Iowa Radon Leukemia Study: A Hierarchical Population Risk Model for Spatially Correlated Exposure Measured with Error

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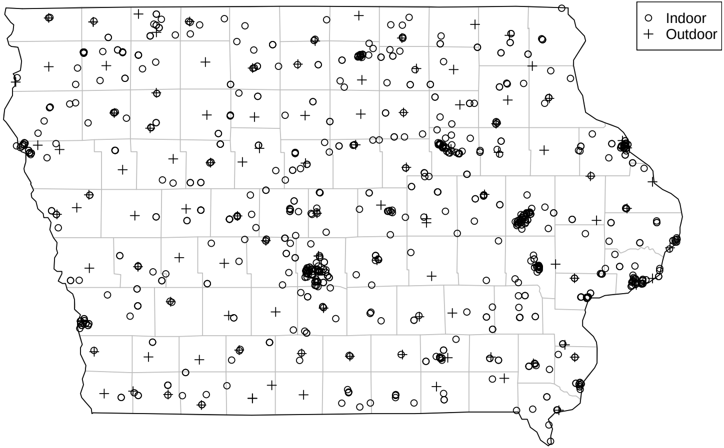
Introduction

- Man-made sources of exposure to ionizing radiation (x-rays and gamma rays) have been implicated as causative agents in several forms of Leukemia.
- Radon is a naturally occurring gas that is the largest contributor to individuals' background exposures to radiation.
- The association between leukemia risk and individuals' exposure to residential radon has not been studied.
- Ecologic radon studies examine associations between disease outcomes and exposures aggregated over geographic regions.
- Exposures in such studies cannot be observed directly and are generally predicted from samples of radon measurements within geographic regions.

Iowa Radon Lung Cancer Study

- Epidemiologic case-control study in Iowa to estimate the effect of residential radon on lung cancer risk.
- 2,590 radon detectors were installed in 614 population-based, control subject homes.
- At least one measurement was taken on each floor of the home, for an average of 4.2 measurements per home.
- Distribution of home sites is similar to that of the general population.
- 136 radon measurements collected from an approximately uniform grid of 109 outdoor sites.

Geographic Radon Monitoring Sites



SEER Cancer Registry

- The NCI Surveillance, Epidemiology, and End Results (SEER) Program collects cancer incidence and survival data.
- Our dataset includes incidence cancers from 1973–2002 in Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, and Utah.
- Leukemia and total population counts by disease type, county, 5-year age strata, gender, race, and calendar year.
- Leukemia cases in Iowa included:
  - 1,189 Acute Lymphocytic Leukemias (ALL)
  - 3,124 Acute Myelogenous Leukemias (AML)
  - 5,393 Chronic Lymphocytic Leukemias (CLL)
  - 1,679 Chronic Myelogenous Leukemias (CML)

Standardized Mortality Ratio

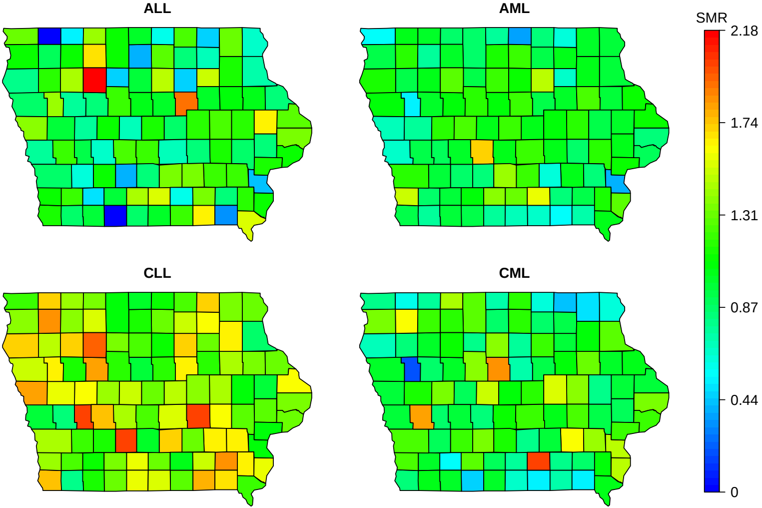
- The expected number of cases in the k^{th} county and l^{th} demographic subgroup is denoted

$$E_{kl} = \sum_i m_{kli} \lambda_i$$

where the summation is over age-gender strata, m_{kli} is the person-years at risk, and λ_i is the stratum-specific rate based on all SEER registry data.

