Cancer risk from exposure to galactic cosmic rays: implications for space exploration by human beings

Francis A Cucinotta, Marco Durante

Space programmes are shifting toward planetary exploration, and in particular towards missions by human beings to the moon and Mars. However, exposure to space radiation is an important barrier to exploration of the solar system by human beings because of the biological effects of high-energy heavy ions. These ions have a high charge and energy, are the main contributors to radiation risk in deep space, and their biological effects are understood poorly. Predictions of the nature and magnitude of risks posed by exposure to radiation in space are subject to many uncertainties. In recent years, worldwide efforts have focussed on an increased understanding of the oncogenic potential of galactic cosmic rays. A review of the new results in this specialty will be presented here.

Introduction
Space exploration is an adventure for humankind, with the potential for discoveries that capture our imaginations and benefit society. The benefits from exploration¹ must be balanced with the cost, safety, and ethical concerns when deciding acceptable risks for astronauts. The main health concerns are exposure to galactic cosmic rays (GCR) and solar proton events, which lead to substantial, but poorly understood, risks of carcinogenesis and degenerative disease.² ³ Spaceflights in low Earth orbit, such as missions on a space shuttle and at the international space station, are partly protected by the Earth’s magnetic field and the solid shielding of the planet. The Apollo space missions ventured away from the protection of the Earth, but lasted only up to 12 days. Proposed missions to the moon (figure 1) in the next decade could last up to 200 days. Furthermore, a possible mission to Mars that could last up to 3 years would lead to whole-body doses of radiation of about 1 Sievert (Sv) or more.⁴ However, the ideas used for prediction of risk on Earth, including use of the dose unit Sv, are perhaps deceptive for GCR exposure. This Essay discusses efforts to improve the understanding of biological effects of densely ionising heavy ions through biomedical research of cancer.

Space radiation environments and risk assessment
In space, astronauts are exposed to: protons; high-energy heavy (HZE) ions that have a high charge (Z) and energy (E); and secondary radiation, including neutrons and recoil nuclei produced by nuclear reactions in spacecraft walls or in tissue. The energy spectrum of GCR peaks near 1000 MeV per nucleon, and these particles are so penetrating that shielding can only partly reduce the doses absorbed by the crew. Thick shielding has problems for spacecraft launch systems because of its mass, and would only reduce effective GCR dose by no more than 25% with aluminium or by about 35% with the more-efficient polyethylene. Present shielding approaches cannot be regarded as a solution for the issue of radiation exposure in space, with the exception of solar proton events, which are effectively absorbed by shielding.⁵

On travelling to Mars, every cell nucleus in an astronaut’s body would be hit by a proton or secondary electron (eg, electrons of the target atoms ionised by the HZE ion) every few days and by an HZE ion about once a month.⁶ Whole-body doses of 1–2 mSv per day accumulate in interplanetary space and about 0.5–1 mSv per day on planetary surfaces.⁷ The high ionisation power of HZE ions makes them the main contributor to risk, despite the low frequency at which they might hit a cell nucleus compared with protons. To undertake ground-based research into space radiation, special facilities are needed to accelerate charged particles (from protons to iron) to very high energies. Only a few such facilities exist in the world, and the National Aeronautics and Space Administration (NASA) has invested in a new facility at Brookhaven National Laboratory, Long Island, NY, USA.

On Earth, radiation workers or patients are most frequently exposed to low-linear-energy-transfer (LET) radiations.¹⁰

Figure 1: A future moon landing
According to the new Vision for Space Exploration (January, 2004), the National Aeronautics and Space Administration (NASA) plans to return to the moon in 2020. The present project anticipates four to six crew members who will complete lunar-surface exploration for 60–180 days. The Earth–moon cruise lasts about 4 days.

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Sievert
Unit of equivalent dose; Sv; m² s⁻²
1 Sv corresponds to 1 Sv for x-rays and to 20 Sv for heavy ions

Nucleon
A proton or neutron, the total of which make up the atomic weight of human beings during the time of study of the problems of cancer.
Astronauts. In the non-targeted model (C), shielding is ineffective in tissue (D) and distinct targets for biological countermeasures are pursued. ATM=ataxia telangiectasia mutated. TGFβ=transforming growth factor β.

