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Commentary

No evidence for an increase in circulatory disease mortality in astronauts following space radiation exposures

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ABSTRACT

Previous analysis has shown that astronauts have a significantly lower standard mortality ratio for circulatory disease mortality compared to the U.S. population, which is consistent with the rigorous selection process and healthy lifestyles of astronauts, and modest space radiation exposures from past space missions. However, a recent report by Delp et al. considered estimates of the proportional mortality ratio for ages of 55–64 y of Apollo lunar mission astronauts to claim a high risk of cardiovascular disease due to space radiation compared to the U.S. population or non-flight astronauts. In this Commentary we discuss important deficiencies in the methods and assumptions on radiation exposures used by Delp et al. that we judge cast serious doubt on their conclusions.

1. Introduction

Astronauts are exposed to various stresses, such as space radiation, microgravity, and hypergravity. Of these, space radiation risks, such as those of cancer, circulatory or cardiovascular disease (CVD)[1], and central nervous system effects, are a concern for long term manned space missions to Mars and other destinations. Most space missions in the past were relatively short in duration, while a mission to Mars would approach 1,000 days in duration, thereby raising concern for radiation risks. A recent report by Delp et al. (2016) makes a claim that the Apollo astronauts have higher CVD mortality due to space radiation exposure compared to other astronauts or the average U.S. population. We are surprised by this report because previous analysis of the astronaut cohort (Cucinotta et al., 2013) showed a standard mortality ratio (SMR) of 0.33 [95% confidence intervals: 0.14, 0.8] for death for National Aeronautics and Space Administration (NASA) astronauts compared to the U.S. population, which is consistent with the expectations of the rigorous selection process for astronauts, healthy lifestyles, and the modest radiation doses from most past missions. We address below several important deficiencies in the methods used by Delp et al. (2016), which we judge cast doubt on their conclusions.

2. Data collection

Delp et al. (2016) do not clarify the precise disease endpoints that are used, in particular they do not define what is meant by CVD. This often refers to a much smaller group of morbidities than circulatory disease, in particular heart and blood vessel disease, including ischemic heart disease (IHD) [ICD-10 I20-I25], hypertensive disease [ICD-10 I10-I15], cerebrovascular disease (CeVD) [ICD-10 I60-I69], and diseases of the veins, arteries and arterioles [ICD-10 I80-I89]. That said, by far the largest number of deaths from circulatory disease are from IHD, which is generally included in CVD (World Health Organization (WHO), 2015), so this imprecision may not matter too much. Data collection was incomplete, and particularly so for non-flight astronauts where death certificates were available for only 49%, with the remaining information coming from newspaper and journal articles. There was no linkage to national mortality data (NDI-Plus), which would be standard in a study of this sort. Data collection was therefore heterogeneous and inconsistent across the different comparison groups in the study. There was no data collected on the major lifestyle

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[1] By circulatory disease we shall mean those morbidity or mortality endpoints with International Classification of Diseases 10th revision (ICD-10) codes I00-I99.

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Table 1
Representative average crew dose and dose-rates for various NASA programs adapted from Cucinotta et al. (2008), Cucinotta et al. (2003).

NASA Program (Number Apollo crew participants)	Badge dose, mGy	Effective dose, mSv	Dose-rate, mGy/d	Effective dose-rate ~~Dose-rate~~, mSv/d
Mercury (2)	0.1	0.15	0.3	0.55
Gemini (17)	1.3	2.2	0.49	0.87
Apollo (All = 29)	4.1	12.0	0.43	1.2
Skylab (2)	40.3	95.0	0.71	1.4
Apollo-Soyuz (1)	1.1	2.3	0.12	0.26
NASA Mir (0)	50.3	115	0.37	0.84
NASA ISS* (0)	29	72	0.19	0.48
Space Shuttle, STS (4)				
STS 28.5°, >400 km	9.5	17.0	1.2	2.1
STS 28.5°, <400 km	0.9	1.6	0.1	0.18
STS >50°, >400 km	2.2	5.2	0.44	1.1
STS >50°, <400 km	1.7	3.8	0.2	0.45

* ISS doses are for years 2000–2007, which occurred at solar maximum and the period between solar maximum and solar minimum, with higher exposures occurring near solar minimum.

