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Space Radiation and Cataracts in Astronauts

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For over 30 years, astronauts in Earth orbit or on missions to the moon have been exposed to space radiation comprised of high-energy protons and heavy ions and secondary particles produced in collisions with spacecraft and tissue. Large uncertainties exist in the projection of risks of late effects from space radiation such as cancer and cataracts due to the absence of epidemiological data. Here we present the first epidemiological data linking an increased risk of cataracts for astronauts with higher lens doses (>8 mSv) of space radiation relative to other astronauts with lower lens doses (<8 mSv). Our study uses historical data for cataract incidence in the 295 astronauts participating in NASA's Longitudinal Study of Astronaut Health (LSAH) and individual occupational radiation exposure data. These results, while preliminary because of the use of subjective scoring methods, suggest that relatively low doses of space radiation are causative of an increased incidence and early appearance of cataracts.

INTRODUCTION

Astronauts face many acute risks during space travel; however, when they return to Earth, a lifetime risk for late effects such as cancer and cataracts persists from exposures to galactic cosmic rays (GCR), trapped protons and electrons in the Earth's magnetic field, and infrequent solar-particle events (*1*). Important differences in the patterns of energy deposition in biomolecules, cells and tissues occur when comparing terrestrial low-linear energy transfer (LET) radiation (*1*, *2*), such as X rays or γ rays, to the high-LET heavy ions and secondary neutrons in space (*1*, *3*), causing the estimation of risks to be uncertain. The phenomenon of light flashes (*4*), which were first observed by the Apollo astronauts (*5*) and which continue to be observed by astronauts on the space shuttle and the International Space Station (ISS), suggested that single heavy particles can affect one or more photoreceptor cells in the retina, raising a concern for damage to other tissues, including the lens (*6*). The mechanisms of cataract formation (*11*, *12*) are not known precisely; however, they are believed to originate from genetic damage in lens epithelial cells, including disruptions in cell cycle controls, apoptosis, abnormal differentiation, and cellular disorganization, or other pathways leading to abnormal lens protein fibers. Radiation-induced cataracts have been studied in cancer patients treated with radiation (*7*, *8*), the survivors of the atomic bombings in Hiroshima and Nagasaki (*9*), and patients undergoing CT scans (*10*). We report here on the first evidence linking an increased incidence and earlier appearance of cataracts in astronauts exposed to higher amounts of space radiation relative to other astronauts.

METHODS

Eye Examinations and Cataract Categorization

The Longitudinal Study of Astronaut Health (LSAH) includes all men and women selected for astronaut service; however, it does not include a small number of mission specialists who have participated in space shuttle missions. Cataract data for astronauts have been collected since the beginning of the space program. Since 1989, all astronauts have undergone eye examinations during pre- and postflight physicals, and are observed every 1 to 2 years at the Flight Clinic at Johnson Space Center (JSC) with slit-lamp biomicroscopy under pupil dilation using 1.0% Mydriacyl. Between 1977 and 1988, eye examinations were performed by referral in the Houston area and records were collected by JSC, and before 1977 examinations were performed at the JSC Flight Clinic. The period since 1989 is especially important because of the larger population of astronauts and because a significant number of astronauts reached an age (>50 years) at which expression of cataracts is more likely to occur. After retirement, most astronauts continue to participate in the LSAH, with only seven censored for lack of follow-up.

Eye examinations have revealed 48 cases of lens opacification in a total of 295 NASA astronauts (27 deceased), including one case of congenital cataracts. No new cases were found at a first eye examination at JSC after 1989. Eight cases were reported prior to 1989 and were reconfirmed at the JSC clinic. Seven cases occurred prior to a first space flight, and two other cases occurred in astronauts who retired without participating in a space mission. Using a subjective method, cataracts have been categorized as posterior subcapsular (PS), anterior subcapsular (AS), nuclear (NC), cortical or dot opacities, and mixed types (Table 1). A further grouping has been made as trace cataracts, when only a small opacification is observed with no apparent loss of visual acuity, and non-trace cataracts, which affect either a larger portion of the lens (for subcapsular or cortical cataracts), produce a significant change in color (for nuclear cataract), or produce mild to severe loss of visual acuity. Visual acuity has been measured using the Snellen high-contrast acuity test. Cataracts have occurred in both eyes in three-fourths of the cases and were nearly

