though the model predicts a shift in the dose-response curve at 70 Bq m^{-3}, exposure values much higher than this inflection point give a decreased odds of cancer as compared to the baseline radon concentration. In fact, solving Equation 3 for values of X that correspond to an AOR ≥ 1.0 and setting X_0 = 4.4 Bq m^{-3} predicts a decreased risk up to an approximate exposure of 545 Bq m^{-3}. However, given the standard errors associated with $\hat{b}_1$ and $\hat{b}_2$, this decreased risk becomes statistically insignificant for exposure values ≥ 157 Bq m^{-3} (e.g. AOR [95% CI] = 0.42 [0.180, 1.00], p = 0.049, for 157 Bq m^{-3} v. 4.4 Bq m^{-3}). Conversely, a decrease in radon exposure in the home from 4.4 Bq m^{-3} to 0 Bq m^{-3} would result in a statically significant predicted *increased* cancer risk of approximately 7% (e.g. AOR [95% CI] = 1.07 [1.01, 1.14], p = 0.021, for 0 Bq m^{-3} v. 4.4 Bq m^{-3}).

When considering a polynomial fit to the dose-response curve, a logistic model using a two-term polynomial incorporating square root and natural log functions of radon exposure was found to best fit the data from among all polynomial models with two power terms as determined by the Stata command 'fracpoly'. This logistic model is given in the form:

$$\text{logit} = \beta_0 + \beta_1\sqrt{X} + \beta_2\sqrt{X}\cdot\ln(X) \qquad \text{[Eq. 4]}$$

where X is the radon concentration (exposure) in Bq m^{-3}. This mathematical relationship for the dose response curve is depicted graphically in Figure 3. The estimates and corresponding standard errors for the parameters β_1 and β_2 were found to $\hat{b}_1$ (se) = -0.708 (0.344) and $\hat{b}_2$ (se) = 0.102 (0.052) while controlling for smoking status, years of residence in the home, years of occupational exposure to possible carcinogens, and education and income status.

Again, for conditional logistic regression, the parameter β_0 is not estimated. Polynomial models with three and four power terms that considered combinations of cubic functions of radon exposure and cubic functions for the natural log of radon exposure in addition to the power terms given in Equation 4 were also considered. However, these higher dimensional polynomial models did not improve the fit of the data as determined by the likelihood-ratio test. As a comparison with the linear spline model, again consider a person with a hypothetical exposure of 70 Bq m^{-3}. Under Eq. 4, this person would have a predicted AOR [95% CI] = 0.32 [0.11, 0.90] as compared to the reference exposure of 4.4 Bq m^{-3}, a result that is statistically significant (p = 0.030). Table 2 gives more comparisons of the predicted AORs for these two models alongside those predicted

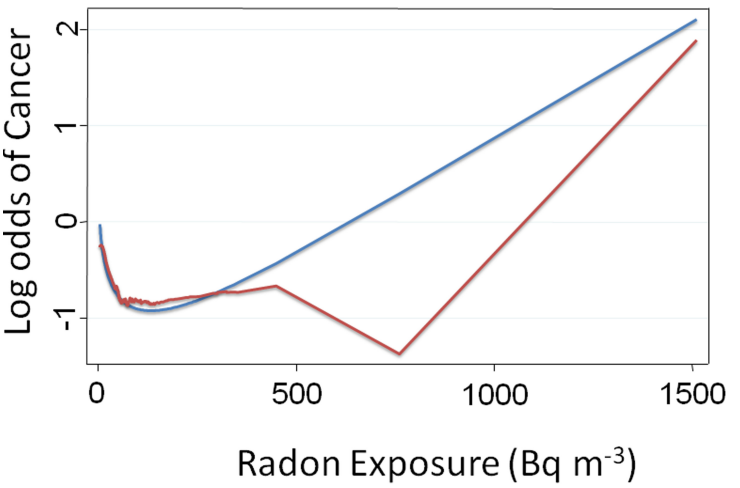

FIGURE 3: Polynomial model superimposed on lowess smoothing of the data. Data are given on the logit (e.g. log odds) scale.