- The observed standardized mortality ratios (SMR) are the number of observed / expected cases and are plotted by Iowa counties on the following slide.

Age and Gender-Standardized Leukemia SMRs



Analysis Goals

- Study the effect of residential radon on leukemia risk in Iowa, while controlling for potential confounding effects of important covariates.
- Relate point-referenced radon and areal leukemia data using a geostatistical model to characterize the continuous spatial distribution of radon.
- Apply a hierarchical Bayesian model to simultaneously predict county-average radon and estimate the associated leukemia risk.
- Resulting risk estimates accurately reflect the uncertainty in predicting radon.

Leukemia Risk Model

- The reported number of cases is assumed to have the following Poisson distribution

$$\begin{aligned} y_{kl} &\sim Poisson\left(E_{kl} \exp\{\psi_{kl}\}\right) \\ \psi_{kl} &= \boldsymbol{\beta}^T \mathbf{x}_{kl} + \beta_r \bar{r}'_k + \theta_{kl} + \phi_k \\ \theta_{kl} &\overset{iid}{\sim} N\left(0, \sigma_h^2\right) \\ \boldsymbol{\phi} &\sim N\left(\mathbf{0}, \sigma_c^2 \left(D_w - \rho_c C\right)^{-1}\right) \end{aligned}$$

- $\mathbf{x}_{kl}$ is a vector of known covariates with mean parameters $\boldsymbol{\beta}$.
- β_r is the effect of the predicted county-average radon $\bar{r}'_k$ on leukemia rate.
- θ_{kl} accounts for state-wide heterogeneity and ϕ_k spatial correlation not due to radon.

Outdoor Radon Model

- Let $r_{os,ij}$ denote the j^{th} radon measurement from outdoor site $i = 1, \ldots, n_{os}$.
- We specify the following model for outdoor measurement:

$$\begin{aligned} \ln r_{os,ij} &= \beta_{OS} + z\left(s_i\right) + \epsilon_{os,ij} \\ \epsilon_{os,ij} &\overset{iid}{\sim} N\left(0, \sigma^2_{os}\right) \end{aligned}$$

  where β_{os} is an overall mean parameter, $\epsilon_{os,ij}$ is an exchangeable error term, and σ^2_{os} is the measurement error variance.
- The $z\left(s_i\right)$ parameter accounts for spatial correlation among radon measurements.

Home Radon Model

- Let $r_{hm,ij}$ denote the j^{th} radon measurement from home site $i = 1, \ldots, n_{hm}$.
- We model home radon measurements as

$$\begin{aligned} \ln r_{hm,ij} &= \boldsymbol{\beta}_{hm}^T \mathbf{x}_{hm,ij} + \gamma_i + z\left(s_i\right) + \epsilon_{hm,ij} \\ \gamma_i &\overset{iid}{\sim} N\left(0, \sigma_{bh}^2\right) \\ \epsilon_{hm,ij} &\overset{iid}{\sim} N\left(0, \sigma_{wh}^2\right). \end{aligned}$$

where $\mathbf{x}_{hm,ijk}$ and $\boldsymbol{\beta}_{hm}$ are vectors of covariates and corresponding mean parameters; γ_i is a random effect for the home; $z\left(s_i\right)$ is the latent spatial parameter; and $\epsilon_{hm,ij}$ is an exchangeable error term.