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TABLE 1
Lens Location of Cataracts Observed in Astronauts for Non-trace Cataracts[a] and for all Cataracts

Type	Non-trace cataracts	All cataracts
Posterior subcapsular	3	5
Anterior subcapsular	1	1
Cortical	9	20
Nuclear	6	8
Dot opacities	2	4
Posterior subcapsular and cortical	3	3
Anterior subcapsular and cortical	1	1
Cortical and nuclear	0	6
Total	25	48

[a] Trace cataracts are defined as cases where no loss of visual acuity is apparent and only a small area of the lens for subcapsular or cortical cataracts or color change for nuclear cataracts is observed.

evenly distributed in the left and right eyes in the remainder. Three cases have led to lens surgery. The incidence of other eye diseases for astronauts with cataracts is small, with the most frequent being four cases of glaucoma (three cases associated with cortical cataracts and one with congenital cataract). Of the seven cases occurring prior to space flight, five occurred prior to astronaut selection (three trace cortical cases, one trace NC, and a congenital case). These cases have been excluded from the analysis. Two other cases occurred after astronaut selection but prior to space flight, and two cases occurred in astronauts who retired without participating in a space mission. These latter four cases are included in the comparisons described below for the age-specific survival probability, but not in the comparisons made as a function of time after first space flight.

Statistical Methods and Lens Doses

Survival analysis using the nonparametric Kaplan-Meier method (*14, 15*) was carried out to study the relationships between age or time after exposure and dose. The Kaplan-Meier method corrects for competing factors that censure data such as age at entry into the study, follow-up time, or death. In survival analysis, the probability of failure in the time interval t_j is given by $q_j = d_j/n_j$, and the probability of survival without failure is $p_j = 1 - q_j$, where d_j is the number of failures and n_j is the number at risk (number free of cataracts) prior to the failure that is corrected for withdrawals in the time interval (*14, 15*). The Kaplan-Meier product limit estimate for the survival probability is

$$S(t_k) = \prod_{j=1}^{k} p(t_j). \tag{1}$$

Standard errors for the survival probability were evaluated using Greenwood's formula (*14*). The log-rank test was used to test for differences in the survival probabilities of astronauts exposed to higher amounts of radiation relative to other astronauts. Here two astronaut groups with different lens doses either from all radiation sources or from space radiation alone are defined such that an approximately equal number of astronauts in each group occurs from age 50 years ($N_{\mathrm{high}} = N_{\mathrm{low}} = 56$) to 65 years ($N_{\mathrm{high}} = N_{\mathrm{low}} = 18$). This grouping leads to a low-dose group that includes astronauts who have not participated in space missions or who participated in missions where only small doses were received (<8 mSv) and a high-dose group (>8 mSv). [Note that there is an insufficient number (<20) of astronauts above age 50 years without a space mission to use as a comparison group.] To test for any bias toward astronauts who have flown on multiple missions, a comparison between astronauts who have flown on zero or one mission to those with two or more space missions was made. The hazard ratio of the high to low exposure groups was compared using the log-rank test (*14, 15*), which tests the null hypothesis that the hazard ratio is equal to unity. The hazard ratio is given in terms of the ratios of observed to expected numbers of failures in the two groups as

$$h(t_k) = \frac{\dfrac{O_H}{E_H}}{\dfrac{O_L}{E_L}}, \tag{2}$$

where the observed number of failures in the low-dose group is $O_L = \Sigma_j d_{Lj}$ and the expected number of failures is $E_L = \Sigma_j n_{Lj} d_j / n_j$, with similar definitions for O_H and E_H. A test statistic for the equivalence of the hazard rates in the two groups, based on the χ^2 statistic on one degree of freedom, is given by (*14*)

$$\chi^2 = \frac{(O_L - E_L)^2}{E_L} + \frac{(O_H - E_H)^2}{E_H}. \tag{3}$$

Significance tests for association with higher lens dose or other factors were evaluated with Fisher's exact test (one-sided *P* test) for the 2×2 contingency table (*14, 15*).

