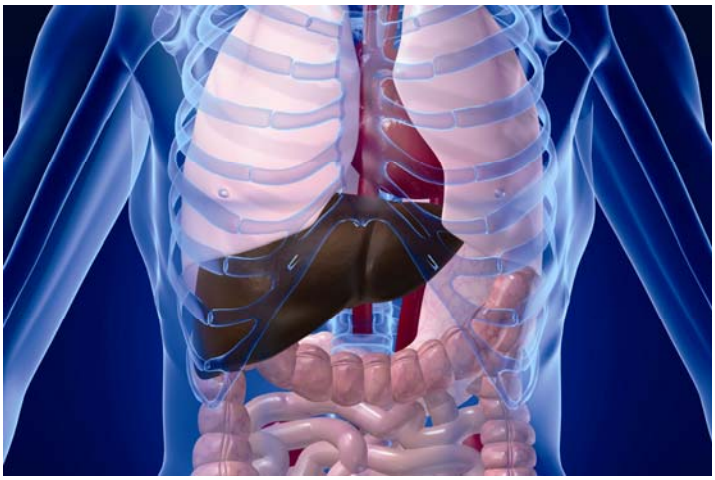
Chapter 7:
Risk of Degenerative Tissue or Other Health Effects from Radiation Exposure

Janice L. Huff
Universities Space Research Association

Francis A. Cucinotta
NASA Johnson Space Center

Occupational radiation exposure from the space environment may result in degenerative tissue diseases (non-cancer or non-CNS) such as cardiac, circulatory, or digestive diseases, as well as cataracts, although the mechanisms and the magnitude of influence of radiation leading to these diseases are not well characterized. Radiation and synergistic effects of radiation cause increased DNA strand and tissue degeneration, which may lead to acute or chronic disease of susceptible organ tissues. Data specific to the spaceflight environment must be compiled to quantify the magnitude of this risk to determine if additional protection strategies are required. – *Human Research Program Requirements Document*, HRP-47052, Rev. C, dated Jan 2009.



Exposure to space radiation may result in non-cancer or non-CNS degenerative tissue diseases, including cardiac, circulatory and digestive disorders, as well as cataracts. NASA's research program in this area currently focuses on determining the risks for these diseases from low dose-rate exposures and for HZE nuclei so that appropriate countermeasures can be developed to mitigate these risks.

Executive Summary

Human epidemiology studies of people who are exposed to various doses of ionizing radiation provide strong evidence that degenerative diseases are to be expected from exposures during long-duration space travel to GCRs or large SPEs in which fluences of more than 10^7 protons per cm^2 with energies that are above 30 MeV occur. The RBE factors for most degenerative diseases that are caused by space radiation are unknown. However, the range of doses that have been observed in human studies is sufficient to make the probability of degenerative disease risks from GCR and SPE exposure during space flight a major concern. The types of radiation that are in space present additional uncertainties in risk estimates for degenerative diseases, and the results of several studies suggest that both quantitative and qualitative differences may occur when comparing LET radiation on Earth, such as X rays and gamma rays, to high-LET radiation in space, such as heavy ions and recoil nuclei and neutrons that are produced in nuclear reactions. A shortened latency is expected for high-LET radiation in space, which increases the detriment above that of identical diseases in the U.S. population. Therefore, the greater likelihood of degenerative diseases presents a risk that is competitive with the already well-documented risks of mortality and morbidity with respect to cancer. As the focus for NASA is on understanding and mitigating risk, space radiation is a large obstacle to mission success. It is unknown at this time whether radiation shielding approaches that are distinct from those needed for the other radiation risks are needed for degenerative risks. Research on individual sensitivity to and biological countermeasures for degenerative risks, except for cataracts, is nonexistent.

Introduction

The environment outside of the shield-like atmosphere and magnetosphere of the Earth contains several types of radiation. Most of the particles in interplanetary space are derived from the solar wind, which produces a constant flux of low-energy particles. Dangerous and intermittent SPEs can produce large quantities of highly energetic protons and heavy ions. An additional constituent of space radiation, GCRs, emanate from outside our solar system and comprise mostly highly energetic protons with a small component of HZE nuclei. Researchers have predicted that an astronaut will receive a total body dose of approximately 1 to 2 mSv each day in interplanetary space and approximately 0.5 to 1 mSv each day on the surface of Mars, and these numbers will increase in the event of an SPE (Cucinotta and Durante, 2006; Saganti et al., 2004).

Exposure to ionizing radiation affects cells and tissues either by directly damaging cellular components or by producing highly reactive free radicals from water and other constituents of cells. Both of these mechanisms can produce sufficient damage to cause cell death, DNA mutation, or abnormal cell function. The extent of damage is generally believed to depend on the dose and the type of particle, and to follow a linear response to radiation dose for initial induction of damage. This is true for high and moderate radiation doses, but it is extremely difficult to measure for lower doses because of the challenges in distinguishing the effects of radiation exposure from those of normal cellular oxidative stress.

As HZE nuclei are the components of space radiation that have the highest biological effectiveness, they are a large concern for astronaut safety. HZE nuclei produce highly ionizing tracks as they pass through matter. In addition, they leave columns of damage at the molecular level when they traverse a biological system – damage that is fundamentally different from the damage that is left by low-LET radiation sources such as gamma and X rays. HZE nuclei impart damage through the primary energetic particle and secondary delta-ray electrons as well as from fragmentation events that produce a spectrum of other energetic nuclei, protons, neutrons, and heavy fragments (Wilson et al., 1995). Therefore, a large penumbra of energy deposition extends outward from the

primary particle track (Cucinotta et al., 2000). The lack of epidemiological data and sparse radiobiological data on the effects of these HZE nuclei leads to a high level of uncertainty in risk estimates for long-term health effects after exposure to GCRs and SPEs.

NASA has funded several previous reports from the NAS and the NCRP that provided evidence for the radiation risks in space. The NCRP is chartered by the U.S. Congress to guide federal agencies such as NASA on the risk from radiation exposures to their workers. Reports from the NCRP and the NRC on space radiation risks are the foundation of how NASA views the wide scientific body of evidence that is used for its research and operational radiation protection methods and plans.

Description of degenerative risks of concern to NASA

The major degenerative conditions of concern that could potentially result from space radiation exposure are as follows:

- Cataract formation
- Degenerative changes in the heart and vasculature (e.g., atherosclerosis and cardiomyopathy)
- Other diseases that are related to aging, including digestive and respiratory disease
- Other aging effects, including premature senescence and endocrine and immune system dysfunction

Note that risks to the CNS may also involve degenerative conditions, but they are treated as a stand-alone risk category by NASA and are described in Chapter 6 of this document.

Current NASA permissible exposure limits

PELs for short-term and career exposures to space radiation have been approved by the NASA Chief Health and Medical Officer, who also sets the requirements and standards for mission design and crew selection. Table 7-1, which is taken directly from NASA-STD-3001, Volume 1 (Table 4, p. 67), lists the current short- and long-term PELs for non-cancer effects (in mGy-Eq. or mGy). The lifetime limits for cataracts and heart disease are imposed to limit or prevent risks of degenerative tissue diseases. The approach here, which uses an estimate of threshold doses for heart and cataracts risk, is quite distinct from that of cancer risk limits, in which a probabilistic assessment of the risk is made using a projection model. Such an approach will likely be needed in the future for the degenerative risks. Career limits for the heart are intended to limit the REID as a result of heart disease, so, those limits fall below the current estimate of a threshold dose (NCRP, 2000); however, exposure would lead to some risk if a linear dose response with no threshold model were established.

Table 7-1. ***Short- and Long-term Dose Limits for Non-cancer Effects***

Organ	30-day limit	1-year Limit	Career
Lens*	1,000 mGy-Eq	2,000 mGy-Eq	4,000 mGy-Eq
Skin	1,500 mGy-Eq	3,000 mGy-Eq	4,000 mGy-Eq
BFO	250 mGy-Eq	500 mGy-Eq	Not applicable
Heart**	250 mGy-Eq	500 mGy-Eq	1,000 mGy-Eq
CNS***	500 mGy-Eq	1,000 mGy-Eq	1,500 mGy-Eq
CNS*** (Z≥10)	–	100 mGy	250 mGy

*Lens limits are intended to prevent early (<5 years) severe cataracts (e.g., from an SPE). An additional cataract risk – sub-clinical cataracts – exists at lower doses from cosmic rays, which may progress to severe types after long latency (>5 years). Although these cataract risks are not preventable by existing mitigation measures, they are deemed an acceptable risk to the program.
**Heart doses calculated as average over heart muscle and adjacent arteries.
***CNS limits should be calculated at the hippocampus.