TABLE 2: AORs (95% CI) given by radon categories while controlling for smoking, residency, job exposure, income, and education (Model 1). Model 2 quantifies exposure with natural cubic spline terms (2 degrees of freedom), Model 3 quantifies exposure with linear splines, and Model 4 quantifies exposure with a polynomial function (2 degrees of freedom).

	Model 1 AOR (95% CI)	Model 2 AOR (95% CI)	Model 3 AOR (95% CI)	Model 4 AOR (95% CI)
<25	1.00 (Reference)	0.75 (0.55, 1.03)[a,b]	0.88 (0.79, 0.98)[i,a,b]	0.65 (0.44, 0.96)[i,a,b]
25–< 50	0.53 (0.24, 1.13)[h]	0.39 (0.14, 1.07)[h,c]	0.59 (0.37, 0.92)[i,c]	0.40 (0.18, 0.91)[i,c]
50–< 75	0.31 (0.13, 0.73)[i]	0.35 (0.12, 1.04)[h,d]	0.39 (0.18, 0.87)[i,d]	0.33 (0.12, 0.90)[i,d]
75–< 150	0.47 (0.20, 1.10)[h]	0.35 (0.13, 0.99)[i,e]	0.38 (0.16, 0.91)[i,e]	0.29 (0.09, 0.90)[i,e]
150–< 250	0.22 (0.04, 1.13)[h]	0.36 (0.12, 1.10)[h,f]	0.46 (0.19, 1.12)[h,f]	0.29 (0.08, 1.01)[h,f]
≥ 250	2.50 (0.47, 13.46)	0.47 (0.11, 2.04)[g]	2.07 (0.14, 31.6)[g]	1.81 (0.11, 29.1)[g]

[a] Reference value at 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] $p \leq 0.05$.

from the cubic spline and categorical models as presented in Thompson *et al.* (2008).

DISCUSSION

Inspection of Table 2 reveals that there is a great deal of consistency in the predicted odds of risk across all models among the exposures that range between 50 and 150 Bq m^{-3}. For example, the cubic spline, linear spline, and polynomial models predict an AOR [95% CI] = 0.35 [0.12, 1.04], 0.39 [0.18, 0.87], and 0.33 [0.12, 0.90], respectively, for radon exposure at 62.5 Bq m^{-3} as compared to an exposure of 4.4 Bq m^{-3}. The biggest difference in these predicted values is that the cubic spline model trends towards statistical significance, while the AORs from the other two models are statistically significant at the $\alpha = 0.05$ level. Similarly, the categorical radon model (Model 1) predicts an AOR [95% CI] = 0.31 [0.13, 0.73] for exposures between 50 and < 70 Bq m^{-3} as compared to the reference group of < 25 Bq m^{-3}.

Greater deviance is seen between models when looking at the exposure values at the extremes. The largest exposure considered in Table 2 was 880.5 Bq m^{-3}, a value chosen as the approximate mid-value between the 250 Bq m^{-3} cut-point and the largest measured radon concentration observed in the study (1511 Bq m^{-3}). At this radon exposure, the cubic spline, linear spline, and polynomial models predict an AOR [95% CI] = 0.47 [0.11, 2.04], 2.07 [0.14, 31.6], and 1.81 [0.11, 29.1], respectively, as compared to the reference exposure. AORs at this high exposure value predicted from these three models are statistically non-significant. The categorical radon model gives an AOR [95% CI] for those with ≥ 250 Bq m^{-3} exposure compared to the reference group of < 25 Bq m^{-3} = 2.50 [0.47, 13.46]. This result is comparable to that seen in the linear spline

model and, to a lesser extent, that of the polynomial model. Based on this comparison, it is evident that the cubic spline model with only two degrees of freedom fails to adequately fit these data at the higher radon concentrations, suggesting that a cubic spline model with greater degrees of freedom and hence more flexibility might provide a better fit of the dose-response curve at these higher exposure values.