A database that includes contributions to lens doses from diagnostic X rays, trapped radiation and GCR, and air-flight training was developed for this analysis. More than 7500 records for diagnostic X rays are included in the database, with information on exposure view, duration, and the number of films used to determine the lens dose. Exposures from aviation were estimated from the number of flight hours with NASA or during prior military service. Only general information on flight routes is available. Since the majority of flights are in the Houston area or between Houston and Florida, we use a dose rate of 2 μSv/h to estimate the lens dose. Records are incomplete for some retired astronauts, and here we use an average number of flight hours for astronauts with similar careers.

Each astronaut has worn a thermoluminescent dosimeter (TLD) badge in space, except during the first four Mercury flights. We evaluated the lens dose equivalent as $H = Q\,\eta D_{TLD}$, where D_{TLD} is the badge reading, Q is the mission-specific average quality factor, and η is a factor that describes the differences in shielding at the lens and a correction to the TLD response for its inefficiency for high-LET particles. Space radiation transport codes (*3*) and spacecraft and anatomical geometry models are used to scale to mission-specific dosimetry data to evaluate Q and η. Along with mission doses from TLD badges, other mission dosimetry including LET or lineal energy spectra at fixed spacecraft locations, albedo radiation, and solar cycle effects are considered. Average quality factors (*1, 3*) are approximately 1.4 for trapped radiation and 3.5 for the GCR contribution. The attenuation factor η is approximately 0.8 for trapped protons and 1.0 for GCR. The distributions in lens dose equivalent for each astronaut from space, aviation and medical procedures are shown in Fig. 1, and a summary of average space exposures is given in Table 2. The distributions in the number of space missions and the average ages for astronauts are shown in Table 3. Tables 2 and 3 show that many astronauts have flown two or more times, and other astronauts have not flown because of their recent selection or other reasons. Only 43 astronauts are female, populating mostly lower age groups (<50 years), and therefore gender differences are not considered here.

RESULTS

Vision is an important factor in astronaut selection, accounting for more than 40% of disqualifications of astronaut candidates. Frequent eye examinations are required for in-service astronauts, and most retired astronauts receive annual examinations as LSAH participants (*13*). This allows us to report cataract incidence data with more than 30 years of follow-up in many cases, and to consider possible age-specific associations with radiation exposure and other

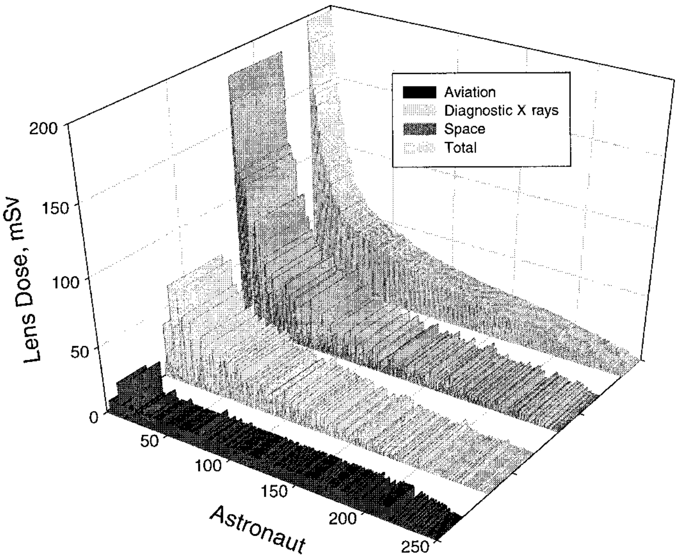

FIG. 1. The cumulative lens dose received by astronauts participating in the LSAH. The comparison shows individual contributions from space radiation exposures measured by radiation badges with corrections for badge efficiency and radiation quality factors, from diagnostic X rays and other medical procedures, and from occupational air training.

TABLE 2
Average Ages at First and Subsequent Space Missions and Number of Astronauts Participating in such Missions for NASA[a]

No. of missions	No. of astronauts	Average age, years
0	73	—
1	62	39.5
2	59	42.1
3	54	43.2
≥4	47	45
>0	222	41.8

[a] Population with zero space missions includes recently selected astronauts and astronauts retiring or deceased without participating in a space mission.

