Quantifying radiation quality for space relevant radiation types: Fitting excess risk models to outbred mice data

Overview

Accurately quantifying the differences in radiation quality between space and terrestrial environments is important for predicting health risks for astronauts. Recently, Edmundson et al. 2020[1] provided valuable new results from outbred mice linking tumor induction and genetic background after exposure to low- and high-LET radiation. The goal of the current study is to more rigorously estimate a relative biological effectiveness (RBE) factor by leveraging the solid tumor data from Edmundson et al. 2020. Excess relative risk (ERR) models and excess absolute risk (EAR) models were fit using Poisson regression similar to the models that the Radiation Effects Research Foundation uses to fit atomic bomb survivor data. Linear ERR and EAR slopes were simulated using Bayesian analyses, and RBE values were calculated from the ratio of the heavy ion linear slope to the gamma linear slope using the full posterior distribution.

Organization of the Data for Analyses

Poisson models were used to fit the outbred mouse data[1]. The analyses were based on a stratified table of mouse-time and number of cases by sex (male or female), attained age (1 month categories from <14, 14-25, and ≥25 months), and radiation type. We were unable to further stratify by dose because there is only one dose per radiation type, though we can still include dose in linear models. The primary outcome of interest was solid cancer tumor rates at the time of morbidity or death of the mice. Mice that became moribund from other causes, died from other causes, or reached age 800 days were censored.

Radiation Effect Models

The effects of radiation were described using ERR models and EAR models. The ERR model was:

$$MM \cdot h_0(a, s)(1 + ERR(s, a, D, r))$$

The EAR model was:

$$MM \cdot (h_0(a, s) + EAR(s, a, D, r))$$

where MM is the number of mouse-months of follow-up in the stratum, a is age in months, s is the sex of the mouse, D is the dose in Gy, and r is the radiation type.

Due to only one dose per radiation type we are limited to linear dose-response functions for each radiation type. Potential effect modifiers included sex (s) and attained age (a). The effect modifiers were included in the models as a single effect modifier for all radiation types or as separate independent effect modifiers for each radiation type.

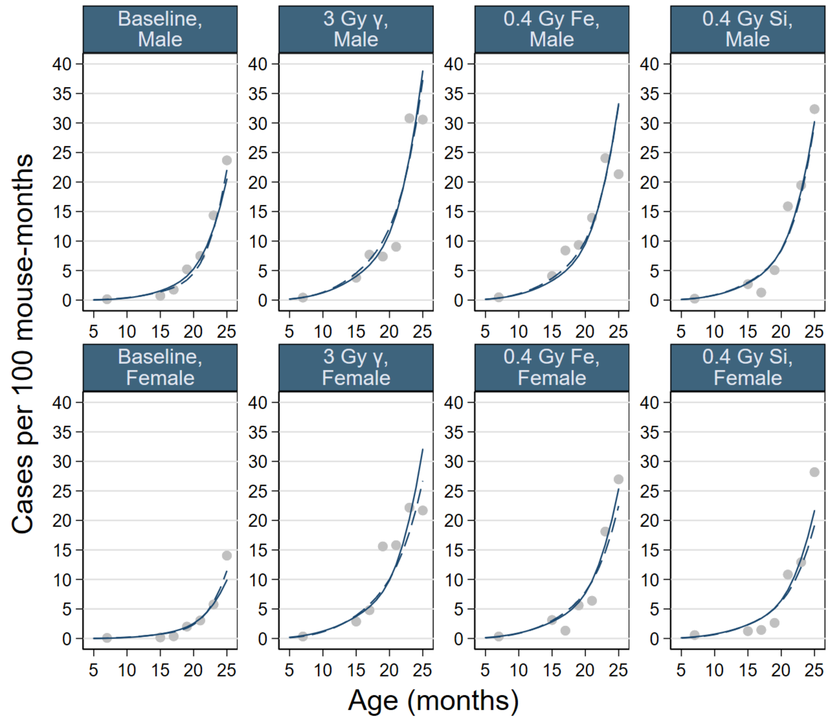
Unexposed Baseline Rates

The baseline rate model included sex and attained age. The background function was parameterized as a restricted cubic spline with a proportional-hazard to make background estimates sex-specific. The background hazard function is centered at age 20 months and has knots at ages 15, 20, and 23 months.