Risk is expected, with research focus on the slope of response as a function of radiation quality and radiation mission duration, and design of biological countermeasures. In the DNA-target model (A), a linear response (B) for radiation such as γ-rays or x-rays. Epidemiological data, mainly from survivors of the atomic bomb in Japan, enable risk estimation of low-LET (ie, sparsely ionising) radiation. However, because no data for exposure to protons and HZE ions exist in human beings, risk estimates for exposure to GCR must rely entirely on experimental model systems and biophysical calculations. At present, predictions are made by use of the double-detriment lifetable for an average population such as that of the USA, which consists of age-dependent and sex-dependent rates of death combined with a model of radiation-induced cancer-mortality rates. The model used for cancer mortality from radiation is based on epidemiological studies of survivors of atomic bombs, which are assumed to be scalable to other populations, dose rates, and radiation types. Two scaling variables with large uncertainties are: the radiation-quality factor, Q, which estimates the increased effectiveness of HZE ions compared with γ-rays for the same dose; and the dose and dose-rate effectiveness factor (DDREF), which reduces estimates of cancer risk at high doses and dose-rates when dose-rates are low (ie, <0.05 Gy/h).

The table shows risks for extended missions to the moon and Mars; in this table, 95% CI are reported that account for uncertainties in epidemiological data, space environments, radiation quality, and DDREF. Maximum acceptable levels of risk for astronauts are typically set at 3% fatal risk (eg, risk of mortality from cancer), but the large uncertainties in predictions and the likelihood of other fatal or morbidity risks (eg, risk of disease) for degenerative diseases precludes whether or not a mission can be made to Mars. Use of data from survivors of atomic bombs to scale mortality for radiation risk to astronauts in space introduces many uncertainties into risk estimates, and important questions remain with respect to the accuracy of any scaling approach because of qualitative differences in the biological effects of HZE ions and γ-rays.

Radiobiology of HZE ions: cellular effects
A necessary step for reducing uncertainties in risk assessment are studies of molecular pathways of cancer initiation and progression, and to extend these studies to learn how such pathways can be disrupted by HZE ions including induction of genetic and epigenetic changes (figure 2). The aim of this research is to establish a more-mechanistic approach to risk estimation, and to answer questions such as: whether HZE effects can be scaled from those of γ-rays; whether risk is linear with low dose-rate; and how individual radiation sensitivity affects risk for astronauts—a population selected for many factors related to excellence in health.

First, we can analyse the initial biophysical events caused by HZE tracks (eg, a heavy ion moves along a straight track in the target material; figure 3) in cells and tissue. Energy deposition by HZE ions is highly heterogeneous, with a localised contribution along the trajectory of every particle and lateral diffusion of energetic electrons (ie, δ-rays, the target atom electrons ionised by the incident HZE ion and emitted at high energy) many microns from the path of the ions. These particles are therefore densely ionising (high-LET) along the primary track (eg, the track followed by the incident heavy ion); however, they have a low-LET component because of the high-energy electrons ejected by ions as they traverse tissue. Biophysical models have shown that energy-deposition events by high-LET radiation produce different DNA lesions, including complex DNA breaks, and that qualitative differences between high-LET radiation and low-LET radiation affect both the induction

Table: Radiation risks for men and women on missions to the moon or Mars

<table>
<thead>
<tr>
<th>Time in space</th>
<th>GCR dose</th>
<th>Absorbed dose (Gy)*</th>
<th>Effective dose (Sv)</th>
<th>Fatal risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lunar mission (180 days)</td>
<td>0.06</td>
<td>0.17</td>
<td>0.68% (0.20–2.4)</td>
<td>0.0% (0–0)</td>
</tr>
<tr>
<td>Mars orbit (600 days)</td>
<td>0.37</td>
<td>1.03</td>
<td>4.0% (1.1–13.5)</td>
<td>4.9% (1.4–16.2)</td>
</tr>
<tr>
<td>Mars exploration (1000 days)</td>
<td>0.42</td>
<td>1.07</td>
<td>4.2% (1.3–13.6)</td>
<td>5.1% (1.6–16.4)</td>
</tr>
</tbody>
</table>