risk factors. The LSAH cataract data were used to calculate the probability of survival without cataracts as a function of age for all cataracts (Fig. 2a), non-trace cataracts (Fig. 2b), and specific types of cataracts. A significantly larger decrease in the probability of survival without cataracts is found for the high-dose astronauts with increasing age, which can be described as a shift to an earlier age of appearance since similar survival probabilities occur in the two groups at older ages. Hazard ratios and 95% confidence intervals for survival without cataracts (Table 4) show a significant increase in cataract risk for astronauts in the high space lens dose group compared to astronauts in the low space lens dose group for all cataracts and non-trace cataracts. Posterior-subcapsular (PS) and nuclear cataracts (NC) have been associated with radiation exposures in the past (*7–10*), while cortical cataracts are associated with exposures to UV radiation (*16*, *17*). We find a significant hazard ratio for the high space dose group for the combined PS, NC or mixed types (P values of 0.012 and 0.006 at ages 60 and 65 years, respectively), but not for cortical and dot opacities (Table 4). Tests for association comparing the high-dose group to the low-dose group using the total lens dose (space radiation, diagnostic X rays and atmospheric radiation) were significant only for non-trace cataracts at age 65 years, and tests for association with diagnostic X rays and atmospheric radiation alone were negative.

Because there appears to be a significant association of cataract risk with space radiation, other possible statistical tests were considered. Three astronauts in the high space lens dose group have had cataracts severe enough to require lens surgery (two PS and one NC) which occurred prior to age 60 years ($P = 0.029$). Radiation quality including the definition of a biological lens dose is an important aspect of space radiation risk assessment. A much higher flux of heavy ions occurs in high-inclination (>50°) and lunar missions than in low-inclination missions (<40°), with lower-inclination missions having a large fraction of the dose from low-LET trapped protons (*1*). We find a significant association between cataracts and high-inclination or lunar missions, with 35 of the 39 cases observed after space flight occurring in astronauts participating in these missions ($P = 0.002$). Alternative nonparametric methods of comparison, including the Poisson regression model and the hazard ratio as function of time after exposure, were considered and indicated increases in relative risk similar to those found above using age-specific survival analysis. Figure 3 shows the probability of cataracts as a function of time after first space mission for all cataracts and non-trace cataracts; only cataracts observed after a first space flight were included in this comparison. Similar results are found if a dose-

TABLE 3
Average Personnel-Badge Doses and Lens Equivalent Doses in NASA Programs

NASA program[a]	No. of astronauts[b]	Average days	Average badge dose (mGy)	Average lens dose (mSv)
Mercury (33°)	6	0.37	0.1	0.2
Gemini (29°)	20	4.04	1.2	2.0
Apollo[c]	33	9.48	4.1	14.0
Skylab (50° × 435 km)	9	57.2	43.2	87.0
Apollo-Soyuz (50° × 230 km)	3	9.0	1.1	3.1
Shuttle (28.5° < 400 km)	210	8.8	0.9	1.7
Shuttle (28.5° > 400 km)	84	7.8	9.7	12.0
Shuttle (39°)	50	12.7	1.3	2.8
Shuttle (>50°)	233	8.7	1.7	3.6
NASA-Mir (51.6° × 350 km)	7	120.1	43.1	91.0

[a] Orbital inclinations and average altitudes indicated in parentheses with shuttle flights divided into several categories.

[b] The sum of the number of astronauts for all NASA programs is larger than the actual number of astronauts (295) because of astronauts participating in multiple missions, as indicated in Table 2.

[c] Apollo missions were Lunar missions except Apollo 7 and 9 missions, which were 34° orbital missions.

