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Relative Biological Effectiveness of ^{12}C and ^{28}Si radiation in C57BL/6J mice

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Abstract

Study of heavy ion radiation–induced effects on mice could provide insight into the human health risks of space radiation exposure. The purpose of the present study is to assess the relative biological effectiveness (RBE) of ^{12}C and ^{28}Si ion radiation, which has not been reported previously in the literature. Female C57BL/6J mice (n=15) were irradiated using 4 to 8 Gy of ^{28}Si (300MeV/nucleon energy; LET 70 keV/μm) and 5 to 8 Gy of ^{12}C (290MeV/nucleon energy; LET 13 keV/μm) ions. Post-exposure, mice were monitored regularly and their survival observed for 30 days. The $LD_{50/30}$ dose (the dose at which 50% lethality occurred by 30-days post-exposure) was calculated from the survival curve and was used to determine the RBE of ^{28}Si and ^{12}C in relation to γ radiation. The $LD_{50/30}$ for ^{28}Si and ^{12}C ion is 5.17 Gy and 7.34 Gy respectively and the RBE in relation to γ radiation ($LD_{50/30}$ – 7.25 Gy) is 1.4 for ^{28}Si and 0.99 for ^{12}C. Determination of RBE of ^{28}Si and ^{12}C for survival in mice is not only important for space radiation risk estimate studies, but also has implications for HZE radiation in cancer therapy.

Keywords

Relative biological effectiveness; RBE; Heavy ion charged particles; Space radiation; linear energy transfer; ^{12}C-ion; ^{28}Si-ion

Introduction

Radiation is a major challenge for human exploratory missions in outer space. With increasing interest in exploring the solar system, astronauts undertaking long duration space missions will be exposed to radiation that is different in dose and quality than terrestrial radiation. Astronauts traveling beyond low-earth orbit are expected to encounter a mixed

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radiation field, which includes high-energy proton and heavy ion radiation at low doses and dose rates [1]. In space, solar particle events (SPEs) are sporadic and consist mainly of high-energy protons with a relative biological effectiveness (RBE) similar to low linear energy transfer (low-LET) radiation like γ-rays [2, 3] and are not predictable. On the contrary, galactic cosmic radiation (GCR) is ambient in space, and high-LET heavy ion radiation, unlike in SPE, contributes significantly towards the dose equivalent in GCR [4]. It is predicted that during SPEs astronauts without shielding may receive radiation dose, which could be lethal and with shielding radiation dose may reach up to 2 Gy [1]. Commonly, space radiation exposures will occur at low doses and dose rates, but protracted exposure during long duration space missions may lead to enough dose accumulation especially of heavy ion radiation to raise long-term health concerns [1, 5]. Furthermore, heavy ion radiation, due to its high-LET nature and densely ionizing tracts, causes damage which is markedly more complex than low-LET radiations, and is a major concern for space travel [6–9]. One way of comparing the long- and short-term biological effects of low-LET radiation for which human data is available to those of high-LET radiation is by determining RBE, or quality factor, for different heavy ion species using relevant biological end points. Risk estimate also demands that different heavy ion species be used at different energies for RBE determination and to study the RBE-LET relationship. Importantly, the RBE-LET relation of heavy ion radiation is dependent not only on the particle energy but also on the Z-value of the particle [10]. Furthermore, RBE differs with the biological endpoints and tissue/cell types under investigation. In general, the RBE for biological endpoints like cell survival, mutation induction, cell transformation, chromosome aberration, and cell inactivation peaks at a LET range of 70–130 keV/μm and the RBE value varies between 1.5 and 5 for different biological end points [11, 12][13–16]. However, most of the available data on RBE-LET relationship for heavy ion radiation were obtained from *in vitro* cell cultures and multi-cellular spheroid models [11, 17, 18]. Studies in *in vitro* cell culture system have typically shown higher RBE of various parameters including cell survival compared to *in vivo* systems, and the RBE has been shown to increase with increasing LET. Literature shows RBE of cell survival for ^{12}C ranges from ~1 to 4 (LET ~13 to 100 keV/μm), for ^{28}Si the range is from 2 to 3 (LET ~44 to 200 keV/μm), and for ^{56}Fe it is from ~ 4 to 2.5 (LET 150 to 400 keV/μm) in human cell lines relative to γ-rays or x-rays [19–24]. Although, *in vitro* cell culture studies help in furthering our understanding of particle radiation at the cellular and molecular level, *in vivo* animal model data are essential to develop risk model through understanding of heavy ion radiation effects in three dimensional tissues with all the cell types and associated microenvironment. Currently, lack of adequate biologically relevant *in vivo* data is adds to the uncertainties, which exist about the consequences of heavy ion radiation exposure on human health. Furthermore, scarce availability of published literature on biological endpoints in *in vivo* systems also limits our ability to develop models to predict with confidence the risks associated with space travel [2, 25, 26]. While we determined the RBE for high-energy protons and ^{56}Fe ions earlier [3], the current study was designed to evaluate the RBE of ^{12}C and ^{28}Si ions relative to γ radiation, as prelude to our space radiation-induced intestinal tumorigenesis studies using an adenomatous polyposis coli (APC) mutant mouse model [27] which is in C57BL/6J background. We report here that in relation to γ radiation, ^{28}Si (300 MeV/nucleon energy; LET 70 keV/micron) and ^{12}C (290MeV/nucleon energy; LET 13 keV/micron) have RBE values of 1.4 and 0.99