References

1. Edmundson et al. 2020: Scince Advances, Vol. 6, Iss. 16
2. StataCorp: Stata Statistical Software, Release 15.
3. Jeffreys 1998: Theory of probability, 3rd ed
4. Lewis et al. 1997: J Am Stat Assoc. Vol. 92, pp. 648-55

Solid Cancer Rates by Radiation Type and Sex



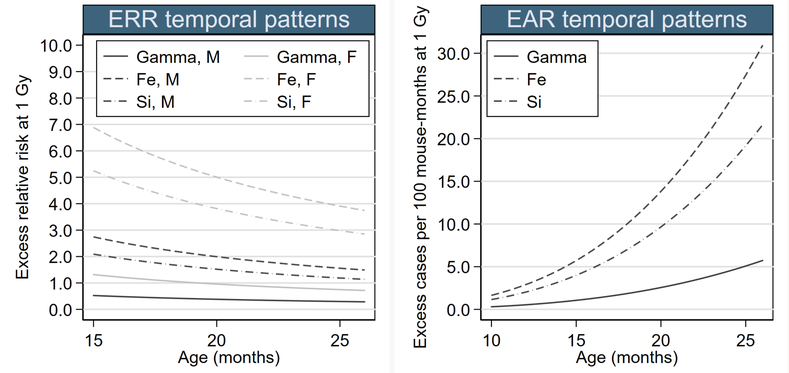
Preferred ERR model fit

Radiation Type	Risk per Gy Male	Risk per Gy Female	Sex ratio (F:M)	Attained age (power)	RBE
γ	0.38 (0.24, 0.55)	0.96 (0.64, 1.36)	2.60 (1.52, 4.23)	-1.11 (-1.96, -0.31)	–
Fe	1.99 (1.14, 3.04)	4.96 (3.17, 7.21)	2.60 (1.52, 4.23)	-1.11 (-1.96, -0.31)	5.24 (3.70, 7.07)
Si	1.52 (0.82, 2.36)	3.80 (2.24, 5.85)	2.60 (1.52, 4.23)	-1.11 (-1.96, -0.31)	4.00 (2.67, 5.57)

Preferred EAR model fit

Radiation Type	Risk per 100 MM per Gy Male	Risk per 100 MM per Gy Female	Sex ratio (F:M)	Attained age (power)	RBE
γ	2.56 (2.05, 3.09)	2.56 (2.05, 3.09)	1.00	3.07 (2.63, 3.63)	–
Fe	13.83 (10.16, 17.73)	13.83 (10.16, 17.73)	1.00	3.07 (2.63, 3.63)	5.45 (3.88, 7.28)
Si	9.66 (6.40, 13.13)	9.66 (6.40, 13.13)	1.00	3.07 (2.63, 3.63)	3.80 (2.48, 5.32)

Attained age effects on solid cancer ERRs and EARs at 1 Gy



Model fitting

Stata 15 software[2] was used to fit a Poisson distribution with means described by the hazard functions in the previous sections using Bayesian Markov chain Monte Carlo (MCMC) sampling. Sampling from the full posterior distributions was achieved using an adaptive Metropolis-Hastings algorithm. Uninformative priors were chosen for all parameters with a Normal(0,10000) distribution. For each analysis, we ran 250,000 MCMC iterations, burning-in for the first 50,000 iterations and storing every 20 iterations. Graphical techniques were used to check the stability, autocorrelation, and convergence of the Bayesian MCMC samples. Means and 95% credible intervals from the full posterior distribution are presented for all parameters and a combination of parameters of interest. Preferred ERR and EAR models were chosen using the DIC and Bayes factors[3,4] compared to the ERR and EAR models with no effect modification as the base models, respectively.

Calculating the Relative Biological Effectiveness factor

RBE factors were calculated comparing the γ linear dose-response function to the Fe and Si linear dose-response functions separately. In excess risk models with no effect modification or with the same effect modification for each radiation type, the baseline rates can be factored out. Since this was the case for all preferred models, the RBE simplified to the ratio of the heavy ion linear slope to the γ linear slope.

Results

Results from this analysis of the outbred mouse data from Edmundson et al. 2020[1] indicate RBE values for solid cancers are 5.24 (95% credible interval (CI): 3.70, 7.07) or 5.45 (95% CI: 3.88, 7.28) for Fe when estimated from the ERR and EAR models, respectively, and 4.00 (95% CI: 2.67, 5.57) or 4.80 (95% CI: 2.48, 5.32) for Si when estimated from the ERR and EAR models, respectively. Notably, the ERR and EAR estimates are similar, with overlapping confidence intervals.

Conclusions

These results suggest that the RBEs used to inform the current NASA Space Cancer Risk Model may result in an overestimation of radiation quality effects. Because of the limited number of doses in this dataset, follow-up studies with more dose points would be needed to validate the RBEs and the linear dose response assumption.

Lori J. Chappell[1], Brock J. Sishc[2], S. Robin Elgart[3]

Lori.Chappell@nasa.gov

[1]KBR, Houston, TX, [2]MEIT, Houston, TX, [3]University of Houston, Houston, TX