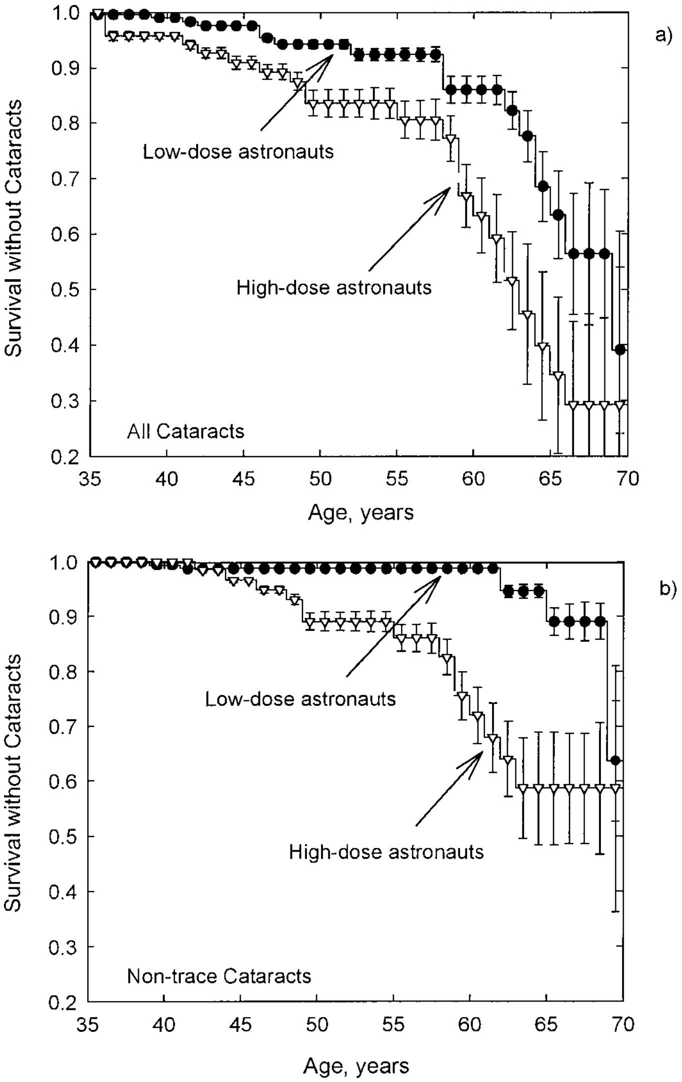

FIG. 2. Results for the probability of survival without cataracts as a function of age for NASA astronauts for the low-dose group (closed symbols) with lens doses below 8 mSv (average 3.6 mSv) and the high-dose group (open symbols) with lens doses above 8 mSv (average 45 mSv). Error bars indicate standard errors. The upper panel is for all cataracts, and the lower panel is for non-trace cataracts.

TABLE 4
Relative Hazard Ratios at Age 60 Years and 65 Years and 95% CI Comparing the High-Dose Group to the Low-Dose Group or Comparing Astronauts with Multiple Space Missions to those with No or One Mission for Specific Cataract Types[a]

Cataract type	Lens dose from all radiation sources[b]	Lens dose from space radiation only[c]	Astronauts with more than one flight[d]
	Age 60 years		
All	1.51 [0.64, 3.59]	**2.35 [1.01, 5.51]**	**2.37 [1.05, 5.36]**
Non-trace	2.47 [0.76, 8.01]	**8.04 [2.51, 25.7]**	2.65 [0.85, 8.22]
Cortical or dot	1.64 [0.51, 5.27]	1.44 [0.46, 4.65]	2.32 [0.74, 7.27]
NC	0.83 [0.18, 3.81]	3.47 [0.79, 15.3]	1.18 [0.07, 19.0]
PS	1.1 [0.67, 18.1]	5.76 [0.97, 34.2]	0.71 [0.06, 8.22]
PS, NC or mixed	1.33 [0.37, 4.83]	**3.73 [1.05, 13.3]**	2.28 [0.69, 7.53]
	Age 65 years		
All	1.88 [0.93, 3.83]	**2.44 [1.20, 4.98]**	1.87 [0.94, 3.70]
Non-trace	**3.85 [1.45, 10.2]**	**7.26 [2.74, 19.3]**	2.27 [0.87, 5.88]
Cortical or dot	1.89 [0.70, 5.14]	1.66 [0.55, 5.00]	1.82 [0.68, 4.87]
NC	1.86 [0.57, 6.1]	**3.44 [1.07, 11.1]**	1.82 [0.27, 12.1]
PS	1.1 [0.67, 18.1]	5.76 [0.97, 34.2]	0.71 [0.06, 8.22]
PS, NC or mixed	1.62 [0.60, 4.36]	**3.37 [1.25, 9.10]**	1.75 [0.68, 4.57]

[a] Values significant with 95% CI are indicated in bold type.

[b] Hazard ratio of astronauts with total lens dose >35 mSv (average 70 mSv) compared to those with lens dose <35 mSv (average 20 mSv).

[c] Hazard ratio of astronauts with a space lens dose >8 mSv (average 45 mSv) compared to those with lens dose <8 mSv (average 3.6 mSv).