respectively. The RBE-LET relation of ^{12}C and ^{28}Si ions was then compared to our published results for proton and ^{56}Fe ions [3].

Materials and Methods

Mice and radiation

Six to eight weeks old female C57BL/6J mice (n=15 mice per radiation dose group) were purchased from Jackson Laboratories (Bar Harbor, ME) and shipped directly from the vendor to Brookhaven National Laboratory (BNL) animal care facility 1 week prior to radiation exposure. Exposures to ^{12}C, ^{28}Si, ^{56}Fe, and proton radiation were performed at the NASA Space Radiation Laboratory (NSRL) at BNL and a ^{137}Cs source was used for γ irradiation. Mice were placed in small rectangular lucite boxes with multiple holes, and these boxes were fitted into a sample holder made of low-density foam. The foam holder was then placed into the beam path at the entrance plateau region of the Bragg's curve to ensure uniform LET throughout the exposure. Irradiation positions and doses were based on pre-determined beam distributions generated by the NSRL beam physics team. The dose rate was 1 Gy/min for all radiation types, and all radiation exposures were lateral exposures (beams were horizontal). Detail information on radiation types including previously published results [3] for comparison is summarized in Table 1. Early morning shipment of the experimental mice from BNL were arranged on the day after irradiation in a temperature and humidity controlled environment and delivered in the afternoon to the Georgetown University (GU) animal facility (same day delivery). Mice were followed at the GU animal facility for 30 days and all animal procedures were performed according to protocols approved by the Institutional Animal Care and Use Committees (IACUC) at the GU and BNL.

Survival and RBE determination

Mice (n=15) were exposed to 4 to 8 Gy of ^{28}Si, 5 to 8 Gy of ^{12}C, 1 to 8 Gy of ^{56}Fe, and 6 to 7.5 Gy of proton. For γ radiation, we used a ^{137}Cs source and mice (n=15) were exposed to 2 to 8 Gy. Survival was monitored for 30 days and all irradiation experiments were repeated two times. However, during our study death as an endpoint was avoided by identifying agonal mice and euthanizing them by applying IACUC approved criteria (reduced activity, hunched posture, and ruffled fur). Survival data were used to determine the $LD_{50/30}$ (the dose at which 50% lethality occurred by 30-days post-exposure) by Probit analysis using StatPlus v5.2.0 software with a 95% confidence interval. RBE was determined using the $LD_{50/30}$ dose of heavy ions and the $LD_{50/30}$ dose of γ radiation using the formula RBE_{beam}=($LD_{50/30}$ of γ radiation)/($LD_{50/30}$ of heavy ion radiation).

Results

Irradiated mice were followed for 30 days and the number of mortality in each group, recorded daily, is plotted (Figure 1A and B). Exposure to ^{28}Si (300 MeV/nucleon) radiation doses (<10 Gy) caused mortality between 5 and 14 days and was similar to ^{56}Fe radiation (<10 Gy) lethality, which we have determined is due to accelerated hematopoietic toxicity [3]. While 40% mortality was observed at 5 Gy, at 6, 7, and 8 Gy of ^{28}Si we observed 100%