Home Radon Model

- In the present analysis, only indicator variables for the floors on which the measurements were taken are included in the covariate vector $\mathbf{x}_{hm,ij}$.
- The error variance σ^2_{wh} is a combination of variability due to systematic differences within the home and random detector measurement error.
- The between-home variance σ^2_{bh} includes unaccounted for differences in home environments.

Latent Spatial Process for Radon

- Let $\mathbf{z}^T = (z(s_1), \ldots, z(s_n))$, for $i = 1, \ldots, n$ and $n = n_{OS} + n_H$.
- The assumed distribution for these latent spatial parameters is

$$\mathbf{z} \sim N\left(\mathbf{0}, \sigma_s^2 R_{\mathbf{z}}(\rho_s)\right)$$

where $R_{\mathbf{z}}(\rho_s)$ is correlation matrix; σ_s^2 is a scalar variance; and ρ_s is a correlation parameters such that

$$\left(R_{\mathbf{z}}(\rho_s)\right)_{ii'} = \exp\left\{-\left\|s_i - s_{i'}\right\|^2 / \rho_s^2\right\}.$$

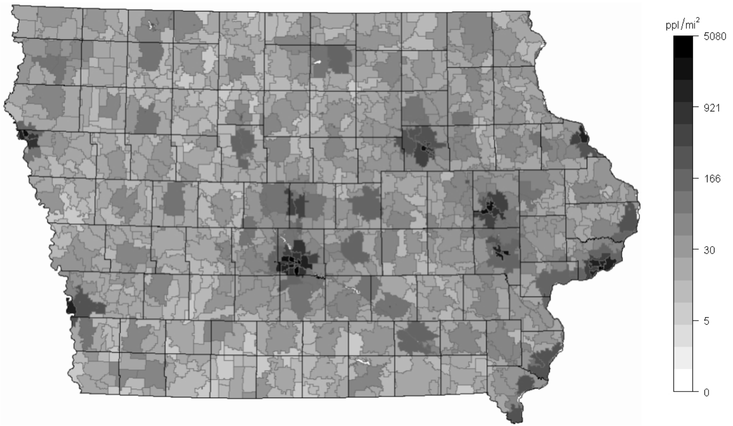
Predicted County-Average Radon

- The county radon concentrations $\bar{r}'_k$ is needed to complete the specification of our risk model.
- For this, we use the average predicted radon concentration defined as

$$\bar{r}'_k = \exp\left\{ \int_{B_k} w(s) \ln r'(s)\, ds \Big/ \int_{B_k} w(s)\, ds \right\}$$

- B_k denotes the geographic region.
- $r'(s)$ is a predicted radon concentration at site s.
- $w(s)$ is a function of location that allows for weighted averaging of radon concentrations within a county.
- We set $w(s)$ to be the population densities (people per square mile) for Iowa state zip codes, as reported in the 2000 U.S. Census.

Population Density by Zip Codes



Numerical Integration

- County-average, first-floor radon concentration is the primary radon exposure of interest.
- The previous integral cannot be solved explicitly due to the irregular shape of geographic regions.
- An alternative is to replace the integration by summation over a new set of sites $\{s_i' : i = 1, \ldots, L_k\}$ so that

$$\bar{r}_k' \approx \exp\left\{ \beta_{hm}^T \mathbf{x}_{hm} + \sum_{i=1}^{L_k} w\left(s_i'\right) z\left(s_i'\right) \Big/ \sum_{i=1}^{L_k} w\left(s_i'\right) \right\}.$$

- We employ a fixed grid of approximately 3,000 equally spaced sites $\{s_i'\}$ across Iowa, thus partitioning the state into 18.5 square-mile regions.