Before comparing in depth the results of the Worcester data with those of other radon studies, first consider the estimated slopes obtained from the North American sites considered by Krewski *et al.* (2006) as depicted in Figure 4. The length of the lines in this plot corresponds to the range of the measured radon exposures seen for each study. Because these studies used the LNT model to estimate AORs and the current study did not, results from Worcester data are not included in this plot. The important point to note from this figure is the large amount of variability in the obtained AOR slopes that define the lung cancer-radon dose-response relationship. By pooling these studies, Krewski *et al.* (2006) are making the implied assumption that all the measured odds ratios estimate the true underlying risk and that deviations from this 'truth' are due to random variability. However, given the variability in measured risks as seen in Figure 4, is it possible that there are some underlying, unknown mechanisms that might be causing this variability? Could these differences in dose-response relationships represent actual differences and not just be due to random noise? Is it possible that the underlying mechanism is due to low LET exposures that are activating adaptive biological responses and leading to various degrees of protection against the damages to the lung tissue from exposure to LET alpha radiation? Or in cases where a site might have high radon exposure and small doses of low LET,

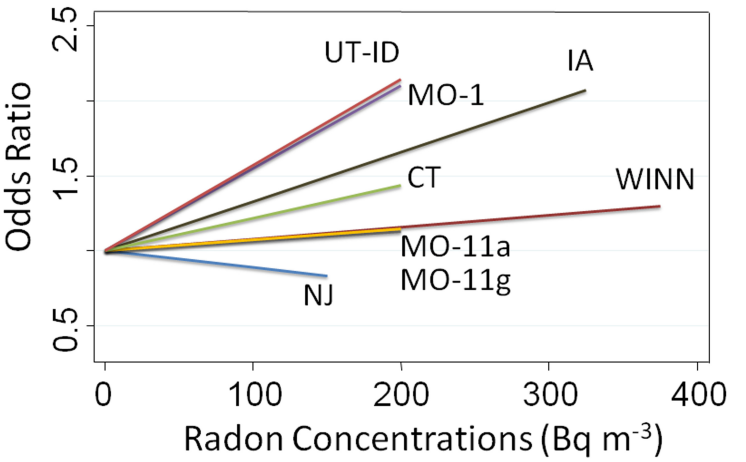

FIGURE 4: Slopes of estimated lung cancer risk as a function of radon exposure based on the LNT model for the North American sites considered by Krewski *et al.* (2006). The length of these lines represents the range of radon exposures observed for each study.

is it possible that the adaptive responses are being suppressed, resulting in large odds of cancer risk at these higher doses of radon exposure?

In considering this hypothesis, it is noteworthy that the dose-response relationship between cancer and radon exposure from the Worcester data is very similar in shape to that predicted from the stochastic HRR model as described in Scott *et al.* (2009) and reproduced here as Figure 5. At the very least, the striking hormetic 'dip' seen from the Worcester data raises the possibility that some underlying mechanism present at this site might be activating an adaptive response that becomes suppressed at the higher values of radon exposure. The fact that there are few study participants at the Worcester site with large measured radon values also suggests the possibility that there is a lack of power to accurately estimate the dose-response relationship in the 'linear zone' and / or 'transition zone B'— hence the positive but non-statistically significant estimate of $\hat{b}_2$ for radon exposure > 70 Bq m^{-3} in Equation 1 above.

Possible additional support for the hypothesis of regional variability in activation of adaptive responses is given by the fact that data from Connecticut and New Jersey, study sites examined by Krewski *et al.* (2006) that are geographically the closest to Worcester County, Massachusetts, also show a trend towards a decreased risk of cancer at intermediate doses of radon, as compared to the respective baseline exposures in these studies. Table 10 in Krewski *et al.* (2006) gives an AOR [95% CI] per 100 Bq m^{-3} = 0.89 [0.56, 2.34] at the New Jersey site when the data are restricted to those study participants with ≤ 2 residences and ≥ 20 years with α-track air monitors. It is worth noting that the AOR is greater than one when all the data are considered (AOR [95% CI] per 100 Bq m^{-3} = 1.56 [0.78, 2.97]). However, even these complete data give an estimated lung cancer