mortality (Figure 1A). On the contrary, most of the lethality after exposure to ^{12}C (290 MeV/nucleon) radiation doses (<10 Gy) occurred between 10 and 20 days with >90% survival at 7 Gy and lower doses (Figure 1B) and this was similar to γ radiation lethality with doses <10 Gy typical of hematopoietic toxicity [3]. To determine the $LD_{50/30}$, the percent survival was plotted against radiation dose. The $LD_{50/30}$ values were calculated at 5.17 Gy for ^{28}Si, and at 7.34 Gy for ^{12}C with 95% confidence limits of 4.65 and 5.69 for ^{28}Si and of 7.15 and 7.52 for ^{12}C radiation (Figure 2A). The $LD_{50/30}$ for γ, proton, and ^{56}Fe were calculated earlier at 7.25, 6.8, and 5.8 Gy respectively [3]. The RBE in relation to γ radiation calculated from the $LD_{50/30}$ studies was 1.4 and 0.99 respectively for ^{28}Si and ^{12}C. For proton and ^{56}Fe the calculated RBE was 1.06 and 1.25 respectively [3]. We now know that radiation-induced lethality is dependent on LET of the incident beam and a lethality peak is observed at an LET of about 100 keV/micron [10, 11] using in vitro models. We combined proton and ^{56}Fe lethality data generated earlier in the laboratory [3] with the lethality data of ^{28}Si and ^{12}C from the current study and plotted against different radiation doses where at least one dose was 100% lethal and one dose was non-lethal (Figure 2B). We find that while ^{12}C-induced lethality was similar to proton (1000 MeV) and γ radiation-induced toxicity; the ^{28}Si radiation-induced mortality pattern was nearer to ^{56}Fe (energy: 1000 MeV/nucleon) results [3] than other radiation types tested (Figure 2B). The RBE is dependent on the LET and the Z-value of a particular particle. To ascertain the relationship, we plotted RBE of each radiation type against respective LET values (Figure 3A). We observed that although ^{12}C was similar to proton and γ radiation, the ^{28}Si showed higher RBE than ^{56}Fe, which could be written as ^{28}Si (1.41) >^{56}Fe (1.25) >Proton (1.07) >^{12}C (0.99). We also plotted RBE of each radiation type against respective Z-values of the particles studied (Figure 3B). In general the RBE increases to reach a peak at an LET of about 100 keV/micron. Importantly, the RBE decreases with LET values beyond 100 keV/micron [10, 11]. Similarly, the RBE rises with increasing Z-value of the incident particle radiation at comparable LET values [10]. However, as we show here and also reported earlier, the LET value takes precedence over Z-value in determining RBE of particle radiation [10]. A striking finding of our *in vivo* studies relative to previously published *in vitro* studies is the very modest effect of LET and Z value on RBE values; e.g. *in vivo* the RBE varied by 40% or less while published studies using *in vitro* models typically show much higher RBE values for HZE ions [21].

Discussion

Beyond earth's protective magnetosphere, astronauts are exposed to space radiation, and risk associated with space radiation exposure increases with the duration of space travel. However, risk estimation of space radiation through establishment of risk models is hindered not only due to unique characteristics of the radiation in space, but also due to limited understanding and data availability of the effects of space radiation *in vivo*. Here we report the determination of RBE factor for survival after ^{12}C and ^{28}Si exposure in relation to γ radiation, thus fulfilling an important knowledge gap in the literature. As discussed previously [27], these RBE values are critical in planning *in vivo* tumorigenesis studies, such as we are carrying out for intestinal neoplasia; e.g., a very high RBE, such as seen in

cell culture models, would limit the range of doses that could be employed in these expensive long-term studies.

Current understanding of space radiation indicates that protons contribute about 90% of SPE. In contrast, the contribution of protons towards dose equivalent in GCR is markedly less, with a greater contribution from high Z and energy (HZE) particles like ^{56}Fe, ^{12}C, ^{28}Si, and ^{16}O. These HZE particles due to their high-LET characteristics are much more damaging than protons and determination of a reliable *in vivo* RBE factor is an important component of space radiation risk model development. In the absence of SPEs, expected radiation doses in space are much lower (<1 Gy) than the doses used in this study and current risk estimates of space radiation are based on low dose and dose rate [1, 28]. However, dose protraction during prolonged space missions like a Mars mission and stays at International Space Station (ISS) may cause significant dose accumulation and long-term health concern in astronauts. Importantly, non-availability of ^{28}Si and ^{12}C RBE of survival in mice in the literature led us to design this study to aid not only in our intestinal tumorigenesis study in the APC mutant mouse model in the dose range (<1 Gy) relevant to space radiation environment but also in determining *in vivo* lethality in terms of RBE-LET relationship of particle radiation. Data presented here show that the RBE is dependent on LET and particle energy and is qualitatively in agreement with earlier observations [10] but the magnitude of the effect was much less *in vivo* where all RBE values were <1.5. We know that LET is dependent on particle energy and RBE is dependent on LET. When we compared 300 MeV/nucleon ^{28}Si (LET-69 keV/micron) with 1000 MeV/nucleon ^{56}Fe (LET – 148 keV/micron), we observed higher RBE for ^{28}Si (RBE – 1.4) than ^{56}Fe (RBE – 1.25) which we believe is due to difference in LET and is supportive of observations in the literature [10]. However, LET and hence RBE is also dependent on the Z value of the particle at similar energy [11]. In this study ^{12}C has a Z value of 6 and ^{28}Si has a Z value of 14 and when similar energy (300 MeV/nucleon ^{28}Si and 290 MeV/nucleon ^{12}C) of these two particles was used we observed significant difference in survival as well as in RBE values (RBE: 1.4 for ^{28}Si and 0.99 for ^{12}C), which is qualitatively similar to previous *in vitro* data. While RBE values <1.0 for ^{12}C ions has been reported for DNA double strand break induction [29, 30] and dicentrics formation [31], the RBE values of > 6.0 have been reported for ^{28}Si and ^{56}Fe [32]. Surprisingly, however, in our *in vivo* study the $LD_{50/30}$ of ^{12}C was high and consequently the RBE value was low and parallels our γ radiation lethality pattern and $LD_{50/30}$. The RBE value of 1.4 for ^{28}Si, although slightly higher than ^{56}Fe, was also unexpectedly very low for high-LET heavy ion radiation and has not been reported previously. More surprising is the fact that the RBE of the heavy ions in our *in vivo* experimental system is lower than the RBE of neutron radiation, which has been reported, depending on energy, to be 1.6 and higher in mice [33, 34].