[c] Hazard ratio of astronauts with two or more space flights compared to those with no or one space flight.

weighted time after exposure is used instead of time after first mission. These results show a significant increase in risk for the high space lens dose group and provide an indication of the time to onset, with an early induction period seen in the high-dose group at 5–10 years after flight and a higher increase compared to the low-dose group at later ages. Information on possible cataract progression from the LSAH medical records and parametric models of relationships between dose, age and age after exposure will be considered elsewhere.

Other cataract risk factors (*16*) including diabetes, renal failure, steroid drug use, or eye disorders were not found to have any association with cataract risk based on LSAH records (*13*) for astronauts. Genetic risk factors (*18*) may also contribute to cataracts. Astronauts are exposed to UV radiation in aviation and in space flight, and UV-radiation exposure has been associated with an increased risk of cortical cataracts (*16*, *17*). Risks are minimized if protective eyewear is worn and established operational procedures are followed. No measurements of astronaut exposures to UV radiation exist. It is possible that the combined effects of exposure to ionizing and UV radiation or other space flight factors could increase cataract risk in an additive or multiplicative manner. To test a model in which other space flight factors are causative of cataracts, the relationship between mission duration and radiation dose must be considered. To minimize this effect, we have considered a possible association with the number of missions rather than time in space. This comparison could also uncover an observation bias for astronauts who have flown on multiple missions. Hazard ratios for astronauts flying two or more missions relative to those with zero or one mission (Table 4) did not show a statistically significant increase. Also, no association with participation in space walks was found.

DISCUSSION

The LSAH data provide a historical record of cataract incidence in astronauts; however, they have been collected using a subjective method to record cataract severity and type. The use of subjective methods can confound inter-

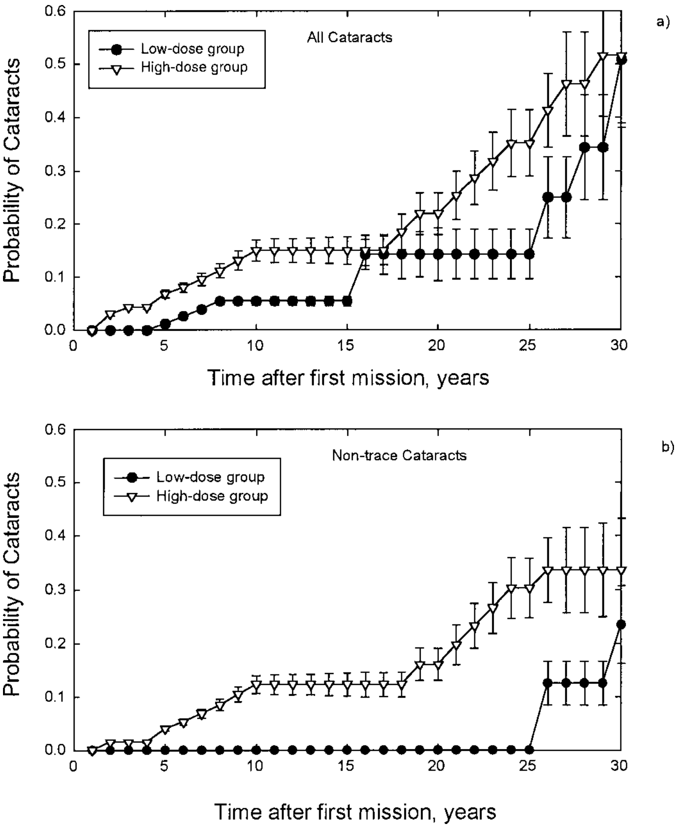

FIG. 3. Results for the probability of cataracts as a function of time after first space mission for NASA astronauts for the low-dose group (closed symbols) with lens doses below 8 mSv (average 4.7 mSv) and the high-dose group (open symbols) with lens doses above 8 mSv (average 45 mSv). Error bars indicate standard errors. The upper panel is for all cataracts, and the lower panel is for non-trace cataracts. Only cataracts occurring after a first space mission are included.