Predictive Distribution

- The joint distribution for the latent spatial parameters at observed and unobserved grid sites is

$$\begin{pmatrix} \mathbf{z} \\ \mathbf{z}' \end{pmatrix} \sim N\left(\begin{pmatrix} \mathbf{0} \\ \mathbf{0} \end{pmatrix}, \sigma_s^2 \begin{pmatrix} R_{\mathbf{z}}(\rho_s) & R_{\mathbf{z},\mathbf{z}'}(\rho_s) \\ R_{\mathbf{z},\mathbf{z}'}^T(\rho_s) & R_{\mathbf{z}'}(\rho_s) \end{pmatrix} \right)$$

so that the predictive distribution for $\mathbf{z}' \mid \mathbf{z}, \sigma_s^2, \rho_s$ is a normal with mean

$$R_{\mathbf{z},\mathbf{z}'}^T(\rho_s) R_{\mathbf{z}}^{-1}(\rho_s) \mathbf{z}$$

and variance

$$\sigma_s^2 \left(R_{\mathbf{z}'}(\rho_s) - R_{\mathbf{z},\mathbf{z}'}^T(\rho_s) R_{\mathbf{z}}^{-1}(\rho_s) R_{\mathbf{z},\mathbf{z}'}(\rho_s) \right).$$

Joint Posterior Distribution

A fully Bayesian approach is taken to obtain the joint posterior distribution of all model parameters.

$$\left[\prod_k \prod_l f\left(y_{kl} \mid \boldsymbol{\beta}, \beta_r, \bar{r}'_k, \theta_{kl}, \phi_k\right)\right] f\left(\boldsymbol{\theta} \mid \sigma_h^2\right) f\left(\boldsymbol{\phi} \mid \sigma_c^2, \rho_c\right) \pi\left(\boldsymbol{\beta}, \beta_r, \sigma_h^2, \sigma_c^2, \rho_c\right)$$
$$\times \left[\prod_i \prod_j f\left(\ln r_{os,ij} \mid \beta_{os}, \mathbf{z}, \sigma_{os}^2\right)\right] \pi\left(\beta_{os}, \sigma_{os}^2\right)$$
$$\times \left[\prod_i \prod_j f\left(\ln r_{hm,ij} \mid \boldsymbol{\beta}_{hm}, \sigma_{bh}^2, \mathbf{z}, \sigma_{wh}^2\right)\right] \pi\left(\boldsymbol{\beta}_{hm}, \sigma_{bh}^2, \sigma_{wh}^2\right)$$
$$\times f\left(\mathbf{z}' \mid \mathbf{z}, \sigma_s^2, \rho_s\right) f\left(\mathbf{z} \mid \sigma_s^2, \rho_s\right) \pi\left(\sigma_s^2, \rho_s\right)$$

where $\bar{r}'_k$ is a function of the home radon mean parameters $\boldsymbol{\beta}_{hm}$ and the predicted latent parameters $\mathbf{z}'$.

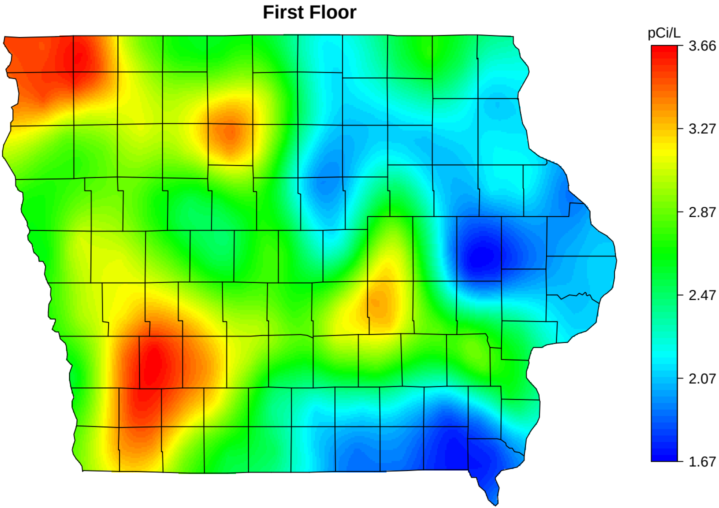
Prior Specification and MCMC Methods

- Vague, independent priors:

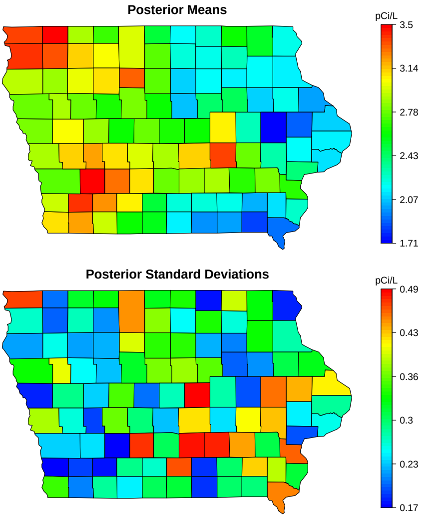
Mean	β	$\sim$	*Normal* $(0, 1000)$
Variance	$1/\sigma^2$	$\sim$	*Gamma* $(0.001, 0.001)$
CAR	ρ_c	$\sim$	*Uniform* $(-1.78, 1.00)$
Spatial Decay	ρ_s	$\sim$	*Uniform* $(0, 100)$

- Markov chain Monte Carlo methods used to sample from the joint posterior.
- Simulated three parallel chains of 50,000 iterations each.
- Analyses performed with a version of R compiled against an ATLAS-tuned BLAS matrix algebra library.

Posterior Mean First Floor Radon



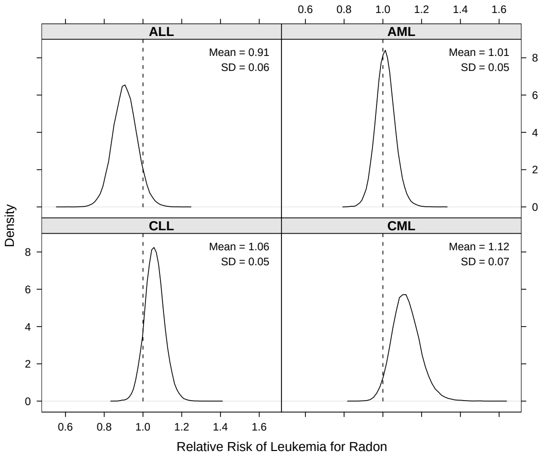
Posterior Mean First Floor County-Average Radon



Posterior Risk Estimates

Covariate		ALL		AML	
		Mean	95% HPD	Mean	95% HPD
Race	Non-black	1.0	-	1.0	-
	Black	0.74	(0.42, 1.09)	0.92	(0.61, 1.27)
Year	1973–1982	1.0	-	1.0	-
	1983–1992	1.06	(0.98, 1.13)	1.12	(1.07, 1.17)
	1993–2002	1.12	(0.97, 1.28)	1.25	(1.14, 1.36)
		ALL		AML	
Race	Non-black	1.0	-	1.0	-
	Black	0.67	(0.43, 0.92)	1.22	(0.70, 1.76)
Year	1973–1982	1.0	-	1.0	-
	1983–1992	1.01	(0.97, 1.05)	0.95	(0.90, 1.01)
	1993–2002	1.02	(0.94, 1.10)	0.90	(0.80, 1.02)

Posterior Distributions of Leukemia Risk for 1 pCi/L Increase in Radon



Discussion

- The Iowa study offers several advantages over previous ecologic radon studies.
- Bayesian approach allows for prediction of county-average radon levels while accounting for spatial dependencies, systematic differences between homes, and detector measurement error.
- Joint distribution of all model parameters.
- Relative risk estimates accurately reflect uncertainties in the predicted radon exposure covariate.
- Iowa has the highest mean residential radon concentration in the United States and provides a wide distribution of county radon concentrations for use in the analyses.
- SEER registry provides accurate information on the leukemia incidence in all counties.
- Ecologic findings should be limited to hypothesis generating and not to determine risk.

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