Studies in *in vitro* cell culture system have typically shown high RBE of various parameters including cell survival. However, a number of *in vitro* cell survival studies using ^{12}C at an LET of 13 keV/μm (used in our study) have reported an RBE of ~1 and is supportive of our *in vivo* observations. In contrast, ^{28}Si RBE for *in vitro* cell survival has been reported to be ~2 at an LET of 70 keV//μm (used in our study) and for both ^{12}C and ^{28}Si, RBE increases with the increase in LET of up to 100 to 200 keV/μm after which RBE decline which has been suggested to be due to the stopping effects of the heavy ion radiation [21]. Although

both *in vitro* and *in vivo* ^{12}C RBE for survival at an LET of 13 keV/μm is near 1 and bears similarity to γ radiation, the RBE for ^{28}Si and ^{56}Fe at an LET similar to our study are markedly higher for *in vitro* cell survival than *in vivo* mice survival. It is important to note that *in vitro* RBE is determined typically at 10% cell survival and requires much lower doses (~2 Gy) for cell killing than *in vivo* animal experiments where typically doses >5 Gy is required to determine the $LD_{50/30}$ dose. While *in vitro* survival is determined in a single cell type, *in vivo* organismal survival is determined through complex interaction of multiple cell types in three-dimensional tissues with its microenvironment. Our results show that *in vivo* lethality increases with increase in Z and/or LET of the particle radiation. A distinct lethality pattern can be seen starting with lower lethality in particles having Z≤6 and LET≤13 and an RBE of near 1 (proton and ^{12}C) and corresponds to hematopoietic lethality pattern of γ radiation observed with doses below 10 Gy [33]. Higher and early lethality pattern with doses < 8 Gy in particles having Z≥6 with LET ≥13 with an RBE >1 (^{28}Si and ^{56}Fe) could be due to accelerated hematopoietic toxicity observed earlier [3] and needs to be taken into considerations for risk estimates of these particles.

The lower RBE for ^{12}C ion and higher RBE for ^{28}Si ion could be due to beam and particle characteristics described earlier, and correlates well with earlier responses observed for testis weight loss by Aplen et al, 1994 [35]. The RBE of heavy ions is related to the LET, Z-Value, and importantly to their energy deposition pattern (Braggs curve). While at the Bragg peak, the LET value is between 50 to 80 keV/μm, ^{12}C at 290 MeV/nucleon shows much lower LET (13 keV/μm in the current study) at the entrance plateau region of the Bragg curve and hence lower RBE in our study. Interestingly, ^{28}Si (Z-14) although has a lower Z value than ^{56}Fe (Z-26) showed higher RBE which could be attributed to difference in energy, and hence LET and is consistent with published literature [21]. Although there are *in vitro* data, here we demonstrate in mice that biological effects of particle radiation is dependent on LET as well as on ion species [22]. In conclusion, we show that the RBE of survival of heavy ions is lower than the values predicted by *in vitro* cell culture and modeling studies and may require a reassessment of RBE of other ion species for more accurate risk estimate.

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References

1. Hamilton SA, Pecaut MJ, Gridley DS, Travis ND, Bandstra ER, Willey JS, Nelson GA, Bateman TA. A murine model for bone loss from therapeutic and space-relevant sources of radiation. J Appl Physiol. 2006; 101:789–793. [PubMed: 16741258]
2. Townsend LW. Implications of the space radiation environment for human exploration in deep space. Radiat Prot Dosimetry. 2005; 115:44–50. [PubMed: 16381680]
3. Datta K, Suman S, Trani D, Doiron K, Rotolo JA, Kallakury BV, Kolesnick R, Cole MF, Fornace AJJ. Accelerated hematopoietic toxicity by high energy (56)Fe radiation. Int J Radiat Biol. 2012; 88:213–222. [PubMed: 22077279]
4. Hayatsu K, Hareyama M, Kobayashi S, Yamashita NKS, Hasebe N. HZE Particle and Neutron Dosages from Cosmic Rays on the Lunar Surface. J Phys Soc Jpn. 2009; 78:149–152.

