Quantifying radiation health effects in the Life Span Study of atomic bomb survivors

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Abstract

Understanding the health effects of radiation exposure is important for establishing recommendations for radiation protection, including limits on occupational exposure to radiation and guidelines for diagnostic and therapeutic uses of radiation. The Life Span Study includes residents of Hiroshima and Nagasaki, Japan, who were within 10 km of the hypocenter at the time of the atomic bombings on August 6, 1945, in Hiroshima and August 9, 1945, in Nagasaki. For these survivors, DS02R1 radiation dose estimates, calculated using the DS02 dosimetry system, are based on the survivor's reported location, the amount and type of shielding between the survivor and the blast, and the orientation of the survivor relative to the direction of the blast. The Life Span Study also includes a sample of Hiroshima and Nagasaki residents who were 'not in city' at the time of the bombings. These residents are thought to be representative of the cities' general population, but without exposure to radiation from the bombs. We analyzed the association between radiation exposure and incidence of first primary solid cancer among 80,205 survivors whose DS02R1 radiation dose could be calculated and 25,239 not-in-city residents. All analyses were based on a highly stratified table of case counts and accrued person-years. Using the *R* package **gnm**, we fit piecewise constant hazard models to quantify heterogeneity in cancer risk according to sex, age, city, and location (e.g, 'not in city'), and to estimate the excess relative risk of cancer associated with radiation dose. Effect modification of the excess relative risk by sex and age was considered. A regression model with internal standardization provided a sex-averaged excess relative risk of 0.510, 95% CI: (0.414, 0.612) per gray of weighted absorbed colon dose, as well as strong evidence of a curvilinear dose response among males (P = 0.008). Our analysis illustrates the flexibility of **gnm**, along with user-specified functions for the model terms, to formulate non-linear regression models.

Introduction

Goal: Estimate the association between radiation exposure and incidence of solid cancer among atomic bomb survivors

Challenge: Requires fitting non-linear regression models with flexible structures for radiation effects and interactions

Methods

Study cohort

- Life Span Study (Hiroshima and Nagasaki, Japan): 120,321 participants
- First primary solid cancers identified by population-based tumor registries (1958–2009); mortality determined from national records [1]
  - 111,917 participants alive and at risk for first primary solid cancer in 1958
- DS02R1 weighted absorbed colon doses estimated by DS02 dosimetry system [2]
  - Weighted doses: Sum of the gamma dose and 10 times the neutron dose
  - Correction for measurement error and truncation of doses $>$4 gray
  - Excluded 6,473 survivors with an unknown dose
- Resultant dataset consisted of 105,444 participants
  - 80,205 atomic bomb survivors; 25,239 not-in-city residents
  - 22,538 first primary solid cancers over 3,079,570 person-years
- Analyses based on a highly stratified table of case counts and accrued person-years
  - Within strata, person-years adjusted for expected migration out of catchment areas
  - Estimated migration rates stratified by city, birth year, sex, and calendar year

Risk models

- Piecewise constant hazard models related the rate of first primary solid cancer λ to the background rate λ_0 and a function of weighted absorbed colon dose d

$$\begin{aligned} \text{Log-linear:} \quad & \lambda = \lambda_0 \exp(\beta d) \\ \text{Linear:} \quad & \lambda = \lambda_0 (1 + \beta d) \end{aligned}$$

  - Linear excess relative risk model preferred because risk is thought to be linear in dose; a log-linear model could under-estimate the risk at low doses
- Background rate λ_0
  - Internal standardization with city-specific zero-dose reference groups based on location (not-in-city) and distance from the hypocenter (proximal, $<$3 km; distal, 3–10 km)
  - Sex-specific non-linear adjustments for age at exposure and log attained age
- Effect modification by sex s, age at exposure e, attained age a, shielded kerma $k > 4$ gray

$$\lambda = \lambda_0 \{1 + \beta d \exp(\gamma_1 e + \gamma_2 \log a + \gamma_3 [k > 4]) (1 + \delta s)\}$$

  - Accommodate heterogeneity in radiation risk by sex and age
  - Multiplicative interaction with age on the excess relative risk scale
  - Form of sex interaction provides sex-averaged excess relative risks
- Alternative dose-response models

$$\begin{aligned} \text{Sex-averaged linear:} \quad & \beta_1 d \\ \text{Sex-specific quadratic:} \quad & \beta_1^m d + \beta_2^m d^2 + \beta_1^f d + \beta_2^f d^2 \end{aligned}$$