Calculations are at solar minimum, where GCR dose is highest behind a 5 g/cm² aluminium shield. *Mean for tissues known to be genotoxically sensitive (primary DNA damage) such as lung, colon, stomach, bladder, bone marrow, and breast and ovaries in women. Competing causes of death are included in calculations because they decrease risk probabilities if high (ie, >5%).
and repair of DNA damage. The number of DNA single-strand breaks and double-strand breaks produced by radiation varies little with radiation type. However, for high-LET radiation, many types of DNA damage are complex (ie, clusters containing mixtures of two or more various types of damage, such as single-strand breaks and double-strand breaks), and occur within a localised region of DNA. Complex damage is uncommon for endogenous damage (eg, DNA damage caused by cellular errors during duplication) or low-LET radiation and has been associated with the increased relative biological effectiveness of densely ionising radiation. Figure 3 compares charged-particle tracks visualised in nuclear emulsions with patterns of DNA double-strand-break distributions in human cells. DNA double-strand breaks are visualised in situ by γ-H2AX immunofluorescence staining—a technique that exploits the rapid phosphorylation of the histone H2AX in the chromatin surrounding a DNA double-strand break. The different patterns of energy deposition for various particles is shown in the different distribution of double-strand breaks in cells.

Repair of double-strand breaks occurs through direct end-joining and homologous recombination. Exposure to high-LET radiation, in which complex double-strand breaks occur with high frequency, seems to result in little repair, and thus cell death. Misrejoining of unreparable ends of DNA with other radiation-induced double-strand breaks leads to large DNA deletions and chromosome aberrations. The high effectiveness in cell killing is the rationale for heavy-ion cancer treatment—ie, hadrontherapy, radiotherapy with high-energy charged nuclei rather than x-rays—but residual damage in surviving cells is of concern for carcinogenesis.

Heavily charged particles effectively produce interchromosomal exchanges, with relative biological effectiveness exceeding 30 in interphase (as visualised by use of premature chromosome condensation) for energetic iron ions. The detailed association between relative biological effectiveness and LET found for total chromosome exchanges is consistent with previous studies of relative biological effectiveness versus LET with respect to mutation and to in-vitro neoplastic transformation in rat cells. For all these endpoints, relative biological effectiveness peaks at about 100–200 keV/µm and decreases at very high LET. However, the nature of chromosome damage is different with heavy ions compared with that of sparsely ionising radiation. Large differences in gene expression are noted on exposure to x-rays compared with that for HZE ions, showing differences in damage-response pathways. Furthermore, qualitative differences between x-rays and HZE in the type of gene mutations have been reported. Multicolour fluorescence-painting techniques of chromosome of human beings have shown that high-LET α-particles and iron ions induce substantially more complex chromosome exchanges in cells than does low-LET radiation. Most of these complex chromosome rearrangements ultimately lead to cell death. Only a small amount of the initial cytogenetic damage is measured in mice 2–4 months after exposure to energetic iron ions. A low relative biological effectiveness for the induction of late chromosome damage has been measured in the progeny of human lymphocytes exposed in vitro to energetic iron ions. However, terminal deletions (eg, single truncated chromosomes) occur at much higher frequency in the progeny of cells exposed to heavy ions compared with those exposed to γ-rays.

Presence of chromosomes without telomeres in the progeny of cells exposed to heavy ions is of particular interest. Sabatier and colleagues found that rearrangements of telomere regions were associated with chromosome instability in human fibroblasts, many generations after exposure to accelerated heavy ions. Telomere dysfunction has a crucial part in initiating or sustaining genomic instability, which is an important step in cancer progression. The effects induced by heavy ions on telomere stability have been studied by use of small-interfering RNA knockdown of components of
and that there is no threshold of exposure below which the biological effects cease to be linear.

DNA-dependent protein kinases in human lymphoblasts.\textsuperscript{42} Exposure of cells with reduced DNA-dependent protein kinase expression to γ-rays or iron particles shows differential effects on telomere dysfunction, mutation frequency, and differential effects between radiation qualities. Different results were found for γ-rays and HZE nuclei: iron nuclei were more effective in producing double-strand breaks—telomere fusions when DNA-dependent protein kinases are inactive. Cells containing telomere-deficient chromosomes either senesce or undergo cycles of breakage, fusion, and bridging cycles, promoting genetic instability. The fate of normal cells containing one truncated chromosome with loss of the telomere is not known, but loss of one telomere in cancer cells can result in instability in several chromosomes.\textsuperscript{43} These results suggest that telomere instability is an important early event in the pathway to cancer induction by HZE nuclei.