5. Cucinotta FA, Wu H, Shavers MR, George K. Radiation dosimetry and biophysical models of space radiation effects. Gravit Space Biol Bull. 2003; 16:11–18. [PubMed: 12959127]
6. Datta K, Neumann RD, Winters TA. Characterization of complex apurinic/apyrimidinic-site clustering associated with an authentic site-specific radiation-induced DNA double-strand break. Proc Natl Acad Sci U S A. 2005; 102:10569–10574. [PubMed: 16024726]
7. Hada M, Sutherland BM. Spectrum of complex DNA damages depends on the incident radiation. Radiat Res. 2006; 165:223–230. [PubMed: 16435920]
8. Curtis SB, Townsend LW, Wilson JW, Powers-Risius P, Alpen EL, Fry RJ. Fluence-related risk coefficients using the Harderian gland data as an example. Adv Space Res. 1992; 12:407–416. [PubMed: 11537038]
9. Brooks A, Bao S, Rithidech K, Couch LA, Braby LA. Relative effectiveness of HZE iron-56 particles for the induction of cytogenetic damage in vivo. Radiat Res. 2001; 155:353–359. [PubMed: 11175671]
10. Alpen EL, Powers-Risius P. The relative biological effect of high-Z, high-LET charged particles for spermatogonial killing. Radiat Res. 1981; 88:132–143. [PubMed: 7302123]
11. Rodriguez A, Alpen EL, Powers-Risius P. The RBE-LET relationship for rodent intestinal crypt cell survival, testes weight loss, and multicellular spheroid cell survival after heavy-ion irradiation. Radiat Res. 1992; 132:184–192. [PubMed: 1438700]
12. Alpen EL, Powers-Risius P, McDonald M. Survival of intestinal crypt cells after exposure to high Z, high-energy charged particles. Radiat Res. 1980; 83:677–687. [PubMed: 7413928]
13. Aoki M, Furusawa Y, Yamada T. LET dependency of heavy-ion induced apoptosis in V79 cells. J Radiat Res (Tokyo). 2000; 41:163–175. [PubMed: 11037583]
14. Chen DJ, Tsuboi K, Nguyen T, Yang TC. Charged-particle mutagenesis II. Mutagenic effects of high energy charged particles in normal human fibroblasts. Adv Space Res. 1994; 14:347–354. [PubMed: 11539970]
15. Lett JT. Damage to cellular DNA from particulate radiations, the efficacy of its processing and the radiosensitivity of mammalian cells. Emphasis on DNA double strand breaks and chromatin breaks. Radiat Environ Biophys. 1992; 31:257–277. [PubMed: 1438677]
16. Suzuki M, Tsuruoka C, Uchihori Y, Kitamura H, Liu CH. Radiation-quality dependent cellular response in mutation induction in normal human cells. J Radiat Res (Tokyo). 2009; 50:395–399. [PubMed: 19680011]
17. Ainsworth EJ. Early and late mammalian responses to heavy charged particles. Adv Space Res. 1986; 6:153–165. [PubMed: 11537215]
18. Blakely EA, Tobias CA, Yang TC, Smith KC, Lyman JT. Inactivation of human kidney cells by high-energy monoenergetic heavy-ion beams. Radiat Res. 1979; 80:122–160. [PubMed: 504567]
19. Asaithamby A, Uematsu N, Chatterjee A, Story MD, Burma S, Chen DJ. Repair of HZE-particle-induced DNA double-strand breaks in normal human fibroblasts. Radiat Res. 2008; 169:437–446. [PubMed: 18363429]
20. Kato TA, Tsuda A, Uesaka M, Fujimori A, Kamada T, Tsujii H, Okayasu R. In vitro characterization of cells derived from chordoma cell line U-CH1 following treatment with X-rays, heavy ions and chemotherapeutic drugs. Radiat Oncol. 2011; 6:116. [PubMed: 21914223]
21. Tsuruoka C, Suzuki M, Kanai T, Fujitaka K. LET and ion species dependence for cell killing in normal human skin fibroblasts. Radiat Res. 2005; 163:494–500. [PubMed: 15850410]
22. Tsuruoka C, Suzuki M, Hande MP, Furusawa Y, Anzai K, Okayasu R. The difference in LET and ion species dependence for induction of initially measured and non-rejoined chromatin breaks in normal human fibroblasts. Radiat Res. 2008; 170:163–171. [PubMed: 18666815]
23. Becker D, Elsasser T, Tonn T, Seifried E, Durante M, Ritter S, Fournier C. Response of human hematopoietic stem and progenitor cells to energetic carbon ions. Int J Radiat Biol. 2009; 85:1051–1059. [PubMed: 19895282]
24. Takiguchi Y, Miyamoto T, Nagao K, Kuriyama T. Assessment of the homogeneous efficacy of carbon ions in the spread-out Bragg peak for human lung cancer cell lines. Radiat Med. 2007; 25:272–277. [PubMed: 17634880]