Evidence

Review of human data

Cataracts

The development of ocular cataracts, which is a degenerative opacification of the crystalline lens, is a well-recognized late effect of exposure to ionizing radiation. The first reports of radiation-induced cataracts appeared early in the 20th century, shortly after the first X-ray machines were developed (Rollins, 1903). It is now clear that radiation-induced cataracts exhibit relationships between radiation dose and disease severity as well as between dose and latency. Evidence for this link comes, most notably, from survivors of radiotherapy who received high doses (>5 Gy) of ionizing radiation using X rays, gamma rays, and proton beams for ocular tumors (Ferrufino-Ponce and Henderson, 2006; Blakely et al., 1994; Gragoudas et al., 1995) and from individuals who received whole-body therapeutic radiation (Belkacemi et al., 1996; Dunn et al., 1993; Frisk et al., 2000).

Evidence of cataract risk (moderate- to low-dose gamma-ray exposures) comes from epidemiological data from atomic-bomb survivors who were followed in the life span study, which is a longitudinal study of Japanese survivors of the bombings of both Hiroshima and Nagasaki, which remains one of the most valuable and informative epidemiological studies for evaluating long-term health effects of radiation exposure (Preston et al., 2003).

Among the atomic-bomb survivors, the frequency and the severity of cataracts are dose-dependent. Severity refers to the size and loss of visual acuity of the cataract, or the presence of conditions requiring lens implants to prevent blindness. Symptoms appeared as soon as several months after exposure for severe cases and several years after exposure for less-severe cases. The frequency of appearance was related to the proximity of the subject to the hypocenter of the atomic bomb. A possible threshold dose was originally estimated to be in the range 0.6 to 1.5 Gy (Junk et al., 1998; Otake and Schull, 1982; 1991), but a non-threshold dose model has been proposed in more recent reports (Neriishi et al., 2007). In a prospective study that follows the development of radiation-induced cataracts in workers who were exposed to radiation during the efforts to clean up after the Chernobyl nuclear power plant disaster, it was found that posterior subcapsular or cortical cataracts were present in 25% of the examined individuals. The investigators estimated that the dose-effect threshold for cataract formation in exposures is less than 1 Gy (Worgul et al., 2007).

As noted by Blakely and Chang (2007a), published data on radiation-induced human cataracts are limited in predicting the risk from chronic exposure to low doses of protons or low fluence of heavy ions, such as that encountered in space, because of the possible qualitative differences in effect.

Cardiovascular Diseases and Other Degenerative Changes

A clear link has been established between exposure to high doses of ionizing radiation and the long-term development of cardiovascular disease and degenerative heart changes. Like the evidence described for cataractogenesis, the major evidence that proves a link between ionizing radiation exposure and the development of degenerative heart and vasculature changes comes from prospective studies that follow the long-term, treatment-related effects in cancer survivors. These patients received relatively high therapeutic doses (~5–50 Gy) of low-LET thoracic radiation exposure in the course of therapy for cancers of the head, neck, and chest, such as Hodgkin's lymphoma and breast cancer (Prosnitz et al., 2005; Darby et al., 2005; Carver et al., 2007; Swerdlow et al., 2007). There is a dose-dependent increase in the development of a wide variety of cardiovascular diseases, including acute and chronic pericarditis, coronary artery disease (CAD), cardiomyopathy, valvular disease, and conduction abnormalities, that lead to arrhythmia in these individuals. A commonality in each of these disorders seems to be damage to the microvasculature and small coronary arteries that result from acute inflammation and ischemia and is followed by progressive degenerative fibrotic changes (Little et al., 2008). Impairment in nitric oxide signal transduction may contribute to degenerative vascular changes (Soloviev et al., 2003). Atherosclerosis that is caused in this manner, as a secondary effect to radiation treatment, looks pathologically similar to atherosclerosis that is caused by other factors. A paucity of data exists on doses and dose-rates that cause atherosclerosis in humans.

Other evidence that supports a link between the occurrence of cardiovascular disease and radiation exposure is derived from prospective studies of atomic-bomb survivors who received moderate doses of radiation (0–2 Gy) as well as from occupationally exposed workers who received continuous low-dose exposure (Darby et al., 2005; Yamada et al., 2004; Preston et al., 2003; Hayashi et al., 2003). In atomic-bomb survivors who are enrolled in the life-span study, the development of health effects has been extensively studied through continuous longitudinal health assessments. The average doses that were received by the atomic-bomb survivors (Preston, 2003) are similar to the effective doses for an ISS mission and somewhat lower than the effective dose that is expected for a Mars mission. A significant dose-response relationship exists for hypertension, stroke, and heart attack in survivors who were exposed at less than 40 years of age; their ERR is estimated to be 14% per Sievert (Sv); but the existence of a threshold dose cannot be excluded for risks that are associated with doses that are less than 0.25 Sv (Table 7-2).

For occupationally exposed workers, such as employees of nuclear power facilities, data are less convincing. A recent study of U.S. workers who were exposed to radiation with doses that were below 1 Sv in nuclear power plants showed a significant correlation between radiation dose and death from cardiovascular disease (Howe et al, 2004). However, similar studies (Table 7-3) have shown risks that are more similar to those of the atomic-bomb survivors, or no increased risk. Further studies are warranted, as evidence at doses that are below 0.5 Sv is suggestive at best (Vrijheid et al., 2007). Finally, follow-up studies of the health risks in Chernobyl recovery workers also show an increased risk for cardiovascular diseases; however, the contribution of lifestyle factors to this risk estimate cannot be eliminated at this point, and further analysis is needed (Ivanov et al., 2006; McGale and Darby, 2005).

Table 7-2. ***Estimates of Excess Relative Risk per Sievert for Non-cancer deaths from Life-span Study of the Atomic-bomb Survivors (Preston et al., 2003). Life-Span Study Cause-Specific, Non-cancer Disease ERR Estimates 1968–1997***

Cause	ERR per Sv	Deaths[a]	Estimated number of radiation-associated deaths
All non-cancer diseases (0–139, 240–279, 290–799)	0.14 (0.08; 0.2)[b]	14,459	273 (176; 375)[b]
Heart disease (390–429)	0.17 (0.08; 0.26)	4,477	101 (47; 161)
Stroke (430–438)	0.12 (0.02; 0.22)	3,954	64 (14; 118)
Respiratory disease (640–519)	0.18 (0.06; 0.32)	2,266	57 (19; 98)
Pneumonia (480–487)	0.16 (0.00; 0.32)	1,528	33 (4; 67)
Digestive disease (520–579)	0.15 (0.00; 0.32)	1,292	27 (0; 58)
Cirrhosis (571)	0.19 (–0.05; 0.5)	567	16 (–2; 37)
Infectious disease (000–139)	–0.02 (< –0.2; 0.25)	397	–1 (–14; 15)
Tuberculosis (010–018)	–0.01 (< –0.2; 0.4)	237	–0.5 (–2; 13)
Other diseases[c] (240–279; 319–389; 580–799)	0.08 (–0.04; 0.23)	2,073	24 (–12; 64)
Urinary diseases (589–629)	0.25 (–0.01; 0.6)	515	17 (–1; 39)

[a]Deaths among potential survivors between 1968 and 1997; [b]90% C.I.; [c]Excluding diseases of the blood and BFOs.

Table 7-3. ***Occupational Studies and Circulatory Disease Mortality (Hoel, 2006)***

Occupationally Exposed Persons			
Study	**Workers (Circulatory deaths)**	**ERR per Sv**	**Comments**
U.K. radiologists (Berrington, 2001)	2,698 (514)	< 0	Time trend in cancer but not in CVD
U.S. radiologists (Matanoski, 1975)	30,084	0.2	Time trend in cancer but not in CVD
U.S. radiology techs (Hauptmann, 2003)	90,284 (1,070)	0.01–0.42	Time trend in both stroke and CHD
Nuclear workers study IARC 3 country study (Cardis, 1995)	95,673 (7,885)	0.26	5% works > 0.2 Sv 2% workers > 0.4 Sv
U.S. power reactors (Howe et al., 2004)	53,698 (350)	8.3	95% C.I.: (2.3, 18.2)
Mayak workers (Bolotnikova, 1994)	9,373 (749)	0.01	
Chernobyl emergency (Ivanov, 2001)	65,095 (1,728	0.79	Exposures 0 to 0.35 Sv

CHD = coronary heart disease; CVD = cardiovascular disease; IARC = International Agency for Research on Cancer.

Digestive and Respiratory Diseases

Figures 7-1 and 7-2 show results from Preston et al. (2003) for the ERR for death vs. dose for several diseases, including digestive and respiratory diseases. Significant risks are observed for doses that are above 1 Sv for the acute gamma-ray exposures that were received by the atomic-bomb survivors. As dose-rates in space are below 5 mSv/hour for GCR and, in most cases, are below 50 mSv/hour for SPE, respiratory and digestive diseases have not been considered a risk for ISS missions. However, for missions to Mars or lunar missions incurring a large SPE, doses that are above 1 Sv are likely. Average years of life-loss for these diseases is about 9 years in the atomic-bomb survivors. Absolute probabilities for disease morbidity will, of course, be higher than those for mortality risks.