**Radiobiology of HZE ions: tissue effects**

Studies in animals generally show that HZE nuclei have a higher carcinogenic effect than does low-LET radiation. Relative biological effectiveness factors comparing γ-rays with HZE ions in mice or rats for tumours of the skin\textsuperscript{44} and of the Harderian\textsuperscript{38} or mammary\textsuperscript{45} glands recorded values as high as 25–40 at low doses. However, the risk of developing cancer, and its effect on factors such as quality of life, cannot be characterised fully until the relation between radiation quality and latency, in which tumours develop earlier after high-LET irradiation than after that of low LET,\textsuperscript{46} is defined adequately. The short latency and increased effectiveness noted for HZE ions compared with sparsely ionising radiation was similar to that of previous studies of neutrons,\textsuperscript{47} and, together with the lack of response for tumour induction in mice by γ-rays recorded in many low-dose studies, suggests that the ideas for scaling used in present risk-assessment approaches are unable to define important qualitative effects and that relative biological effectiveness factors are potentially not definable or are faulty.

Studies have discussed the importance of DNA damage and mutation or extracellular-matrix remodelling and other non-targeted effects as initiators of carcinogenesis.\textsuperscript{48} Tissue effects independent of DNA damage associated with cancer initiation or progression include genomic instability,\textsuperscript{49} extracellular-matrix remodelling,\textsuperscript{49} persistent inflammation,\textsuperscript{50} and oxidative damage.\textsuperscript{51} Other studies are investigating: the relations between radiation, activation of dormant tumours, and modulation of angiogenesis;\textsuperscript{52} the acceleration of non-cancer risks that occur during aging, including cataracts;\textsuperscript{49} and damage to the CNS.\textsuperscript{49}

So-called bystander or non-targeted effects\textsuperscript{49,53} could have important consequences for space exploration. These effects occur in cells that are not hit directly by an ionising particle, but which are affected by signals from irradiated cells in tissue up to about 1 mm away.\textsuperscript{49} These long-range effects in tissues are important in assessment of the risk exposure to low-dose radiation. Non-targeted effects might increase the risk at low doses, thus reducing the effectiveness of spacecraft shielding; however, they might have a protective effect if cells surrounding the hit cell are removed by apoptosis from the organism. Both potential effects challenge the conventional linear no-threshold-risk model assumption,\textsuperscript{47} which is used for radioprotection on Earth and in space, but is still disputed in the scientific community.\textsuperscript{49} Moreover, these effects suggest important targets for biological countermeasures likely to be more effective than those targeting DNA damage.\textsuperscript{49}

**Conclusion**

Radiation-induced cancer is one of the main health risks for manned exploration of the Solar system. Epidemiological studies on Earth have shown that exposure to moderate to high doses of ionising radiation increases the risk of cancer in most organs. Leukaemia and cancers of the breast, thyroid, colon, and lung are particularly sensitive to induction by radiation.\textsuperscript{10} However, risk uncertainties for space radiation tumorigenesis are still very high because the radiation quality in space is very different from that on Earth. Reduction of the uncertainties in risk assessment, which are needed before a mission to Mars, has led to many investigations guided by molecular and genetic research on carcinogenesis and degenerative diseases. The main uncertainties in risk-projection models will be reduced only by improvement of basic understanding of the underlying biological processes and their disruption by space radiation. Unique features are involved in this approach because of the specific challenges to biological systems presented by space radiation, especially HZE ions. The issue of radiation risk during space exploration is unlikely to be solved by a simple countermeasure, such as shielding or radioprotective drugs. The risk will be understood and controlled only with further basic research in cancer induction by charged particles.

**Conflicts of interest**

We declare no conflicts of interest.

**Acknowledgments**

We thank NASA Space Radiation Health Program and the Italian Space Agency (ASI) for their support to research activity, and Kerry George, Wile Laboratories, Houston, TX, USA for critical reading of our report.

**References**

5. **Cucinotta FA, Nikjoo H, Goodhead DT. The effects of delta rays on the number of particle-track transversals per cell in laboratory and space exposures. Radiat Res 1998; 150: 115–19.**