25. Cucinotta FA, Townsend LW, Wilson JW, Golightly MJ, Weyland M. Analysis of radiation risk from alpha particle component of solar particle events. Adv Space Res. 1994; 14:661–670. [PubMed: 11538031]
26. Schimmerling W, Wilson JW, Cucinotta F, Kim MH. Evaluation of risk from space radiation with high-energy heavy ion beams. Phys Med. 1998; 14(Suppl 1):29–38. [PubMed: 11542638]
27. Trani D, Datta K, Doiron K, Kallakury B, Fornace AJJ. Enhanced intestinal tumor multiplicity and grade in vivo after HZE exposure: mouse models for space radiation risk estimates. Radiat Environ Biophys. 2010; 49:389–396. [PubMed: 20490531]
28. Cucinotta FA, Schimmerling W, Wilson JW, Peterson LE, Badhwar GD, Saganti PB, Dicello JF. Space radiation cancer risks and uncertainties for Mars missions. Radiat Res. 2001; 156:682–688. [PubMed: 11604093]
29. Hirayama R, Furusawa Y, Fukawa T, Ando K. Repair kinetics of DNA-DSB induced by X-rays or carbon ions under oxic and hypoxic conditions. J Radiat Res (Tokyo). 2005; 46:325–332. [PubMed: 16210789]
30. Terato H, Watari H, Shimazaki Y, Hirayama R, Furusawa Y, Ide H. Analysis for complexity of clustered DNA damage generated by heavy ion beams. Nucleic Acids Symp Ser (Oxf). 2008:443–444.
31. Monobe M, Ando K. Drinking beer reduces radiation-induced chromosome aberrations in human lymphocytes. J Radiat Res (Tokyo). 2002; 43:237–245. [PubMed: 12518984]
32. Kawata T, Durante M, Furusawa Y, George K, Takai N, Wu H, Cucinotta FA. Dose–response of initial G2-chromatid breaks induced in normal human fibroblasts by heavy ions. Int J Radiat Biol. 2001; 77:165–174. [PubMed: 11236923]
33. Hall, EJ.; Giaccia, AJ. Radiobiology for the Radiologist. 2006. p. 1-521.
34. Tochilin G, Shumway B, Kohler G, Bond VP. Re-evaluation of fast neutron RBE values on the basis of improved cross-section data. Radiat Res. 1959; 11:343–344. [PubMed: 13838602]
35. Alpen EL, Powers-Risius P, Curtis SB, DeGuzman R, Fry RJ. Fluence-based relative biological effectiveness for charged particle carcinogenesis in mouse Harderian gland. Adv Space Res. 1994; 14:573–581. [PubMed: 11539994]