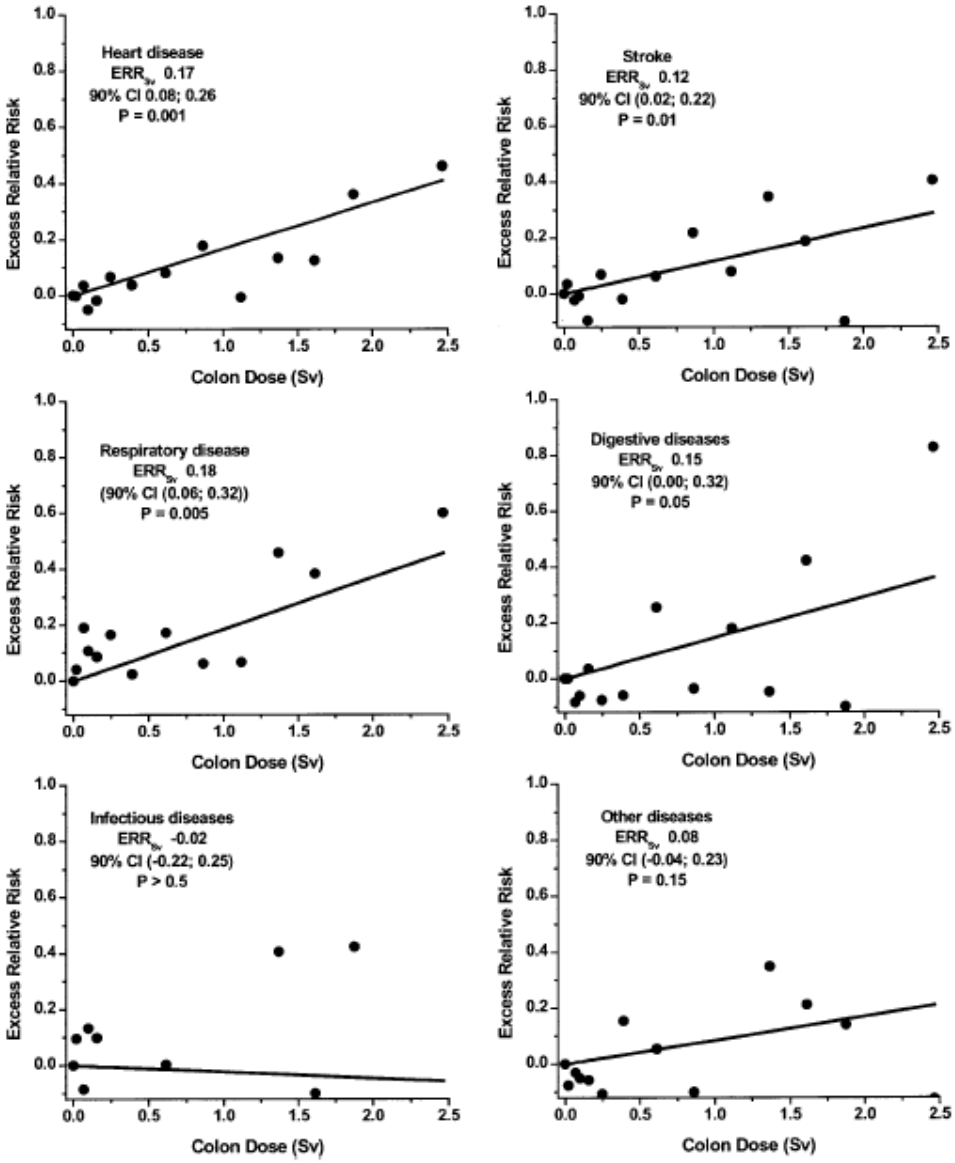


Figure 7-1. ***Preston et al. (2003): Cause-specific dose-response functions for non-cancer deaths. The plots display the best-fitting ERR models together with nonparametric ERR estimates for 20 dose categories.***

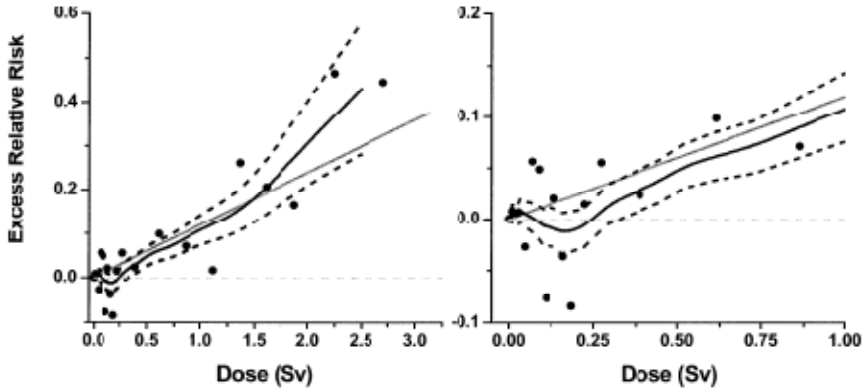


Figure 7-2. ***Preston et al. (2003): Non-cancer dose-response function for the period 1968–1997. The solid line indicates the fitted linear ERR model without any effect modifications by age at exposure, sex, or attained age. The points are dose-category-specific ERR estimates, the solid curve is a smoothed estimate derived from the points, and the dashed line indicates upper and lower one-standard-error bounds on the smoothed estimate. The right panel shows the low-dose portion of the dose-response function in more detail.***

In summary, the link between exposure to acute doses of 1 Gy or more of ionizing radiation and the development of degenerative diseases is clearly established, while the health risks of low-dose and low-dose-rate ionizing radiation remain largely unknown. These risks are more difficult to assess because multiple factors are believed to play a role in the etiology of the diseases (BEIR VII, 2006). Similarly, no human data are available on the effects of high-LET radiation on the development of degenerative heart and cardiovascular complications.

Evidence for Other Age-related Effects Caused by Radiation

Several biological processes that are commonly found to be degraded with increasing age are accelerated by radiation exposure, including changes in endocrine function, fibrosis, and premature cellular senescence. Examples of studies showing radiation effects on markers of aging include the following (NCRP Report No. 156, 2006):

- Studies of structural changes in specific organs
- General life-span longevity studies that are performed on animal models
- Analyses of biochemical and molecular markers of cellular aging, including senescence

The possibility of radiation-induced accelerated aging was noted very early on in follow-up studies of the atomic-bomb survivors (Anderson et al., 1974). Current studies show that atomic-bomb survivors exhibit a decrease in immune function that is similar to that seen during normal aging, and that the effect depends on the dose of radiation that was received (Kusunoki and Hayashi, 2007). This impairment may be associated with disease development seen in the survivors. It is also possible that the damage that was caused by oxidative stress is the basis for the link between radiation exposure and aging (Burhans and Weinberger, 2007; Toussaint et al., 2002).

Radiation Effects on Endocrine Function

The endocrine system controls hormone production, secretion, metabolism, and hormone levels in circulating blood. Age-related changes to the endocrine system occur in most older people. The hypothalamus is responsible for releasing hormones that stimulate the pituitary gland. During aging, individuals suffer impaired secretion of some hypothalamic hormones and pituitary response, resulting in a decreased capability

for the endocrine system to respond to the internal environment and external stresses of the body. Adenomas, which are hyperplasias in the parathyroid gland, are observed in patients who are treated with low-LET radiation with doses that are below 1 Gy (Tezelman et al., 1995; Tissel et al., 1985) and in the atomic-bomb survivors (Fujiwara et al., 1992).

Premature Cellular Senescence

Radiation also increases senescence in cells, which may accelerate the aging process (Campisi, 2003). Senescent cells have exited the cell cycle and are no longer capable of cell division. The principle mechanism by which senescence occurs is through shortening of telomeres, which are the DNA structure that caps the ends of chromosomes, below a critical length (~4 kilo base-pairs). The capacity to assume this phenotype may function as an anticancer mechanism in which a genetically damaged cell is shut down before it can be converted to a cancer cell (Campisi and d'Adda di Fagagna, 2007; Mallette and Ferbeyre, 2007). Telomere length has been correlated with longevity in several studies (reviewed by Shay and Wright, 2005).

Reviews of space flight issues

The NAS Space Science Board first reviewed space flight issues in 1967 (NAS/NRC, 1967) and revisited these issues in 1970 (NAS/NRC, 1970). These reviews led to the establishment of dose limits that were used at NASA until 1989. Extensive reviews of human and experimental radiobiology data for space risks were also provided to NASA in 1989, 2000, and 2006 via NCRP reports (NCRP 1989; 2000; 2006). The 1989 and 2000 NCRP Reports led to updates in the NASA dose limits. The issues of cataracts and degenerative tissue effects have been discussed in many of these reports. Reviews on other degenerative risks have been given more priority in the more recent of the reports. The more recent reviews suggest that the threshold doses may be lower than previously estimated or do not occur, especially for high-LET radiation. A major question also remains on the categorization of these risks as deterministic vs. stochastic, which has major implications for radiation protection.

