Cancer Incidence and Mortality in the U.S. Astronaut Corps, 1959-2017

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Abstract

Background: Cancer incidence and mortality are important outcomes in the surveillance of long-term astronaut health. In this research, we compare cancer incidence rates, cancer-specific mortality rates, and cancer case fatality ratios in US astronauts with those in the US general population.

Methods: We use standardized incidence ratios and standardized mortality ratios to index the incidence and mortality of various cancers against rates in the US general population, from the US astronaut cohort inception in April 1959 through 31 December 2017. We also compare the lethality of these cancers in astronauts and the general population using the relative case fatality ratio.

Results: The astronaut cohort included 338 individuals and over 9600 person-years of follow-up time. The counts of most cancers were under 3, though there were 11 cases of melanoma and 30 cases of prostate cancer. Both prostate and melanoma had statistically significant increases in incidence, though only melanoma had a significant increase in mortality. Lung cancer had a statistically significant deficit of both cases and deaths, while colon cancer had sizable (but not statistically significant) reductions in incidence and mortality. Three cancers showed evidence of detection bias (colon, hematologic, prostate), possibly a result of astronaut health screening protocols. For all cancers combined, astronauts showed a non-significant reduction in incidence and mortality, and a significant reduction in case fatality ratio.

Conclusions: Though there were observed increases in both incidence and mortality from melanoma among astronauts, these increases are consistent with those observed repeatedly among aircraft pilots, suggesting this may be associated with ultraviolet radiation or lifestyle factors rather than any astronaut-specific exposure. The increase in prostate cancer incidence is likely explained by detection bias, and the same may be true for hematologic cancers. The lack of statistical significance in the reduction of incidence and mortality for colon cancer may be attributable to relaxed screening practices for astronauts in recent years. As astronaut health surveillance continues and evolves, the growing database will lead to a clearer picture over time. The methods employed here provide a useful structure for ongoing analysis of this unique occupational cohort.

Background

In the ongoing investigations of the long-term consequences of space travel, one of the most significant health risks for astronauts is cancer. We can examine at least two broad issues: whether, in comparison to other populations, astronauts develop cancers at differential rates (cancer-specific incidence) and whether they die of cancer at differential rates (cancer-specific mortality). On the one hand, the healthy worker effect (HWE) might predict decreased cancer incidence and mortality among astronauts in comparison to the general population.[1] On the other hand, unique occupational exposures – particularly ionizing space radiation from galactic cosmic rays, the Van Allen belts, and solar particle events – may increase the risk of cancer for astronauts.

Though the long-term risk of cancer among American astronauts has been under surveillance at the US National Aeronautics and Space Administration (NASA) for many years, cancer incidence has been infrequently reported to the broader scientific community. Results from a 2003 briefing to the National Academies indicated a statistically significant 46% reduction in cancer incidence for US astronauts in comparison to the US general

population.[2] This estimate was based on the occurrence of 14 cancers among 312 astronauts and excluded non-melanoma skin cancers. Since then there have been more than 50 additional cancer diagnoses recorded among astronauts, highlighting the need for a reassessment.

Prior research on this cohort has documented substantial reductions in cancer mortality risk for astronauts in comparison to different populations. The first study to publish this, in 1998, reported astronauts to be at half the risk of cancer mortality as the general population, albeit based on only 3 observed deaths.[3] A study of astronauts selected before 1970, with follow-up through February 2017, also reported astronauts to be at less than half the risk of death from all cancers in comparison to the general population.[4] Within the full cohort and with follow-up through October 2017, astronauts were reported to be at only 62% the risk of the general population for mortality from all cancers (95% CI = 37–97%).[5] Finally, in comparison to professional basketball players, astronauts were at no differential risk of cancer mortality, with only a nominal and non-significant 10% lower mortality rate for astronauts.[6]

In the present work, we analyze standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) to compare astronaut cancer incidence and mortality rates with those of the general population. When these measures are less than 100, they represent a lower (cause-specific) incidence or mortality rate in the astronaut cohort compared to the U.S. general population, while values greater than 100 indicate higher rates for astronauts.

