Quantifying radiation quality for space relevant radiation types: Fitting excess risk models to three combined HZE-irradiated mouse datasets

Overview

Radiation health risks are predominantly derived from low linear energy transfer (LET) terrestrial exposures; however, space radiation includes exposure to high-LET and high-charge, high-energy (HZE) particles. Accurately quantifying the differences in radiation quality between the space and terrestrial radiation environments is important for assessing and predicting health risks for astronauts. Weil et al. 2009 and 2014 used two different inbred mouse strains to study differences in hepatocellular carcinoma (HCC) tumorigenesis after exposures to low- and high- LET radiation[1-2]. More recently, Edmondson et al. 2020 provided valuable new tumor data in outbred mice that were exposed to low- and high-LET radiation[3]. The present study aims to rigorously investigate a relative biological effectiveness (RBE) factor by leveraging the HCC tumor data from the three datasets[1-3]. The three experiments were similarly designed, allowing the raw data to be combined into a pooled dataset to estimate excess relative risk (ERR) and excess absolute risk (EAR) models using Bayesian Poisson regression.

Data description

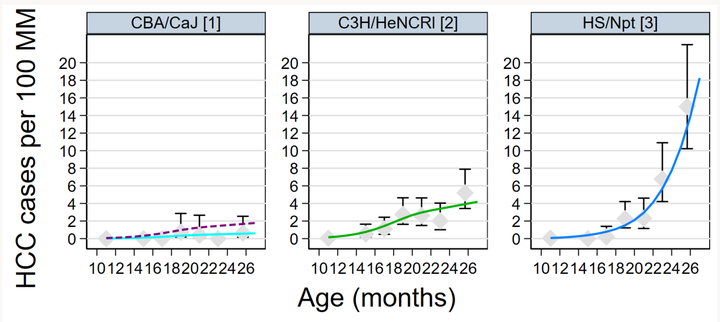
Source	Mouse strain	Sex	Age at exposure (weeks)	Radiation types and doses (Gy)
1	CBA/Caj	Male	7-13	Gamma: 1, 2, 3 Fe 1000 MeV/u: 0.1, 0.2, 0.4, 1
2	C3H/HeNCrl	Male	7-10	Gamma: 1, 2, 3 Proton 30-80 MeV/u: 1, 2 Si 300 MeV/u: 0.1, 0.2, 0.4, 1 Fe 600 MeV/u: 0.1, 0.2, 0.4, 1
3	HS/Npt	Male	7-12	Gamma: 3 Si 240 MeV/u: 0.4 Fe 600 MeV/u: 0.4

Organization of the data for analyses

Poisson models were used to fit the three combined mouse datasets[1-3]. The analyses were based on a stratified table of mouse-time and number of cases by mouse strain (i.e., study), attained age (2 month categories from <14, 14-24, and ≥25 months), radiation type and dose. The primary outcome of interest was HCC tumor rates at the time of moribundity or death of the mice. Mice that became moribund from other causes, died from other causes, or reached age 800 days were censored.

Background hazard model

Different background hazard functions (h_0) were defined for each mouse strain (shown in figure below). Outbred mice (solid blue line) and inbred mice were parameterized by different restricted cubic spline terms centered at age 20 months with knots at ages 15, 20, and 23 months. A proportional hazard (PH) parameter was used to describe the difference between the C3H/HeNCrl (solid green line) and CBA/CaJ (solid cyan line) mice. An additional PH parameter was needed because not all the CBA/CaJ mice traveled to Brookhaven (dashed purple line).



Radiation effect models

The effects of radiation were described using ERR models:

$$MM \cdot h_0 \cdot (1 + ERR)$$

where MM is the number of mouse-months of follow-up.
The deviance information criterion (DIC)[4] was used to choose the preferred ERR model:

- All radiation types modeled together
  - Linear (L) dose response terms for each radiation type
  - Single pooled quadratic (Q) term for HZE radiations
- Log-linear attained age modification
  - Different parameters for low-LET and HZE radiation
    - Single pooled term for gamma and proton
    - Single pooled term for HZE

Table 1. Preferred ERR model fit

	Dose response term			
Radiation Type	L	Q	Attained age	RBE*
Gamma	0.33	–	-2.09	–
	(0.19, 0.50)		(-3.14, -1.08)	
Proton 30-80 MeV/u	0.32	–	-2.09	0.97
	(-0.16, 0.54)		(-3.14, -1.08)	(0.54, 1.62)
Si 300 MeV/u	1.53	-0.94	1.99	4.64
	(0.59, 2.86)	(-2.11, -0.10)	(-0.50, 4.02)	(2.12, 8.05)
Fe 1000 MeV/u	2.20	-0.94	1.99	6.66
	(0.87, 4.15)	(-2.11, -0.10)	(-0.50, 4.02)	(2.86, 12.93)
Fe 600 MeV/u	1.82	-0.94	1.99	5.50
	(0.80, 3.22)	(-2.11, -0.10)	(-0.50, 4.02)	(2.84, 9.20)

* RBE at the low dose peak near 0 Gy and age 20 months for HZE

Figure 1. The shape of the dose response is different for low-LET radiation and HZE radiation