The most recent external report of the evidence of space radiation effects was published in 2006 by the NCRP (NCRP Report 153, 2006). The stated purpose of this report was to identify and describe the information that is needed to make radiation protection recommendations for space missions beyond LEO. The report contains a comprehensive summary of the current body of evidence for radiation-induced health risks and makes recommendations on areas requiring future experimentation. For the non-cancer, late effects of radiation, the authors of this report recommend that experiments be conducted using protracted or extended exposure times and low dose rates of protons, heavy ions, and neutrons in energy ranges that are relevant to space radiation exposure scenarios. Specifically, the authors of the report recommend that analyses should be conducted on the effects of protracted exposures on the lens, whole-body vasculature, gastrointestinal tract, gonadal cell populations, and hematopoietic and immune systems, as well as fertility.

Cataracts in astronauts

Cucinotta et al. (2001) reported the first epidemiological evidence for an exposure-dependent increase in the risk of cataract formation in astronauts. Health records for 295 astronauts who were enrolled in the NASA Longitudinal Study of Astronaut Health, which spans more than 3 decades, were evaluated for incidence and type of cataract. Data were analyzed for astronaut age at the time at which the cataract appeared or the amount of time after the first mission when the cataract appeared (figure 7-3). Astronauts were grouped by individual occupational radiation exposure records that allowed for the separation of exposures from low-LET diagnostic X rays, atmospheric radiation that was received during aviation training, and exposure that was received during space flight. These data reveal an increased cataract incidence for astronauts who have a higher lens dose-equivalent

(average of 45 mSv) of space radiation relative to that of other astronauts with zero or low lens dose (average 8 mSv). These studies also show a significant association between radiation quality and cataract incidence. Astronauts who flew on high-inclination (>50 deg) and lunar missions, which are associated with a higher flux of high-LET heavy ions, had a higher incidence of cataract formation than those who flew on low-inclination missions, on which a large proportion of the dose is from low-LET trapped protons. Further evidence for the link between cataract formation and exposure to space radiation was presented in a 2002 study of cosmonauts and astronauts (Rastegar et al., 2002), in which a trend for increased opacification in the posterior cortical and posterior capsule regions of the lens was evident in a group of cosmonauts and astronauts as compared to that of the controls. As astronauts were screened for vision at entry into the Astronaut Corps and were observed with distinct methods, comparisons to other studies are inconclusive. In fact, it is very likely that astronauts, prior to their exposure to space radiation, have a baseline incidence of cataracts that is well below that of members of the general population.

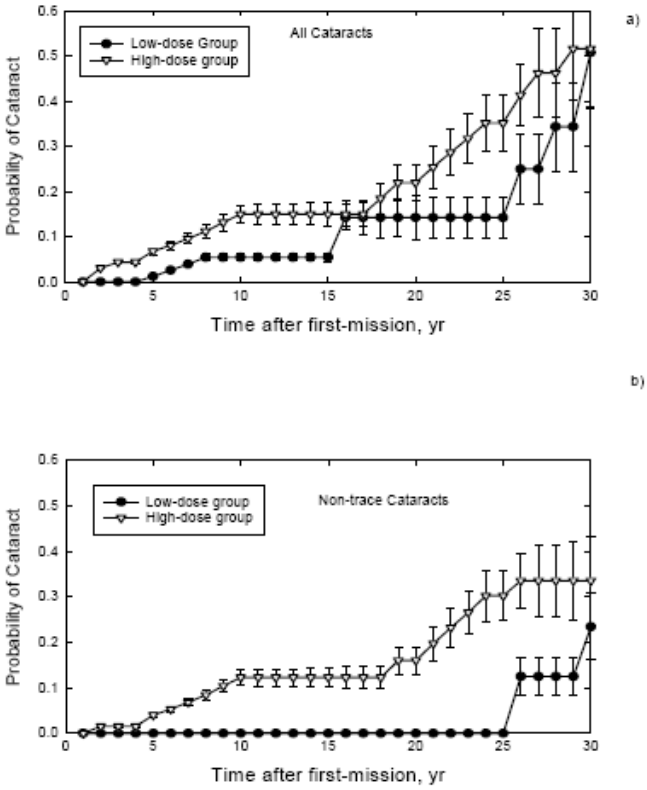


Figure 7-3. Cucinotta et al. (2001): ***Results for the probability of survival without cataracts vs. time after the first space mission for NASA astronauts for a low-dose group (closed symbols) with a lens dose below 8 mSv (average 4.7 mSv) and a high-dose group (open symbols) with a lens dose above 8 mSv (average 45 mSv). Error bars indicate standard errors of the mean. The upper panel is for all cataracts, and the lower panel is for non-trace (vision-impairing or large-area) cataracts. Only cataracts occurring after a first space mission are included.***

Radiobiology studies of the risk of degenerative tissues diseases

Cataract Studies with Protons, Neutrons, and HZE Nuclei

Although the largest body of information on radiation-induced cataractogenesis comes from studies using low-LET radiation sources, substantial data also describe the induction of cataracts in a variety of animal species by different types of particle radiation sources that are similar to those that are encountered in space, including protons and high-LET particle radiation. The United States Air Force (USAF)/NASA Proton Bio-effects Project was an effort to identify delayed or late effects of X rays, electrons, and protons of differing energies on the long-term health of a colony of Rhesus monkeys. A subpopulation of the primates that were

studied in the USAF/NASA project was monitored for about 30 years for late effects including cancer, cataracts, and shortening of life. Analyses of these primates for signs of cataractogenesis began 20 years after exposure, and significant opacifications of the eye lens were seen in these monkeys 20 to 24 years after exposure to 55-MeV protons at 1.25 Gy and higher levels. The results that were obtained from these experiments suggest that the dose-response relationship for induction of cataracts by protons is similar to that seen with low-LET radiation (Lett et al., 1991; Cox et al., 1992). These findings are supported by other studies on cataract formation in animal models using high-energy proton beams (Niemer-Tucker et al., 1999; Fedorenko, 1995). In many studies of heavy ions, cataractogenesis that was induced by individual high-LET components of the space radiation spectrum was analyzed. The conclusions that were derived from these studies are that a trend exists for the latency between the exposure and the appearance of cataract lesions to decrease, and that this occurs at lower dose thresholds for heavy ions than for low-LET X rays and protons. Table 7-4 lists representative studies for different heavy-ion species.

Table 7-4. ***References for Cataractogenesis Studies Conducted with High-LET Radiation***

High-LET Component	Selected References
Neutrons	Ainsworth, 1986; Riley et al., 1991; Worgul et al., 1996; Christenberry et al., 1956
Argon	Merriam et al., 1984; Lett et al., 1980; Worgul, 1986; Abrosimova et al., 2000; Jose and Ainsworth, 1983
Neon	Lett et al., 1980; Abrosimova et al., 2000; Jose and Ainsworth, 1983
Iron	Brenner et al., 1993; Lett et al., 1991; Medvedovsky et al., 1994; Riley et al., 1991; Tao et al., 1994; Worgul, 1986; Worgul, 1993
Protons	Niemer-Tucker et al., 1999; Fedorenko, 1985; Lett et al., 1991; Cox et al., 1992

Studies in animals showed an age-dependent sensitivity, with the younger animals exhibiting a lower dose threshold for cataract induction than the older animals (Cox et al., 1992).

Animal Studies and Heart Damage

Systematic studies on the progression of radiation-induced heart diseases were first conducted in rabbits (Fajardo and Stewart, 1970) and in rats (Yeung and Hopewell, 1985; Lauk et al., 1985) with high doses of X rays in the range of 10 to 20 Gy. Similar studies were conducted for heavy ions during the course of the JANUS program at Argonne National Laboratory, in which ultrastructural studies of the mouse heart and vasculature were performed after the animals had been irradiated with neutrons (Yang et al., 1976; 1978; Stearner et al., 1979). The results of the studies were compared with results from irradiating mice with low-LET radiation, and showed vessel morphological changes, including marked fragmentation of vascular smooth muscle layers as well as an increase in deposition of extracellular matrix in vessel walls. Clear distinctions were observed between the damage that was caused by neutrons and that caused by low-LET radiation (Yang et al., 1976; 1978; Stearner et al., 1979). RBEs for neutron effects increased with decreasing dose or fractionation of the dose, thus dividing the total dose into several doses that were spread out over time, and exceeded values of 100 when exposure protraction over 24 weekly fractions was tested. Similar results were found with low doses of Ne and Ar ions (Yang and Ainsworth, 1982). Further studies that were conducted on rats that had been irradiated in the head with low doses of heavy ions showed a clear correlation between radiation dose and bleeding in the cerebral cortex, with heavy ions inducing more hemorrhages than X rays at the same dose (Yang and Tobias, 1984). Studies of the atherogenic changes that are associated with irradiation were

conducted in dogs to compare the effects of fractionated doses of fast neutrons (15 MeV avg.) with those of low-LET photons. The RBE of neutrons was estimated at 4 to 5 from these studies (Bradley et al., 1981).