A complication for interpretation of the SMR is that the expected number of deaths due to a given cancer, an integral part of the calculation, is a reflection of both incident and prevalent tumors in the general population. For some specific cancers, the number of expected deaths due to a given tumor is larger than the number of incident tumors observed in the astronaut population (and in some rare instances, even larger than the number of incident tumors expected based on incidence rates in the general population during the period of available observation time for astronauts). It is unrealistic to expect to see more deaths due to a specific cancer (or all cancers) in astronauts than there are incident tumors, given that it is highly unlikely an astronaut would be selected who had a prevalent (malignant) tumor, other than skin cancers. In light of all of these issues, interpretation of cancer-specific SMRs for astronauts is challenging and invites an alternative approach to indexing the lethality of cancers among astronauts.

In this study, we will use the case fatality ratio, and in particular the relative case fatality ratio (RCFR), to help us understand the lethality of specific cancers (and of all cancers combined) among astronauts, while accounting for the observed incidence of the respective tumors (or all tumors combined). The RCFR will complement the SIR and SMR, aiding our interpretation of these two measures as well as providing information on how comparatively deadly each cancer is for astronauts. This information can be useful in trying to ascertain and mitigate the cancer risk associated with space flight exposures. By comparing the astronauts to the general population, we can identify risks that are potentially elevated due to space exposures. However, the astronaut cohort is relatively unusual in being selected for better health and being more regularly monitored for medical problems than the general population. This paper identifies astronaut cancer risks that are significantly different than the general population and assess them in the light of the likely healthy worker effect and possible detection bias as an initial step in determining potentially elevated risks from space flight exposures.

Methods

Study Population and Data

The population under study comprises all astronauts selected to the US Astronaut Corps between 1959 and 2013 (astronaut classes 1-21). Follow-up for each astronaut begins at the date of selection to the Astronaut Corps and ends with the earlier of an astronaut's date of death and December 31, 2017. These data were taken from a database originally constructed from publicly available information about the astronauts, including NASA's Astronaut Fact Book, astronaut biographies on NASA's website, and other publicly available information on the internet. The database has been used extensively in prior publications concerning astronaut mortality.[5-7]

Counts of tumors and cancer deaths were obtained from the 2019 issue of the newsletter of the Lifetime Surveillance of Astronaut Health (LSAH) at NASA, with input from the LSAH on specific tumor and death counts.[8] In comparison to the original source table, 2 cancers (1 melanoma and 1 testicular) were removed from the tumor counts, as they were diagnosed prior to time of selection to the Astronaut Corps. Figure 1 shows the tumor counts by body site among the astronauts under study.

General Population Incidence and Mortality Rates

Cancer-specific incidence and mortality rates were obtained from the Wide-ranging ONline Database for Epidemiologic Research (WONDER) from the US Centers for Disease Control (CDC). Incidence rates were available for the years 1999 to 2016, while mortality rates were available for the years 1968 to 2016. For years prior to 1999, we used the 1999 incidence rates to compute expected numbers of tumors, and for years prior to 1968 we used the 1968 mortality rates to compute expected numbers of deaths. For both incidence and mortality, we used the 2016 rates for 2017 data. Both types of rates (incidence and mortality) were available stratified on year, age category, sex, and race. Table 1 shows the ICD-8, ICD-9, and ICD-10 codes used to match cancers with general population incidence and mortality rates. To harmonize the data with the available racial strata for general population rates, we considered categories of Asian, Black, White, and Other.

Table 1. ICD codes used for cancer types			
	ICD-8	ICD-9	ICD-10
Brain	191	191	C71
Breast	174	174	C50
Colon	153	153	C18
Head and Neck	140-149	140-149	C0-C14
Hematologic	200-209	200-208	C81-C96
Kidney	189	189	C64-C65
Lung	162	162	C34
Melanoma	172	172	C43
Mesothelioma	158	158	C45
Pancreas	157	157	C25
Prostate	185	185	C61
Sarcoma	171	171	49.9
Thyroid	193	193	C73

Standardized Incidence Ratios (SIRs)

We used SIRs to index cancer-specific incidence for astronauts against that of the general population. SIRs are computed through indirect standardization with an external reference population. Each SIR is the quotient of the observed number of cases of a particular cancer in the study population (astronauts) and the expected number based on rates from the reference population(US general population) applied to exposure times (person-years) for astronauts.

The expected number of cases, and the SIR, is adjusted for calendar year, age, sex, and race. This is done by first summing the observed person-years in the astronaut cohort within the various strata of calendar year, age, sex, and race. These sums are then multiplied by general population incidence rates for each respective stratum to obtain the stratum-specific number of expected cases. These expectations are then summed over all strata to obtain the total expected number of cases for use in the SIR calculation.