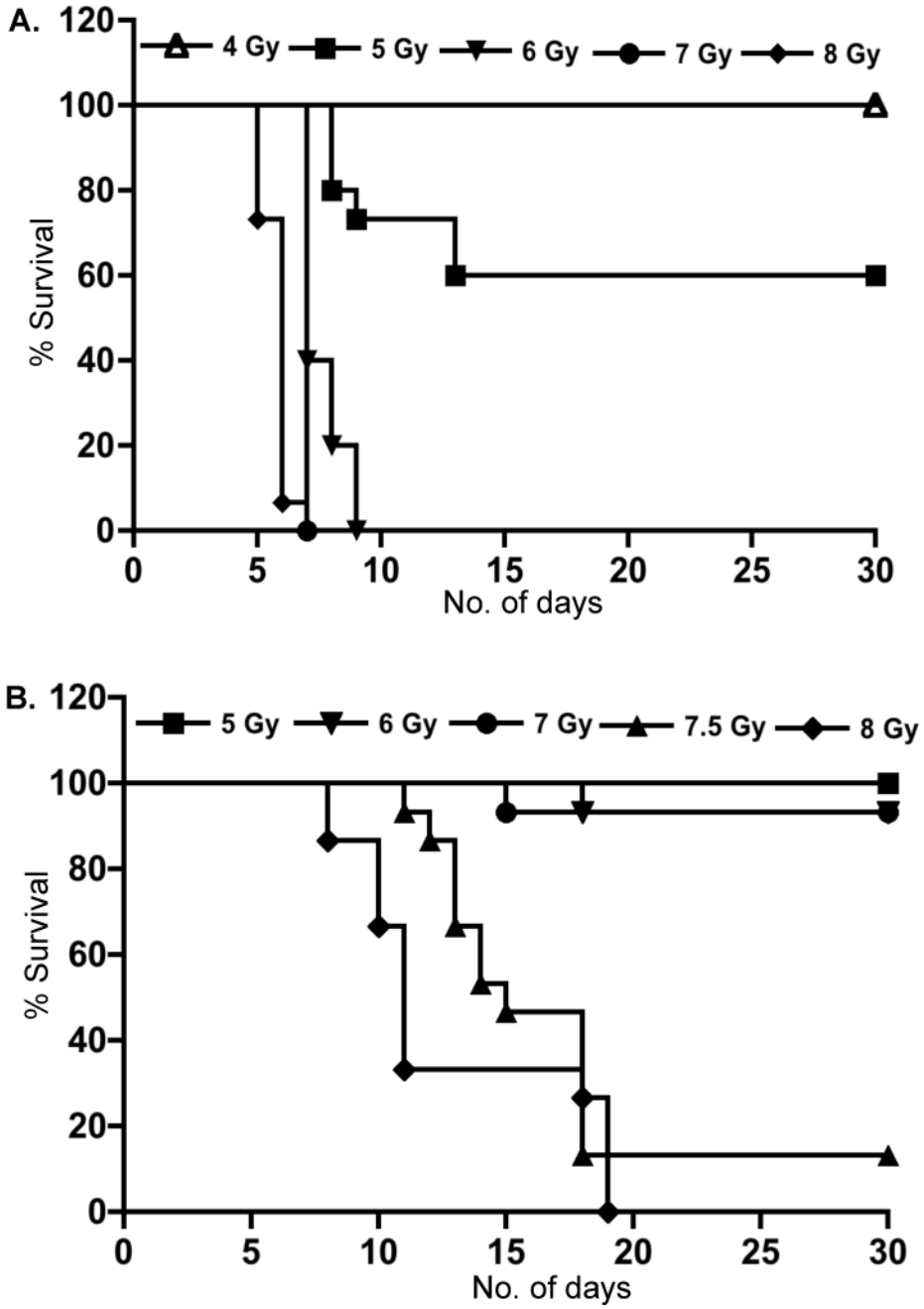

Figure 1.

Survival pattern of 6 to 8 weeks old female C57BL/6J mice for 30 days after exposure to different doses of ^{28}Si and ^{12}C radiation. A) The survival pattern after exposure to ^{28}Si radiation is plotted for doses 4 to 8 Gy. Most of the lethality after ^{28}Si radiation occurred before 10th post-radiation day with 6, 7, and 8 Gy showing 100% lethality. B) The survival pattern after exposure to ^{12}C radiation is plotted for doses 5 to 8 Gy. Most of the lethality after ^{12}C radiation occurred after 10th post-radiation day with 7.5 and 8 Gy showing 100% lethality.

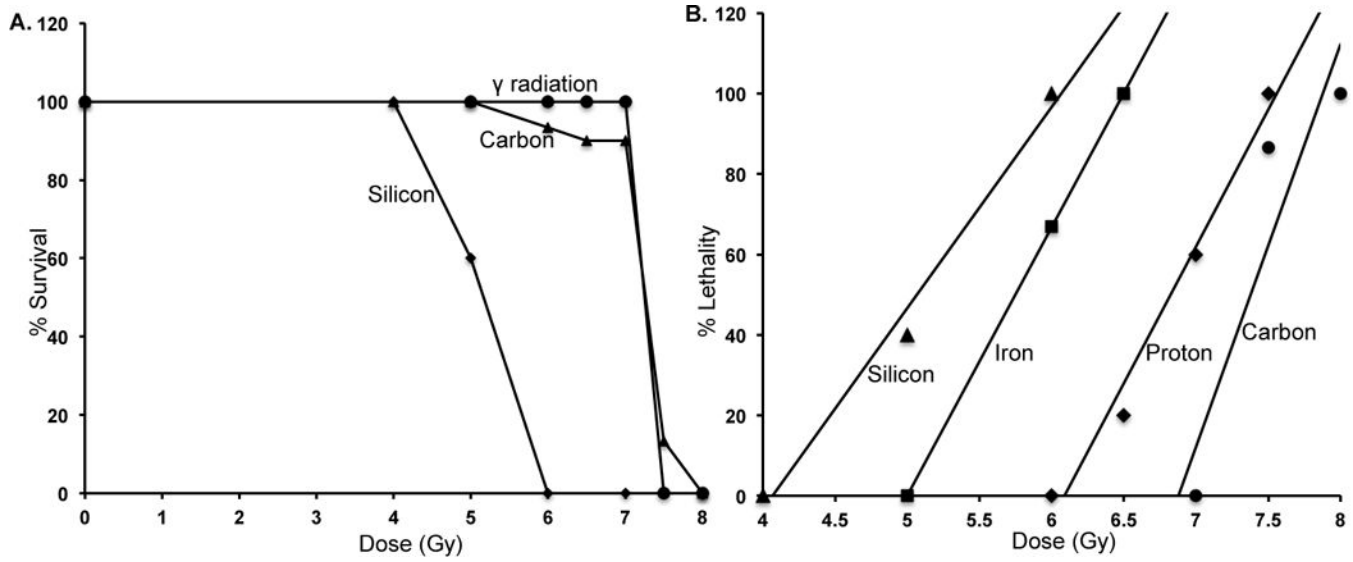

Figure 2.