More recently, studies that were aimed at defining the mechanisms by which radiation induces heart diseases were conducted using atherosclerosis-prone animal models. Increased oxidative stress (from the formation of ROS) and promotion of inflammation have been implicated as possible mechanisms by which radiation promotes atherogenesis. For example, accelerated formation of aortic lesions occurred in a dose-dependent manner in X-irradiated mice that were on a high-fat diet (figure 7-4), while smaller lesions were observed in their irradiated transgenic littermates that over-expressed CuZn-superoxide dismutase, which is expected to decrease chronic oxidative stress and lead to a decreased susceptibility to degeneration (Tribble et al., 1999). The lowest dose in these studies was 2 Gy. In another study (Stewart et al., 2006), radiation was shown to accelerate the formation of macrophage-rich inflammatory atherosclerotic lesions in atherosclerosis-prone mice, who were lacking the gene for ApoE. These mice were given a single high dose of 14 Gy to the neck, supporting the notion that radiation promotes degenerative heart diseases though an inflammatory mechanism.

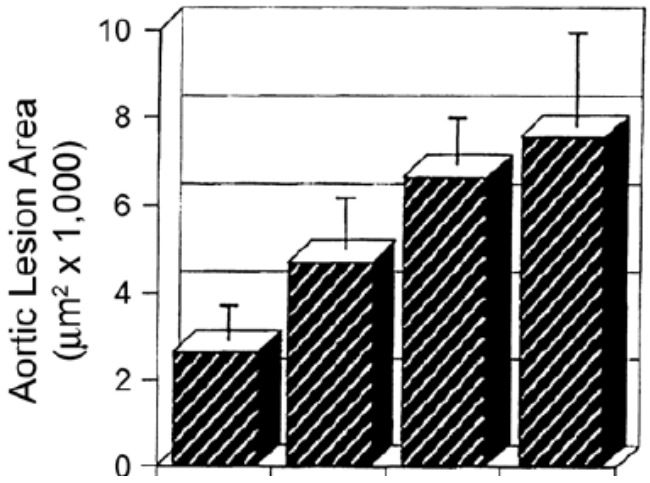


Figure 7-4. ***Dose-dependent effects of ionizing radiation on aortic lesion formation in fat-fed mice (repeated-measures analysis of variance: P = 0.02) (Tribble et al., 1999).***

In summary, substantial evidence from human epidemiology data and animal studies suggests that low-LET radiation strongly impacts the development of degenerative heart and cardiovascular diseases, which may be related to the overall acceleration of aging processes. However, data on these same effects that were caused by irradiation with protons or heavy ions are clearly lacking.

Radiobiology studies on aging

One consequence of radiation exposure and other genotoxic stressors at the cellular level is an enhancement of cellular senescence, which is a characteristic of aging. Studies that were conducted using low-LET irradiation in mouse models have shown a decline in the total number of cells and an increase in the number of cells with the senescent phenotype in bone marrow stem cells after radiotherapy and chemotherapy. These changes may contribute to the long-term deficits in bone marrow function that occur after these treatments (Wang et al., 2006).

Evidence of radiation-induced signs of aging has been uncovered in several studies that use heavy-ion irradiation of CNS targets. For example, mice that received whole-body irradiation with 1 GeV/nuc iron showed a

dose-dependent decrease in the number of newly formed cells in the hippocampus as well as altered expression of biochemical markers and alterations in the distribution of cells – changes that are consistent with the aging process (Rola et al., 2004; Casadesus et al., 2005). In fact, the newly formed cells that were affected by radiation are a type of neural stem cell. Stem cells in all tissues are of fundamental importance in the process of aging because any age-related decline in the number or functional capability of stem cells will impair the ability of the body to form and replace committed cells, with potentially deleterious cost for tissue maintenance. Genes that could modify individual susceptibility and radiation-induced aging would occur in the DNA damage response pathway, cell cycle controls, and telomere regulation, including Atm, Nbs1, Wrn, p16, and p21.

High-LET radiation also has an enhanced ability to damage the telomeres structures that are at one end of each chromosome and that are believed to be involved in the aging process (Durante et al., 2006). Some investigators report very high levels of telomere deletion in the progeny of human lymphocytes after irradiation with low doses of iron nuclei (Durante et al., 2006). Bailey (2007) is studying changes to telomeres as a function of radiation quality. Possible quantitative differences between low- and high-LET damage in causing telomere shortening or premature senescence are thus a concern for space radiation risk assessment.

Other effects

An additional effect of irradiation that was revealed by the proton bioeffects studies that were conducted in Rhesus monkeys was a significant increase in the risk of developing endometriosis, which is an abnormal growth of the uterine lining. This disease occurred in about 25% of all of the unirradiated female primates and in more than 50% of the irradiated primates. Although they are not normally life-threatening in humans, these conditions proved fatal to several of the animals before proper treatment plans were put into effect. Endometriosis was evident even when relatively low-energy protons (32 MeV; penetrating to a depth of about 1 cm) and low-exposure doses (0.2 to 1.13 Gy) were used (Yochmowitz et al., 1985; Fanton and Golden, 1991). As very few humans have been exposed to high-LET radiation, other health effects may arise that have not been documented to date for terrestrial forms of radiation at low to moderate doses (< 2 Gy).

Computer-based Simulation Information

Computer models of degenerative risks have not been developed at this time. Epidemiological data are severely lacking, precluding an approach that is similar to the ones that were used to project cancer risks. Only a few biological models are available that describe the degenerative processes that are caused by ionizing radiation, and that would be needed to form a computer model. This is probably because these processes are less studied than radiation carcinogenesis and are, in many cases, complicated by other lifestyle factors that influence the disease process. One model that was proposed by Rubin and Casarett (1968), which is called the "vascular hypothesis," states that late radiation effects are caused by damage to blood vessels. This vascular injury, which has a long latency that reflects the slow turnover time of the vasculature, leads to vessel occlusion, ischemia, and secondary loss of parenchymal cells, which are the cells that are specific to particular tissues and organs.

Risk in Context of Exploration Mission Operational Scenarios

Projections for space missions

No existing biophysical model projects degenerative risks for the entire range of particle types and energies that are found in space. The large RBEs that are found in the few studies that have been performed suggest that organ dose-equivalent based on radiation quality factors can be used to make a first approximation for risk estimates;

however, the shape of the dose-response for specific diseases and dose-rate modifiers is unknown. Dose-rate modifiers could be higher than observed for cancer risks because of the possibility of threshold effects.

The estimates for ERR per Sievert, which was provided by studies of the atomic-bomb survivors, are not sufficient alone to estimate risk for astronauts because a risk transfer approach is needed together with estimates of RBE and dose-rate modifiers. The baseline risk of CHD is several-fold larger in the U.S. than in Japan, while the risk of stroke is comparable. To determine the cancer risks, the NCRP suggests using multiplicative and additive transfer models to transfer risks between populations. Figure 7-5 (Cucinotta, unpublished) shows estimates of cancer and CHD risks if the RBE and the DDREF are assumed to be identical for cancer and CHD. In this calculation, the multiplicative transfer model is used to transfer the CHD risk from the Japanese to the U.S. population as well as to transfer the model of NCRP Report No. 132 (NCRP, 2000) for cancer risks. NASA uses the model of NCRP Report No. 132, which derives risks from the atomic-bomb survivor data using a mixture model that combines the arithmetic average of the additive and multiplicative transfer models to project cancer risks in the U.S. population. In the example calculation that is shown in figure 7-5, the CHD risk alone is about half that of the risk of cancer in all organs combined, and is less dependent on age than is the cancer risk. Death by CHD exceeds cancer deaths when an individual is 50 years or older at the time of exposure. The example that is shown in figure 7-5 uses many simplified assumptions, but clearly suggests the importance of collecting new data to estimate the factors that enter into CHD and other degenerative risk prediction models.