comparison of data from different observers or different cohorts (*16, 19*); however, the LSAH data are self-consistent, comparing astronauts to other astronauts, with the same methods and observers. Direct comparison of the LSAH data to population study data (*20, 21*) show similar levels of prevalence; however, such a comparison is fraught with difficulties because of the use of subjective methods, the role of preselection of astronauts for vision, differences in other environmental factors, and healthy worker effects (*16, 22*). Many of the cataracts in astronauts are not clinically significant; however, early cataracts increase the risk for progression to more severe types (*22*). Klein *et al.* (*22*) reported odds ratios for cataract surgery of 35.58 (10.12, 125.17) if a nuclear cataract is present at age 50 years and 15.51 (8.27, 29.09) if posterior subcapsular cataracts occur. Based on the present findings, a cross-sectional study and revised longitudinal study using objective methods is planned and is needed to understand severity and progression factors.

The present results suggest that radiation-induced cataracts occur after low fluences of space radiation. In comparison, early studies of cancer therapy patients (*7*) indicated a dose threshold for cataracts of 2 Gy for X rays and a significant sparing effect from dose fractionation. More recent studies of the Japanese atomic bomb survivors (*9*) and patients undergoing CT scans (*10*) indicate a much lower dose threshold or a lack of one. Studies of the effects of low-LET protons in rhesus monkeys (*22*) and cancer therapy patients (*9*) show a risk similar to that for X rays, and a negligible risk is predicted (*1*) at the low doses of low-LET radiation received by astronauts in the past. The high-LET space radiation components are more likely causative of the increased cataract risk found here for astronauts exposed to higher amounts of space radiation, as demonstrated by the correlation observed with high-inclination or lunar missions, where doses are dominated by GCR exposures rather than trapped protons. Animal models studying cataracts after heavy-ion or neutron irradiation (*1, 24–28*) provide some support for our findings, including evidence for early stationary cataracts. Analysis of the neutron component of the atomic bomb blasts includes the possibility of a large biological effectiveness of low doses of neutrons (*9*). Other experiments (*26–28*) found that the effects of heavy ions are increased by fractionation, possibly carrying implications for astronauts who receive low-dose-rate exposures in missions lasting weeks to several months and who often return to space several times. Radiation protection practices (*1*) recommend quality factors of 20 for heavy ions and neutrons and assume that clinically significant cataracts occur only above a threshold dose higher than that of past NASA missions. However, data suggesting the lack of a dose threshold (*9, 10*), the definition of a biological lens dose in terms of radiation quality (*1*), and studies showing an increased risk for cataract surgery if early stationary cataracts occur (*22*) pose important questions for risk assessment for cataracts for astronauts. The present results indicate that a new understanding of space radiation effects will be needed to answer such questions.

Postulated mechanisms of radiation-induced cataract formation have evolved in recent years. Older studies centered on the role of cell killing in the lens, while the focus of more recent models is on damage to the genome leading to altered gene expression and abnormal lens fiber protein (*1, 11, 29*). The average number of hits per cell by high-LET particle tracks during short-duration space missions is small (*30*); however, several thousand high-LET particles (LET > 30 keV/μm) pass through the lens on an average 10-day space mission. Studies of cancer induction in mice irradiated with heavy ions also indicate a risk when less than one heavy ion on average hits a target cell (*31, 32*). High-LET radiation has an increased efficiency for producing complex DNA breaks and mutations (*1, 2*) and has been shown to cause damage to the extracellular matrix (*33*), possibly altering normal cell differentiation. Late degenerative damage to tissues similar to that occurring during aging has been described after irradiation (*24, 34*) or oxidative damage (*35*), and unique age effects have been observed in animal models after heavy-ion irradiation (*36*). Approaches to mitigate cataract risks in space could include high hydrogen content shielding materials (*3*) or the development of biochemical countermeasures (*11*).

In summary, astronauts on Apollo (*5*) and subsequent Skylab (*37*), space shuttle,[2] and Mir (*38*) missions have observed light flashes that raise a concern for adverse tissue effects from single heavy-ion tracks (*6*). We report here preliminary results that indicate that low doses of space radiation increase the risk for cataracts, with possible implications for future space missions including the International Space Station and missions returning to the moon or exploring Mars. The present report and prior studies (*24*, *31–34*, *36*) suggest that damage from ionizing radiation can cause adverse tissue effects in a dose- and LET-dependent manner that will require further study to understand the mechanisms and the nature of such risks for space travel.

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