Determination of $LD_{50/30}$ dose (the dose at which 50% lethality occurs at 30-day) for ^{28}Si and ^{12}C radiation. A) Mice were irradiated with ^{28}Si (4 to 8 Gy), ^{12}C (5 to 8 Gy), and γ (2 to 8 Gy) radiation. Mice were monitored daily for 30 days and data plotted as percent survival against radiation doses and was used to calculate $LD_{50/30}$ dose of ^{28}Si (5.17 Gy) and ^{12}C (7.34 Gy). B) The 30-day lethality patterns of proton doses (6, 6.5, 7, and 7.5 Gy) and ^{56}Fe doses (5, 6, 6.5 Gy) (published earlier; [3]) are compared to those of ^{28}Si and ^{12}C. For each radiation type a non-lethal, a 100% lethal, and an intermediate dose (2 for proton) was used to plot the graph. The ^{28}Si (RBE: 1.4) radiation showed highest lethality followed by that of ^{56}Fe (RBE: 1.25), proton (RBE: 1.06) and ^{12}C (RBE: 0.99) respectively.

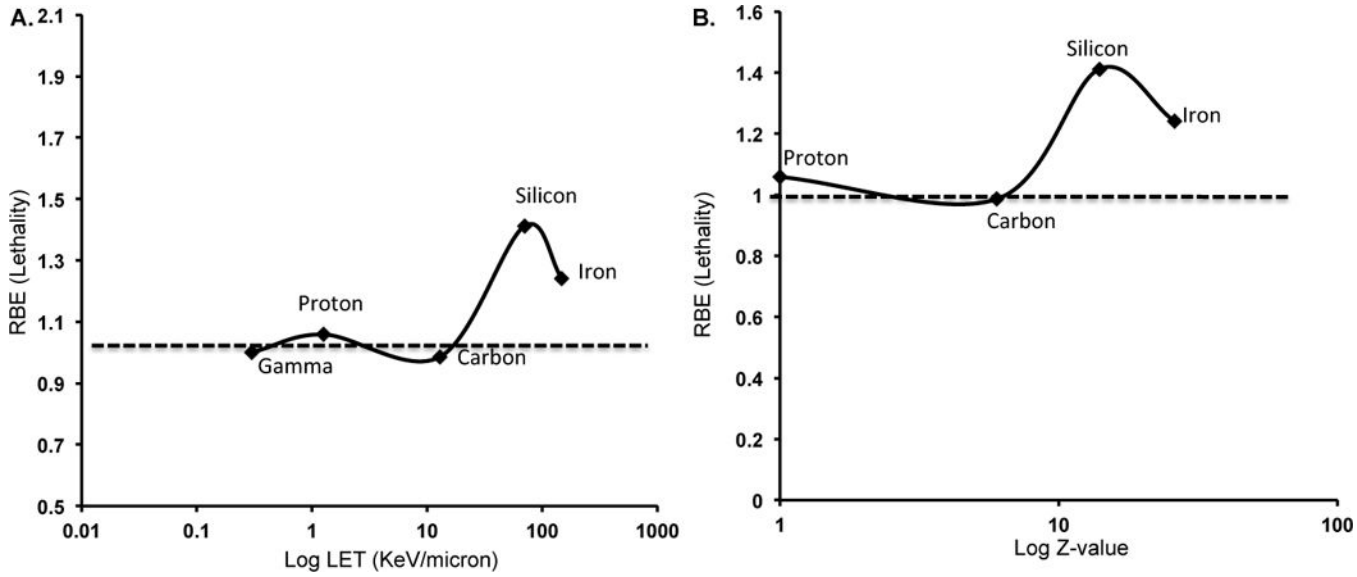

Figure 3.

Relationship between RBE and LET and RBE and Z-value showed a trend similar to what has been reported in literature. A) Taking γ-radiation value as 1, the RBE values of proton, ^{12}C, ^{28}Si, and ^{56}Fe are plotted against respective LET values. Peak RBE at a LET value of 70 keV/micron and a decline in RBE at a LET value of 148 keV/micron was observed and supports earlier observations [11]. B) Considering proton value of 1, the Z-values of ^{12}C (6), ^{28}Si (14), and ^{56}Fe (26) were plotted against respective RBE values. RBE increases with increasing LET and Z-value of the ion. However, with increasing Z-value RBE may be lower if the LET is >100 keV/micron and is consistent with what has been reported earlier [10, 11].

Table 1

Radiation type and their characteristics.

Radiation type	Z value	LET range (KeV/micron)	Energy	Dose rate (Gy/min)
Gamma (Cesium-137)	N/A	0.3	0.662MeV	1
Proton	1	1.26	1,000 MeV/nucleon	1
^{12}C	6	12.95	290 MeV/nucleon	1
^{28}Si	14	69.17	300 MeV/nucleon	1
^{56}Fe	26	148	1,000 MeV/nucleon	1