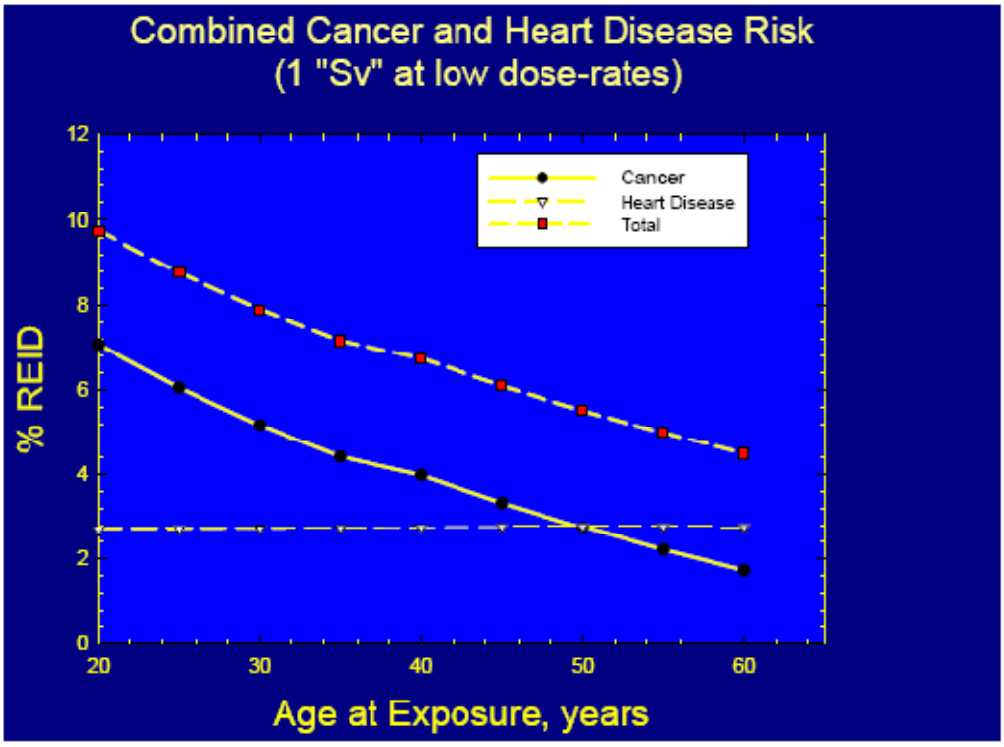


Figure 7-5. ***Comparison of projections for risk per Sievert for cancer and heart disease as a function of age at exposure. Calculations are made using the multiplicative transfer model and baseline rates for the U.S. population. Comparisons assume that RBE (quality factor) and DDREF are the same for each risk. The effects of competing risks are accounted for in the model (Cucinotta, private communication).***

Potential for biological countermeasures

Excessive production of free radicals produces oxidative damage to cellular structures, which includes proteins, DNA, and lipids, and contributes to the radiation-induced degenerative changes that are associated with aging, cardiovascular disease, and cataract formation. The identification of safe and effective agents that will protect and mitigate against these effects of radiation exposure are a high priority both for radiotherapy purposes, where the sparing of normal tissue is critical, and for the health of the general public in the event of a terrorist attack with nuclear weapons.

Two main types of countermeasures have been used to protect normal vasculature from ionizing radiation: the sulfhydryl or thiol compounds, and antioxidants. Both of these classes of compounds function by scavenging the free radicals that are produced by the interaction of ionizing radiation with water. WR2721 – which is also known as amifostine and gammaphos – is the best-described member of the sulfhydryl class and is the only drug that is approved by the Food and Drug Administration (FDA) to help prevent excess damage to normal tissues during radiotherapy. The mechanism of action of this drug is thought to be scavenging the free radicals that are produced by radiation and H-atom donation to protect against the damage that is done by free radicals. This compound has been tested as a countermeasure for both cataract formation and vascular damage (Kador, 1983; Mooteri et al., 1996; Warfield et al., 1990; Plotnikova et al., 1988). Radical scavenging vitamins such as C and E have also been shown to protect the lens and vascular system (Bantseev et al., 1997; Jacques et al., 1997; Taylor and Hobbs, 2002). In addition, growth factor treatments have been shown to decrease blood vessel stenosis (Fuks, 1994). In all of these examples, the compounds were administered prior to radiation exposure.

Synergistic effects with other flight factors

No reports have been published on the possible synergistic effects from non-radiation risk factors on the degenerative risks from space radiation. However, studies of radiation effects on bone loss due to microgravity have been suggested. No studies at doses that are below 1 Gy have been made in this area. Ambient oxygen levels may be altered in space flight. For low-LET radiation, oxygen enhancement ratios (OERs) (i.e., the ratio of doses to produce the same effects for varying oxygen levels) can exceed 2; however, for high-LET radiation, less dependence on oxygen levels is observed with OERs reducing to unity (Hall, 2000). There is only a small probability for low-LET radiation from SPEs to reach high enough doses to cause degenerative effects if proper operational procedures and radiation shielding are in place. However, chronic exposure to high-LET heavy ions is an important concern where a dose threshold will not likely occur. In this area, very little is known, and studies at nominal oxygen levels are needed to achieve a basic understanding of the mechanism and to obtain animal data for risk assessments. On completion of such studies, further studies at varying oxygen levels may be warranted.

Conclusion

The association between ionizing radiation exposure and the long-term development of degenerative tissue effects such as heart disease, cataracts, immunological changes, and premature aging is well-established for moderate to high doses of low-LET radiation. The majority of this evidence is derived from epidemiological studies on the atomic-bomb survivors in Japan, radiotherapy patients, and occupationally exposed workers, and is supported by laboratory studies using animal models (Blakely and Chang, 2007a; 2007b). The risks for these diseases from low dose-rate exposures and for HZE nuclei are much more difficult to assess due to their multifactor nature and long latency periods; therefore, these risks remain debatable for short-term lunar missions. Note, however, that the risks are more likely for long-term lunar or Mars missions. It also remains unclear whether

low-dose (<0.5 Gy) exposures influence the same biological pathways that have been shown to be involved in disease progression following moderate- to high-dose radiation exposures (Little et al., 2008). Likewise, very little information is available on the effects of space radiation on these disease processes, the role of individual susceptibility, and the possible synergistic effects from other space flight factors. It will be essential to obtain this knowledge to successfully mitigate the degenerative risk for astronauts for lunar and Mars missions.

References

Abrosimova AN, Shafirkin AV, Fedorenko BS. (2000) Probability of lens opacity and mature cataracts due to irradiation at various LET values. *Aviakosm. Ekolog. Med.*, 34(3):33–41.

Ainsworth EJ. (1986) Early and late mammalian responses to heavy charged particles. *Adv. Space Res.*, 6:153–165.

Anderson RE, Key CR, Yamamoto T, Thorslund T. (1974) Aging in Hiroshima and Nagasaki atomic bomb survivors. Speculations based upon the age-specific mortality of persons with malignant neoplasms. *Am. J. Pathol.*, 75:1–11.

Bantseev V, Bhardwaj R, Rathbun W, Nagasawa H, Trevithick JR. (1997) Antioxidants and cataract: (cataract induction in space environment and application to terrestrial aging cataract). *Biochem. Mol. Biol. Int.*, 42:1189–1197.

BEIR VII. (2006) *Health risks from exposure to low levels of ionizing radiation: BEIR VII – Phase 2 committee to assess health risks from exposure to low levels of ionizing radiation, National Research Council*. National Academies Press, Washington, D.C.

Belkacemi Y, Ozsahin M, Pene F, et al. (1996) Cataractogenesis after total body irradiation. *Int. J. Radiat. Oncol. Biol. Phys.*, 35:53–60.

Berrington A, Darby SC, Weiss HA, Doll R. (2001) 100 years of observation on British radiologists: mortality from cancer and other causes 1897–1997. *Br. J. Radiol.*, 74:(882)507–519.

Blakely EA Daftari IK, Meecham WJ, et al. (1994) Helium-ion-induced human cataractogenesis. *Adv. Space. Res.*, 14:501–505.

Blakely EA, Chang PY. (2007a) A review of ground-based heavy-ion radiobiology relevant to space radiation risk assessment. Cataracts and CNS effects. *Adv. Space Res.*, 40:1307–1319.

Blakely EA, Chang PY. (2007b) A review of ground-based heavy-ion radiobiology relevant to space radiation risk assessment. Part II: Cardiovascular and immunological effects. *Adv. Space Res.*, 40:461–469.

Bolotnikova MG, Koshurnikova NA, Komleva NS, Budushchev EB, Okatenko PV. (1994) Mortality from cardiovascular diseases among male workers at the radiochemical plant of the "Mayak" complex. *Sci. Total Environ*., 142(1–2):29–31.

Bradley EW, Zook BC, Casarett GW, Rogers CC. (1981) Coronary arteriosclerosis and atherosclerosis in fast neutron or photon irradiated dogs. *Int. J. Radiat. Oncol. Biol. Phys.*, 7:1103–1108.

Brenner DJ, Medvedovsky C, Huang Y, Worgul BV. (1993) Accelerated heavy particles and the lens. VIII. Comparisons between the effects of acute low doses of iron ions (190 keV/microns) and argon ions (88 keV/microns). *Radiat. Res.*, 133:198–203.

Burhans WC, Weinberger M. (2007) DNA replication stress, genome instability and aging. *Nucleic Acids Res.*, 35:7545–7556.

Campisi J. (2003) Cancer and aging: rival demons. *Nat. Rev. Canc.*, 3:339–349.

Campisi J, d'Adda di Fagagna F. (2007) Cellular senescence: when bad things happen to good cells. *Nat. Rev. Mol. Cell. Biol.*, 8:729–740.

Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, Beral V, Cowper G, Douglas A, Fix J, Fry, SA, Kaldor, J, Lave, C, Salmon, L, Smith, PG, Voelz, GL, Wiggs LD. (1995) Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat. Res*., 142:(2)117–132.

Carver JR, Shapiro, CL, Ng A, Jacobs L, Schwartz C, Virgo KS, Hagerty KL, Somerfield MR, Vaughn, DJ. (2007) American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J. Clin. Oncol.*, 25:3991–4008.