factors related to circulatory disease risk such as male sex, family history of heart disease, use of tobacco products, elevated total cholesterol or elevated low density lipoprotein (LDL) cholesterol or reduced high density lipoprotein (HDL) cholesterol, diabetes, and obesity (body mass index), all of which can independently modify circulatory disease risk by at least a factor of two (Burns, 2003; Wilson et al., 1998). The Apollo crews were all male; however, females account for about 20% of later astronaut groups, and have a lower circulatory disease risk compared to males (Mosca et al., 2011). Use of tobacco products is a major risk factor for circulatory disease and cigarette smoking generally decreased in the U.S. after 1970s and 1980s following the first (Public Health Service, 1964) and various subsequent reports of the U.S. Surgeon General on health risks of smoking. This reduction in smoking prevalence was paralleled in the astronaut cohort, and complicates a direct comparison of Apollo crews with later mission crews unless some adjustment for smoking is performed. Whether such lifestyle risk factors could confound the radiation dose response will be determined by the extent to which they are correlated with radiation exposure. In many radiation-exposed groups that have lifestyle information, there is no evidence that lifestyle factors interact with radiation risk of circulatory disease (Azizova et al., 2014; Azizova et al., 2010; Darby et al., 2013; Shimizu et al., 2010; Yamada et al., 2004), presumably reflecting the absence of correlation between such lifestyle factors and radiation exposures in these datasets.

3. Data analysis

The use of proportional mortality ratios (PMR) by Delp et al. (2016) is another significant weakness. Elevated PMRs can result from increases in the cause of death under consideration, but can also arise because of decreases in mortality from the remaining causes. The restriction of the analysis to a single age group (55–64 years) is an oddity. It is standard epidemiological practice to analyze all ages, from the point of entry of each subject to the astronaut cohort onwards. Selection of such a single age group is a type of *post-hoc* data selection, and invalidates statistical inference. Delp et al. (2016) ignore the absence of circulatory disease deaths for Apollo astronauts before age 55 or ~~in~~ ages 65–84 years; it is very likely that had they considered all ages the risks would not have been elevated. In any case, a comparison with external populations, such as the US national population, is very likely to be misleading, because of the high degree of selection that was entailed in being judged fit (and competent) enough to be an astronaut. Most occupational cohorts are healthier, in particular have lower age-specific mortality rates, than the national populations from which they are drawn, because of healthy worker selection, i.e., the fact of being available to work automatically excludes the group of long-term sick and disabled, who have elevated rates of morbidity and mortality (Bell and Coleman, 1987; Carpenter, 1987; Doll et al., 1965). The most appropriate analysis is therefore an internal type of survival analysis, in particular using Cox proportional hazards models (Cox, 1972) or Poisson regression (McCullagh and Nelder, 1989), assessing risks in relation to the putative risk factor, in this case presumably the occupational radiation dose or job category, as well as the lifestyle risk factors, the magnitude of the effect of which is likely to dwarf the expected radiation effect, as discussed below. It is also vital that account be taken of the variation of occupational and lifestyle factors over time, which may correlate with (and therefore confound the effects of) occupational radiation dose; the analysis of Delp et al. (2016) does not attempt this.

4. Radiation analysis and microgravity

Delp et al. (2016) did not consider the participation of Apollo lunar mission crew in other missions, radiation doses, and time in space under microgravity conditions. Table 1 makes it clear that several Apollo astronauts also participated in low Earth orbit (LEO) missions, including 2 on Mercury, 17 on Gemini, 2 on Sklyab, 1 on Apollo-Soyuz, and 4 on space shuttle (Space Transportation System, STS) missions. There are substantial variations in radiation dose, depending on the specific missions, and concomitant radiation exposures received by astronauts (Cucinotta, 2001; Cucinotta et al., 2008; Cucinotta et al., 2003; National Council on Radiological Protection and Measurements (NCRP), 1989). Doses from medical diagnostic exposures and the use of experimental protocols using radioisotopes were much higher for astronauts participating in the Apollo program compared to more recent astronauts (Cucinotta, 2001; National Council on Radiological Protection and Measurements (NCRP), 1989). Several Apollo astronauts received small doses during training with the lunar rover at the Nevada (nuclear weapons) Test Site prior to their missions. Astronauts accumulate significant radiation doses from aviation with large individual variations occurring due to factors such as military backgrounds, and aviation frequency for pilots versus mission specialists.