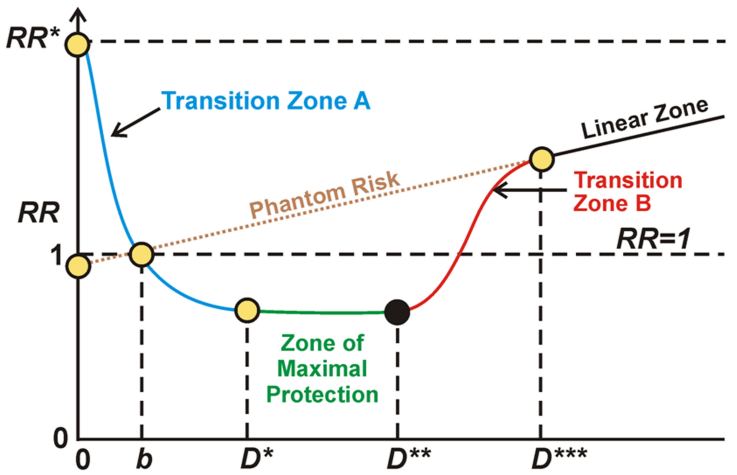

FIGURE 5: Graphic depiction of the stochastic hormetic relative risk model as given in Scott *et al.* (2009).

risk for those in the 100-149 Bq m^{-3} exposure range that is half that of those in the reference exposure group of < 25 Bq m^{-3} (AOR [95% CI] = 0.49 [0.11, 2.32]; see Table 9 in Krewski *et al.* 2006). For the complete data from the Connecticut study as given in Table 9 of Krewski *et al.* (2006), those in the exposure range of 75 to < 100 Bq m^{-3} have a predicted AOR [95% CI] = 0.62 [0.31, 1.24] when compared to baseline exposure. When the data are restricted to participants with ≤ 2 residences and ≥ 20 years with α-track air monitors, the adjusted odds ratio for this exposure category moves closer to unity, but is still less than 1 (AOR [95% CI] = 0.78 [0.31, 1.94]). It is also noteworthy that both the New Jersey and Connecticut sites had the lowest mean concentrations seen among the Krewski *et al.* (2006) studies, with the average concentrations among the New Jersey and Connecticut study subjects at 26 Bq m^{-2} and 33 Bq m^{-3}, respectively.

Finally, when comparing the results of the Worcester data to those data presented in Krewski *et al.* (2006), it is worth examining the Iowa data in greater detail. From sensitivity analyses performed by these investigators, it is clear that the significant positive linear slope in cancer risk is driven entirely by the Iowa results. When the data from this study are removed, the overall AOR per 100 Bq m^{-3} is reduced from 1.18 to statistically non-significant value = 1.13 (95% CI = 0.98, 1.41) for the restricted data. Subjects in the Iowa study had an overall estimated mean radon exposure of 127 Bq m^{-3}, second only to Winnipeg among the Krewski *et al.* (2006) studies, and approximately twice that seen among the Worcester study participants.

Due to high radon concentrations present in Iowa, subjects were assumed to have background exposures of between 7.4 Bq m^{-3} and 56 Bq m^{-3} based on outdoor concentrations observed among the 111 geographic sampling sites in the state, giving a mean background exposure rate of 30.3 Bq m^{-3} for this study (Field *et al.* 2000). Background radon exposure in the Worcester area was < 10 Bq m^{-3} and was thought to be sufficiently low as to be ignored. Furthermore, as noted by Table 9 in Krewski *et al.* (2006), no participants in the Iowa study had a total radon exposure < 25 Bq m^{-3}, and only about 34.5% of cases and 34.9% of controls had radon exposures < 75 Bq m^{-3}. In contrast, a total of 437 subjects or 73.2% in the Worcester study had radon exposures < 75 Bq m^{-3}. The LNT model from the Iowa data produced a statistically significant AOR [95% CI] per 100 Bq m^{-3} = 1.44 [1.05, 2.59] when all the data in the study are considered (see Table 9 of Krewski *et al.* 2006).