Casadesus G, Shukitt-Hale B, Stellwagen HM, Smith MA, Rabin BM, Joseph JA. (2005) Hippocampal neurogenesis and PSA-NCAM expression following exposure to ^{56}Fe particles mimics that seen during aging in rats. *Exp. Gerontol.*, 40:249–254.

Christenberry KW, Furth J, Hurst GS, Melville GS, Upton AC. (1956) The relative biological effectiveness of neutrons, X rays, and gamma rays for the production of lens opacities: observations on mice, rats, guinea-pigs, and rabbits. *Radiol.*, 67:686–696.

Cox AB, Lee AC, Williams GR, Lett JT. (1992) Late cataractogenesis in primates and lagomorphs after exposure to particulate radiations. *Adv. Space Res.*, 12:379–384.

Cucinotta FA, Nikjoo H, Goodhead DT. (2000) Model of the radial distribution of energy imparted in nanometer volumes from HZE particles. *Radiat. Res.*, 153:459–468.

Cucinotta FA Manuel F K, Jones J, Iszard G, Murrey J, Djojonegro B, Wear M. (2001) Space radiation and cataracts in astronauts. *Radiat. Res.*, 156:460–466.

Cucinotta FA, Durante M. (2006) Cancer risk from exposure to galactic cosmic rays: implications for space exploration by human beings. *Lancet Oncol.*, 7:431–435.

Darby SC, McGale P, Taylor CW, Peto R. (2005) Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol.*, 6:557–565.

Dunn JP, Jabs DA Wingard J, Enger C, Vogelsang G, Santos G. (1993) Bone marrow transplantation and cataract development. *Arch. Ophthalmol.*, 111:1367–1373.

Durante M, George K, Cucinotta FA. (2006) Chromosomes lacking telomeres are present in the progeny of human lymphocytes exposed to heavy ions. *Radiat. Res.*, 165:51–58.

Fajardo LF, Stewart JR. (1970) Experimental radiation-induced heart disease. I. Light microscopic studies. *Am. J. Pathol.*, 59:299–316.

Fanton JW, Golden JG. (1991) Radiation-induced endometriosis in Macaca mulatta. *Radiat. Res.*, 126:141–146.

Fedorenko BS. (1995) The biological effects of heavy charged particles. The main results and prospective research in the context of interplanetary flights. *Aviakosm. Ekolog. Med.*, 29(2):16–21.

Ferrufino-Ponce ZK, Henderson BA. (2006) Radiotherapy and cataract formation. *Semin. Ophthalmol.*, 21:171–180.

Frisk P, Hagberg H, Mandahl A, Soderberg P, Lonnerholm G. (2000) Cataracts after autologous bone marrow transplantation in children. *Acta Paediatr.*, 89:814–819.

Fujiwara S, et al. (1992) Basic fibroblast growth factor protects endothelial cells against radiation-induced programmed cell death in vitro and in vivo. *Canc. Res.*, 54:2582–2590.

Fuks Z, Persaud RS, Alfieri A, McLoughlin M, Ehleiter D, Schwartz JL, Seddon AP, Cordon-Cardo C, Haimovitz-Friedman A. (1994) Basic fibroblast growth factor protects endothelial cells against radiation-induced programmed cell death in vitro and in vivo. *Canc. Res.*, 54:2582–2590.

Gragoudas ES, Egan KM, Walsh SM, Regan S, Munzenrider JE, Taratuta V. (1995) Lens changes after proton beam irradiation for uveal melanoma. *Am. J. Ophthalmol.*, 119:157–164.

Hall EJ. (2000) *Radiobiology for the radiologist*. Lippincott Williams and Wilkins, Philadelphia, Pa.

Hauptmann M, Mohan AK, Doody MM, Linet MS, Mabuchi K. (2003) Mortality from diseases of the circulatory system in radiologic technologists in the United States. *Am. J. Epidemiol.,* 157:(3)239–248.

Hayashi T, Kusunoki Y, Hakoda M, Morishita Y, Kubo Y, Maki M, Kasagi F, Kodama K, Macphee DG, Kyoizumi S. (2003) Radiation dose-dependent increases in inflammatory response markers in A-bomb survivors. *Int. J. Radiat. Biol.*, 79:129–136.

Hoel DG. (2006) Ionizing radiation and cardiovascular disease. *Ann. New York Acad. Sci.*, 1076:309–317.

Howe GR, Zablotska LB, Fix JJ, Egel J, Buchanan J. (2004) Analysis of the mortality experience amongst U.S. nuclear power industry workers after chronic low-dose exposure to ionizing radiation. *Radiat. Res.*, 162:517–526.

Ivanov VK, Gorski AI, Maksioutov MA, Tsyb AF, Souchkevitch GN.(2001) Mortality among the Chernobyl emergency workers: estimation of radiation risks (preliminary analysis). *Health Phys.,* 81:(5)514–521.

Ivanov VK, Maksioutov MA, Chekin SY, Petrov AV, Biryukov AP, Kruglova ZG, Matyash VA, Tsyb AF, Manton KG, Kravchenko JS. (2006) The risk of radiation-induced cerebrovascular disease in Chernobyl emergency workers. *Health Phys.*, 90:199–207.

Jacques PF, Taylor A, Hankinson SE, Willett WC, Mahnken B, Lee Y, Vaid K, Lahav M. (1997) Long-term vitamin C supplement use and prevalence of early age-related lens opacities. *Am. J. Clin. Nutr.*, 66:911–916.

Jose JG, Ainsworth EJ. (1983) Cataract production in mice by heavy charged argon, neon, and carbon particles. *Radiat. Res.*, 94:513–528.

Junk A, Kundiev Y, Vitte P, Worgul, B. (1998) Ocular radiation risk assessment in populations exposed to environmental radiation contamination: proceedings of the Advanced Research Workshop, Kiev Ukraine. *NATO science series. Partnership sub-series 2, environmental security*. Kluwer Academic Publishers, the Netherlands.

Kador PF. (1983) Overview of the current attempts toward the medical treatment of cataract. *Ophthalmol.*, 90:352–364.

Kusunoki Y, Hayashi T. (2007) Long-lasting alterations of the immune system by ionizing radiation exposure: implications for disease development among atomic bomb survivors. *Int. J. Radiat. Biol*., 83:1–14.

Lauk S, Kiszel Z, Buschmann J, Trott KR. (1985) Radiation-induced heart disease in rats. *Int. J. Radiat. Oncol. Biol. Phys*., 11:801–808.

Lett JT, Cox AB, Keng PC, Lee AC, Su CM, Bergtold DS. (1980) Late degeneration in rabbit tissues after irradiation by heavy ions. In: Holmquist R (Ed.), *Life sciences and space research, Vol. XVIII*. Pergamon Press, Oxford, pp. 131–142.

Lett JT, Lee AC, Cox AB. (1991) Late cataractogenesis in rhesus monkeys irradiated with protons and radiogenic cataract in other species. *Radiat. Res.*, 126:147–156.

Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, Tapio S, Elliott PA. (2008) Systematic review of epidemiological associations between low and moderate doses of ionizing radiation and late cardio-vascular effects, and their possible mechanisms. *Radiat. Res.*, 169:99–109.

Mallette FA, Ferbeyre G. (2007) The DNA damage signaling pathway connects oncogenic stress to cellular senescence. *Cell Cycle*, 6:1831–1836.

Matanoski GM, Seltser R, Sartwell PE, Diamond EL, Elliott EA.(1975) The current mortality rates of radiologists and other physician specialists: specific causes of death. *Am. J. Epidemiol.,* 101:(3)199–210.

McGale P, Darby SC. (2005) Low doses of ionizing radiation and circulatory diseases: a systematic review of the published epidemiological evidence. *Radiat. Res.*, 163:247–257.

Medvedovsky C, Worgul BV, Huang Y, Brenner DJ, Tao F, Miller J, Zeitlin C, Ainsworth EJ. (1994) The influence of dose, dose-rate and particle fragmentation on cataract induction by energetic iron ions. *Adv. Space Res.*, 14:475–482.

Merriam GR Jr, Worgul BV, Medvedovsky C, Zaider M, Rossi HH. (1984) Accelerated heavy particles and the lens. I. Cataractogenic potential. *Radiat. Res.*, 98:129–140.

Mooteri SN, Podolski JL, Drab EA, Saclarides TJ, Onoda JM, Kantak SS, Rubin DB.(1996) WR-1065 and radioprotection of vascular endothelial cells. II. Morphology. *Radiat. Res.*, 145:217–224.

NAS/NRC. (1967) Radiobiological factors. In: Langham WH (Ed.), *Manned spaceflight, report of Space Radiation Study Panel of the Life Sciences Committee*. National Academy Press, Washington, D.C.

NAS/NRC. (1970) *Radiation protection guides and constraints for space-mission and vehicle-design studies involving nuclear systems*. National Academy Press, Washington, D.C.