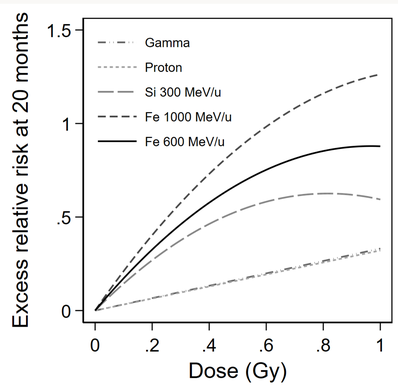


Figure 2. Attained age modifies effect differently for low-LET radiation and HZE radiation

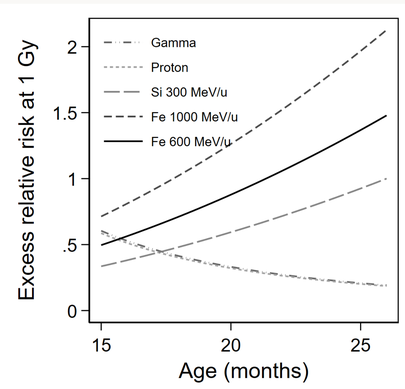


Figure 3. The RBE is a function of dose for HZE

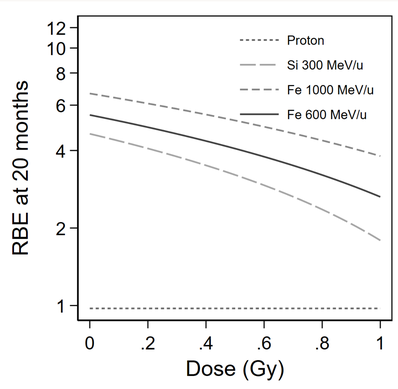
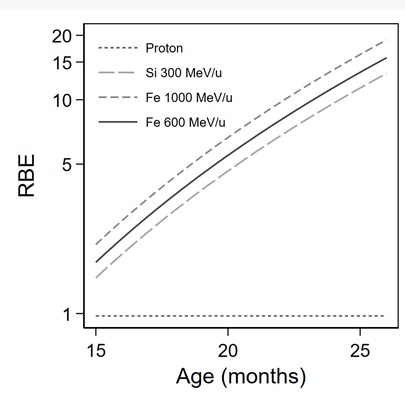


Figure 4. The RBE is a function of age for HZE



Model fitting

Stata 17 software[5] was used to fit a Poisson distribution with medians 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 1,010,000 MCMC iterations, burning-in for the first 10,000 iterations and storing every 20 iterations. Graphical techniques were used to check the stability, autocorrelation, and convergence of the Bayesian MCMC samples. Medians and 95% credible intervals (CrI) from the full posterior distribution are presented for all parameters and the RBE.

Relative biological effectiveness factor

RBE factors were calculated comparing the gamma dose-response function to the dose-response functions for the other radiation types separately. Since gamma and proton had linear slopes and the same age modification term, the RBE simplifies to the ratio of the linear dose response slopes (shown in the Table 1). Since gamma has a linear dose response function and each HZE radiation has a linear quadratic dose response function, the RBE is a function of dose (shape shown in Figure 3). Since gamma and HZE radiations have different age modification terms, the RBE is a function of age (shape shown in Figure 4). The RBE values for the HZE radiation types shown in Table 1 represent the RBE at the low dose peak near 0 Gy and age 20 months.

Results

Results from this analysis of the three combined mouse datasets[1-3] indicate RBE for HCC is a function of dose and age for HZE. The RBE values for HCC are 0.97 (95% CrI: 0.54, 1.62) for Protons, 4.64 (95% CrI: 2.12, 8.05) for Si, 6.66 (95% CrI: 2.86, 12.93) for Fe 1000 MeV/u, and 5.50 (95% CrI: 2.84, 9.20) for Fe 600 MeV/u at the low dose peak near 0 Gy and age 20 months.
These analyses were repeated using EAR modeling techniques, leaving out studies, and using each study/mouse strain individually. Due to space restraints these results are not shown.

Conclusions

These effect estimates from the pooled data provide greater power to calculate a data driven RBE. 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. Including the time component in the analysis allows exploration of temporal effects that were not included in the original individual analyses [1-3]. The finding that RBE may be a function of attained age could have implications for other mouse models that sacrifice mice at a specific age instead of following the mice over time. Careful consideration is needed for choosing a time of sacrifice.
Additional extensive sensitivity analyses will test the robustness of RBE estimates to various model assumptions. We will explore whether the effect estimates and RBE estimates are different by excess risk model and mouse strain. Additional studies will be needed to validate the findings from these exploratory analyses.

References

1. Weil et al. 2009: RadRes, Vol. 172, Iss. 2
2. Weil et al. 2014: PLoS ONE, Vol. 9, Iss. 8
3. Edmondson et al. 2020: Science Advances, Vol. 6, Iss. 16
4. Jeffreys 1998: Theory of probability, 3rd ed
5. StataCorp: Stata Statistical Software, Release 17.

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