Average absorbed doses due to space radiation exposures received by astronauts are recorded based on crew personal dosimeters, and used to make estimates of effective doses that adjust for radiation quality effects and tissue shielding. Table 1 shows average dose and dose-rates for crew participating in various NASA flight programs, which vary with mission parameters such as orbital inclination, altitude and phase in the solar cycle. Missions

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in LEO encounter galactic cosmic rays (GCR) along with trapped protons and electrons in the Earth's inner radiation belt, however behind spacecraft shielding GCR dominate organ dose equivalents (Cucinotta et al., 2008), with the exception of high altitude missions (>400 km) that spend more time in the radiation belts. The Apollo lunar missions passed through the radiation belts contributing to crew doses, and a small neutron dose came from a radioisotope thermoelectric generator (RTG) for the lunar surface missions with a higher neutron dose on the aborted Apollo 13 mission. The Apollo 14 crew received about half of their mission dose on the return passage through the radiation belts with a smaller variable percentage on other missions. The composition of GCR in transit to the Earth's moon and in LEO is similar; however, in LEO, the GCR dose-rate is reduced by a third due to the Earth's shadow, and lower energy particles are deflected by the Earth's magnetic field. The particle species and linear energy transfer (LET) composition of organ doses on LEO missions is similar to that of the Apollo lunar missions (Cucinotta, 2001; Cucinotta et al., 2003, 2008; National Council on Radiation Protection and Measurements (NCRP), 2010; National Council on Radiological Protection and Measurements (NCRP), 1989). The average effective dose for a nominal 180-d mission on the International Space Station (ISS) or Russian space station Mir (about 80 mSv) is much higher than those of the Apollo missions (about 15 mSv). The Skylab missions also had much higher effective doses (95 mSv) compared to the Apollo missions.

There are known short term effects of microgravity on the circulatory system (Arbeille et al., 2016), although long-term effects are still unknown. Microgravity effects in LEO or transit to the Earth's moon are expected to be similar, while gravity on the lunar surface is about a sixth of that of Earth. It is not known how radiation and microgravity would interact even in relation to short-term effects on the circulatory system in the astronaut cohort.

Thus time-varying radiation dose, mission duration, the number of missions, and time spent on the lunar surface should all be taken into account in analysis of circulatory disease risk in astronauts. No conclusion on circulatory disease risk in Apollo lunar crew in relation to their radiation exposure can be drawn from a PMR evaluation such as that reported by Delp et al. (2016).

5. Circulatory disease risks from low dose radiation

Circulatory disease risks following high dose radiotherapy of cancer are well known (Little, 2016). Epidemiologic studies among the Japanese atomic bomb survivors (Shimizu et al., 2010) suggest that there are elevated risks of circulatory disease at somewhat lower dose, above about 0.5 Sv. More recently, ~~there is a concern for circulatory disease risks at lower doses with a~~ meta-analysis ~~of results made by~~ Little (2016), Little et al. (2012) summarizing the major studies of occupational and environmental exposures. Radiation risks are shown to vary between circulatory disease components such as IHD and non-IHD, while there is significant heterogeneity between the results of various epidemiological studies. There is continued debate as to the nature of the low dose risk, including the role of dose thresholds, and whether circulatory disease is a tissue reaction (deterministic) or stochastic consequence of radiation exposure (ICRP, 2012; Hamada et al., 2014). Whether or not there really is a threshold in radiation dose, which would imply no risk at sufficiently low radiation doses, there is consistent evidence that relative risks are modest at low doses, so that at a dose of 1 Sv, the relative risk of all types of circulatory disease would be expected to be between 1.10 and 1.20 (Little, 2016; Little et al., 2012), and therefore likely to be dwarfed by the variations associated with the other major risk factors for circulatory disease discussed above. As such the five-fold elevated risk suggested by Delp et al. (2016), in a cohort that is likely to have accumulated less than 0.6 Sv, is improbable.

In summary, we find the methods of Delp et al. (2016) to be flawed in a number of critical respects, and the conclusions therefore cannot be supported. Research on the health risks from cosmic rays should be a priority for space programs. Epidemiological studies of space missions should be performed with appropriate methods, although they are likely to be of low statistical power, because of the small numbers in the astronaut cohorts and the modest radiation exposures. Radiobiological and other mechanistic modeling investigations are likely to be more useful in developing an understanding of space radiation health effects.

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