NCRP. (1989) *Guidance on radiation received in space activities*. NCRP Report No. 98. NCRP, Bethesda, Md.

NCRP. (2000) *Recommendations of dose limits for low Earth orbit*. NCRP No. Report 132. NCRP, Bethesda, Md.

NCRP. (2006) *Information needed to make radiation protection recommendations for space missions beyond low-Earth orbit*. NCRP Report No. 153. NCRP, Bethesda, Md.

Neriishi K, Nakashima E., Minamoto A., Fujiwara S, Akahoshi M., Mishima HK, Kitaoka T, Shore RE. (2007) Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. *Radiat. Res.*, 168:404–408.

Niemer-Tucker M, Sterk CC, de Wolff-Rouendaal D, Lee AC, Lett JT, Cox A, Emmanouilidis-van der Spek K, Davelaar J, Lambooy AC, Mooy CM, Broerse JJ. (1999) Late ophthalmological complications after total body irradiation in non-human primates. *Int. J. Radiat. Biol.*, 75:465–472.

Otake M, Schull WJ. (1982) The relationship of gamma and neutron radiation to posterior lenticular opacities among atomic bomb survivors in Hiroshima and Nagasaki. *Radiat. Res.*, 92:574–595.

Otake M, Schull WJ. (1991) A review of forty-five years study of Hiroshima and Nagasaki atomic bomb survivors. Radiation cataract. *J. Radiat. Res. (Tokyo)*, 32(Suppl.):283–293.

Plotnikova ED, Levitman MK, Shaposhnikova VV, Koshevoj JV, Eidus LK. (1988) Protection of microvasculature in rat brain against late radiation injury by gammaphos. *Int. J. Radiat. Oncol. Biol. Phys.*, 15:1197–1201.

Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. (2003) Studies of mortality of atomic bomb survivors. Report No. 13: Solid cancer and noncancer disease mortality: 1950–1997. *Radiat. Res.*, 160:381–407.

Prosnitz RG, Chen YH, Marks LB. (2005) Cardiac toxicity following thoracic radiation. *Semin. Oncol.*, 32:S71–S80.

Rastegar N, Eckart P, Mertz M. (2002) Radiation-induced cataract in astronauts and cosmonauts. *Graefes Arch. Clin. Exp. Ophthalmol.*, 240(7):543–547.

Riley EF, Lindgren AL, Andersen AL, Miller RC, Ainsworth EJ. (1991) Relative cataractogenic effects of X rays, fission-spectrum neutrons, and ^{56}Fe particles: a comparison with mitotic effects. *Radiat. Res.*, 125:298–305.

Rola R, Raber J, Rizk A, Otsuka S, VandenBerg SR, Morhardt DR, Fike JR. (2004) Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. *Exp. Neurol.*, 188:316–330.

Rollins W. (1903) Notes on x-light: the effect of x-light on the crystalline lens. *Boston Med. Surg. J.*, 148:364–365.

Rubin P, Casarett GW. (1968) Clinical radiation pathology as applied to curative radiotherapy. *Cancer*, 22:767–778.

Saganti PB, Cucinotta FA, Wilson JW Simonsen LC, Zeitlin CJ. (2004) Radiation climate map for analyzing risks to astronauts on the Mars surface from galactic cosmic rays. *Space Sci. Rev.*, 110:143–156.

Shay J, Wright H. (2005) Senescence and immortalization: role of telomeres and telomerase. *Carcinogenesis*, 26:867–874.

Soloviev AI, Tishkin SM, Parshikov AV, Ivanova IV, Goncharov EV, Gurney AM. (2003) Mechanisms of endothelial dysfunction after ionized radiation: selective impairment of the nitric oxide component of endothelium-dependent vasodilation. *Br. J. Pharmacol.*, 138:837–844.

Stearner SP, Yang VV, Devine RL. (1979) Cardiac injury in the aged mouse: comparative ultrastructural effects of fission spectrum neutrons and gamma rays. *Radiat. Res.*, 78, 429–447.

Stewart FA Heeneman S, Te Poele J, Kruse J, Russell NS, Gijbels M, Daemen M. (2006) Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am. J. Pathol.*, 168:649–658.

Swerdlow AJ, Higgins CD, Smith P, Cunningham D, Hancock BW, Horwich A, Hoskin PJ, Lister A, Radford JA, Rohatiner AZ, Linch DC. (2007) Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J. Natl. Canc. Inst.*, 99:206–214.

Tao F Powers-Risius P, Alpen EL, Medvedovsky C, David J, Worgul BV. (1994) Radiation effects on late cytopathological parameters in the murine lens relative to particle fluence. *Adv. Space Res.*, 14:483–491.

Taylor A, Hobbs M. (2002) The 2001 assessment of nutritional influences on risk of cataract." In: Rosenberg IH, Sastre A (Eds.), *Nutrition and aging*. Nestlé Nutrition Workshop Series Clinical & Performance Program, Vol. 6, Nestec Ltd. Vevey/S. Karger AG, Basel, Switzerland, pp. 163–191.

Tezelman S, Rodriquez JM, Shen W, Siperstein AE, Duh QY, Clark OH. (1995) Primary hyperparathyroidism in patients who have received radiation therapy and in patients who have not received radiation therapy. *J. Am. Coll. Surg.*, 180:81–87.

Tissel LE, et al. (1985) Hyperparathyroidism subsequent to neck irradiation: risk factors. *Cancer*, 56:1529–1533.

Toussaint O, Royer V, Salmon M, Remacle J. (2002) Stress-induced premature senescence and tissue ageing. *Biochem. Pharmacol.*, 64:1007–1009.

Tribble DL, Barcellos-Hoff MH, Chu BM, Gong EL. (1999) Ionizing radiation accelerates aortic lesion formation in fat-fed mice via SOD-inhibitable processes. *Arterioscler. Thromb. Vasc. Biol.*, 19:1387–1392.

Vrijheid M, Cardis E, Ashmore P, et al. (2007) Mortality from diseases other than cancer following low doses of ionizing radiation: results from the 15-country study of nuclear industry workers. *Int. J. Epidemiol.*, 36(5):1126–1135.

Wang Y, Schulte B A, LaRue AC, Ogawa M, Zhou D. (2006) Total body irradiation selectively induces murine hematopoietic cell senescence. *Blood*, 107:358–366.

Warfield ME, Schneidkraut MJ, Ramwell PW, Kot PA. (1990) WR2721 ameliorates the radiation-induced depression in reactivity of rat abdominal aorta to U46619. *Radiat. Res.*, 121:63–66.

Wilson JW, Kim M, Schimmerling W, Badavi F, Thibeault S, Cucinotta FA, Shinn J, Kiefer R. (1995) Issues in space radiation protection. *Health Phys.*, 68:50–58.

Worgul BV. (1986) Cataract analysis and the assessment of radiation risk in space. *Adv. Space Res.*, 6:285–293.

Worgul BV, Brenner DJ, Medvedovsky C, Merriam GR Jr, Huang Y.(1993) Accelerated heavy particles and the lens. VII: The cataractogenic potential of 450 MeV/amu iron ions. *Investig. Ophthalmol. Vis. Sci.,* 34:(1)184–193.

Worgul BV, Medvedovsky C, Huang Y, Marino SA, Randers-Pehrson G, Brenner DJ. (1996) Quantitative assessment of the cataractogenic potential of very low doses of neutrons. *Radiat. Res.*, 145:343–349.

Worgul BV, Kundiyev YI, Sergiyenko NM, Chumak VV, Vitte PM, Medvedovsky C, Bakhanova EV, Junk AK, Kyrychenko OY, Musijachenko NV, Shylo SA, Vitte OP, Xu S, Xue X, Shore RE. (2007) Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exposures. *Radiat. Res.*, 167:233–243.

Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G. (2004) Noncancer disease incidence in atomic bomb survivors, 1958–1998. *Radiat. Res.*, 161:622–632.

Yang VV, Stearner SP, Tyler SA. (1976) Radiation-induced changes in the fine structure of the heart: comparison of fission neutrons and ^{60}Co gamma rays in the mouse. *Radiat. Res.*, 67:344–360.

Yang VV, Stearner SP, Ainsworth EJ. (1978) Late ultrastructural changes in the mouse coronary arteries and aorta after fission neutron or ^{60}Co gamma irradiation. *Radiat. Res.*, 74:436–356.

Yang VV, Ainsworth EJ. (1982) Late effects of heavy charged particles on the fine structure of the mouse coronary artery. *Radiat. Res.*, 91:135–144.

Yang TC, Tobias CA. (1984) Effects of heavy ion radiation on the brain vascular system and embryonic development. *Adv. Space Res.*, 4:239–245.

Yeung TK, Hopewell JW. (1985) Effects of single doses of radiation on cardiac function in the rat. *Radiother. Oncol.*, 3:339–345.

Yochmowitz MG, Wood DH, Salmon YL. (1985) Seventeen-year mortality experience of proton radiation in Macaca mulatta. *Radiat. Res.*, 102:14–34.