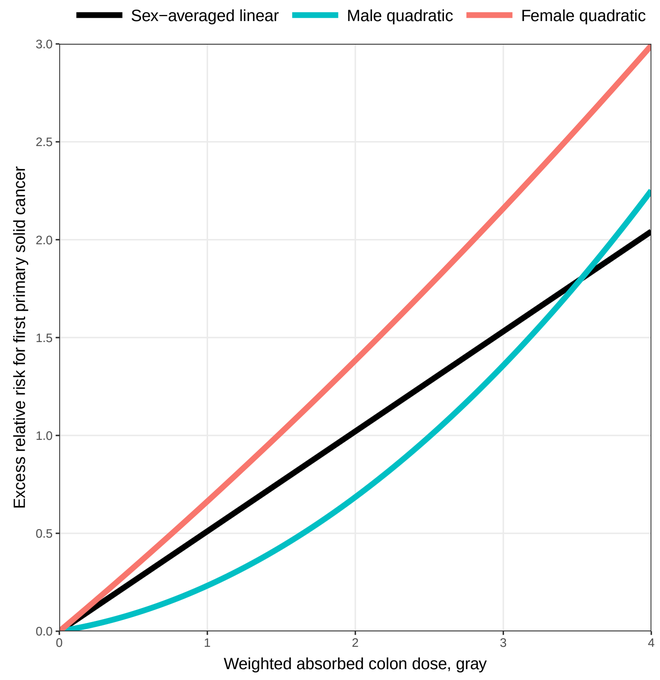
with focus on $\hat{\beta}_1$, $H : \beta_2^m = 0$, and $H : \beta_2^f = 0$

Implementation using gnm [3]

```
# Sex-averaged linear dose response

LogRR3 <- function(..., inst=NULL){
  list(predictors=match.call(expand.dots=FALSE)[["..."]],
       term=function(predLabels, ...){
         paste("log(1+(", predLabels[1],
               ")*exp(", predLabels[2],
               ")*(1+",  predLabels[3], "))", sep="")},
       call=as.expression(match.call()))

gnm(solid ~ -1 + factor(msex) + factor(city)
    + factor(group=='not-in-city'):factor(city)
    + factor(group=='proximal'):factor(city)
    + factor(group=='distal'):factor(city)
    + factor(msex):(e30 + e30sq + lage70 + lage70sq + lage70sp)
    + LogRR3(dose, e30 + lage70 + hidose, msex)
    + offset(log(pyr/10000)), family=poisson, data=data)

# Sex-specific quadratic dose response

LogRR2 <- function(..., inst=NULL){
  list(predictors=match.call(expand.dots=FALSE)[["..."]],
       term=function(predLabels, ...){
         paste("log(1+(", predLabels[1],
               ")*exp(", predLabels[2], "))", sep="")},
       call=as.expression(match.call()))}

gnm(solid ~ -1 + factor(msex) + factor(city)
    + factor(group=='not-in-city'):factor(city)
    + factor(group=='proximal'):factor(city)
    + factor(group=='distal'):factor(city)
    + factor(msex):(e30 + e30sq + lage70 + lage70sq + lage70sp)
    + LogRR2(dose:factor(msex) + dosesq:factor(msex),
             e30 + lage70:factor(msex) + hidose)
    + offset(log(pyr/10000)), family=poisson, data=data)
```

Results

- Sex-averaged excess relative risk: 0.510, 95% CI: (0.414, 0.612) per gray
- Strong evidence for curvature among males (P = 0.008) but not females (P = 0.63)



Discussion

- **gnm** facilitated estimation of radiation excess relative risks for first primary solid cancer
- RERF data are publicly available and free for download

www.rerf.or.jp/library/dl_e/index.html

References

[1] Grant EJ, et al. Solid cancer incidence among the Life Span Study of atomic bomb survivors: 1958–2009. *Radiation Research* 2017; 187:513–37.

[2] Cullings HM, et al. DS02R1: Improvements to atomic bomb survivors' input data and implementation of dosimetry system 2002 (DS02) and resulting changes in estimated doses. *Health Physics* 2017; 112:56–97.

[3] Turner H, Firth D. Generalized nonlinear models in R: An overview of the gnm package. R package version 1.0-8, 2015.