Taken together, the contrasts listed above between the Iowa and the Worcester studies suggest the possibility that data from each study are estimating lung cancer risk at different zones of the HRR dose-response curve. Perhaps the higher radon exposures seen in the Iowa data are such that the low LET adaptive responses are silenced and the Iowa data are

providing an accurate estimate of the dose-response relationship in the 'transition zone B' and / or the 'linear zone'. Furthermore, is it possible that for exposure values ≥ 70, Equation 1 is also estimating the dose response in the 'transition zone B' and / or 'linear zone', although in the log odds domain and with much less power than the Iowa study due to a smaller number of study participates with large exposures? As a way of comparison between the Iowa results and the linear spline model for X ≥ 70 Bq m^{-3} in the Worcester data, consider what happens if the reference point of X_0 = 4.4 Bq m^{-3} in Equation 3 is replaced with X_0 = 70 Bq m^{-3}, the inflection point in the dose-response relationship. For this new reference value, the predicted AOR [95% C] per 100 Bq m^{-3} (e.g 170 Bq m^{-3} v. 70 Bq m^{-3}) = 1.25 [0.88, 1.77], p = 0.221) for the Worcester study participants. It should be noted that the LNT model used in the Krewski *et al.* (2006) study to analyze the Iowa data gives a linear slope in the AOR domain, while the logit model used for the Worcester data is linear in the log(AOR) domain. Nevertheless, the remarkable consistency between the estimated AOR per 100 Bq m^{-3} from both the Iowa data and the Worcester data for exposures ≥ 70 Bq m^{-3} provides possible support for the above hypothesis. Research further testing this hypothesis could begin by applying the HRR model as currently proposed by Scott *et al.* (2009) to both the Iowa and Worcester data.

In contrast to the dose-response relationship at high exposures, is it possible that the Worcester radon concentration data < 70 Bq m^{-3} are primarily estimating the cancer risk in the 'zone of maximal protection'? And, is it possible that the lowest radon concentrations seen in the Iowa study lie in the 'zone of maximal protection', causing a 'shift' in the background exposure such that an overall positive increase in risk is seen as the higher exposures in the 'linear zone' are compared to a reference value somewhere in this 'zone of maximal protection'? Furthermore, is it also possible that the lower radon values seen in the Worcester data lie in the 'transition zone A', which would then produce a decreased risk for the majority of the higher exposure data that happen to lie in the 'zone of maximal protection'? These questions need to be seriously considered and evaluated if the hypothesis that regional differences in adaptive responses on an ecological level account for the various risk estimates among the several radon studies conducted.

CONCLUSION

Data are presented here from a case-control study of radon and lung cancer conducted in Worcester County, Massachusetts, that suggest the possibility that radio-adaptive responses on a human scale are active and present in the population under study. Differences in regional activation of adaptive responses provide an underlying mechanism that could explain the variable risk estimates seen among the several radon case-con-

trol studies conducted over the past two decades. Of course, the possibility can not be discounted that the decreased risk of cancer as exposure increases as seen in the Worcester study, along with other studies that have shown a decreased cancer risk from radon, are simply due to random variations.

In order to thoroughly test the hypothesis that radio-adaptive response can be detected at the ecological level and are possibly mitigating the harmful effects of radon, further case-control studies need to be conducted that accurately measure and assess both the low LET ambient exposure as well as the high LET alpha radon exposure of a population under study. However, several questions arise about such studies. First, given the great deal of variability in human biology as well as the complicated biological processes that lead to cancer, is it even possible to detect the 'signals' of adaptive responses above the 'noises' present at the ecological level? Second, is it possible to accurately quantify the sum total of all the alpha, beta, and gamma radiation exposures experienced by any one human population given the multitude of sources of both low and high LET radiation? And finally, how would a study of this nature be powered? And are there adequate sources of *in vivo* data to provide the basis for such power calculations? Nevertheless, such questions and challenges need to be answered before the mechanisms, actions and effects of radio-adaptive responses at the human and ecological levels are truly understood.

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