We obtained exact 95% confidence intervals on the cause-specific SIRs by using the exact method outlined by Breslow and Day (1987), which assumes that the observed tumor count,n_{obs}, is a Poisson random variable taken from a distribution with meanmdetermined as those lower and upper values CI_L and $CI_U$for which the upper and lower Poisson tail probabilities $P[N \geq n_{act} \mid m = CI_L] = P[N \leq n_{act} \mid m = CI_U] = a/2$are equal to half the nominal significance levela, i.e. 0.025 for 95% CI (a = 0.05).

Standardized Mortality Ratios (SMRs)

SMRs are estimated in a similar way to SIRs, using general population mortality rates for the calculation of expected numbers of events, with deaths from the specified cause rather than tumor diagnoses. Calculation ofexact 95% confidence intervalsalso used the exact method described above.[9]

Relative Case fatality Ratios (RCFRs)

We calculatedtheRCFR as follows. First, the expected-case fatalityratio (ECFR) for each cancer type is calculated by dividing the expected number of deaths for each specific cancerin the general population(as computed for the SMR) by the expected number of incident cases of the same cancer in the general population(as computed for the SIR). In general, it is possible to have more deaths than incident cases when observing a cohort over time, as members of the cohort may die of cancers that were prevalent at the start of follow-up. This could lead to an ECFR greater than 1.0 for any given observation period. However, all tumors included in the current astronaut dataset were incident over the follow-up period.Thus,assuming no deficiencies in ascertainment,there could not be more deaths from any given tumor among astronauts than there were observed cases among astronauts. For these reasons, in any case where the ECFR was greater than 1.0, we capped the expected number of deaths among astronauts at the observed case count.

Second, the observed CFR (OCFR) for astronauts is calculated by dividing the observed number of deaths by the observed number of cases for a given cancer. Finally, the relative CFR (RCFR) is the OCFR divided by ECFR. Equivalently, the RCFR is equal to the number of observed deaths in the astronaut cohort for a given cancer divided by the expected number of deaths for that same cancer, the latter being the product of the ECFR and the number of observed cases of cancer in the astronaut cohort.

We computed the two-tailed binomial probability p-value for the observed number of deaths under the null hypothesis that the probability of death for a person with a given cancer diagnosisis the ECFR for that cancer. We considerp-values less than 0.05 to be statistically significant.

Results

The demographic and actuarial characteristics of the astronaut cohort as of December 31, 2017 are presented in Table 2. The cohort consisted of 338 NASA astronauts selected between 1959 and 2013, who generated 9613 person-years of follow-up time, for an average follow-up time of 28.4 yr. (SD=13.8 yr) The mean age at selection was 34.4 yr (SD=3.6 yr), while the mean age at death of astronauts who died during the study period was 58.8 yr (SD=18.1 yr), and the mean age of survivors (to the end of follow-up) was 63.6 yr (SD=11.4 yr). The cohort was 85% male, 90% White, 70% had military experience, and 70% were licensed pilots.

The distribution of person-years of follow-up by age and sex is shown in Figure 2. As astronauts are selected to the Astronaut Corps at a mean age of 34.4 yr, there is most follow-up in the interval of ages 35 to 49, diminishing over age 50. Cancer incidence generally begins to increase after age 50, and 48% of the follow-up time (4,639 person-years) is from ages 50 and older. Women contributed a small proportion of the follow-up time in any given age group and for all ages between ages 25 and 75. Their comparatively late entry into the

Astronaut Corps (1978) means that, as of December 2017, no female astronauts have yet reached age groups greater than 75 years.

Table 2. Astronaut cohort characteristics		
	Count	**%**
Cohort size	338	100.0
Person-years	9613	100.0
Sex		
Female	50	14.8
Male	288	85.2
Race		
White	304	89.9
Black	17	5
Hispanic	12	3.6
Other	5	1.5
Education		
Bachelor	54	16.0
Master	172	50.9
Doctoral	112	33.1
Military Background	237	70.1
Licensed pilot	235	69.5
	Mean	**SD**
Age (yr)		
Selection	34.4	3.62
Death (all causes)	58.8	18.12
Study end (survivors)	62.9	11.38
Follow-up time (yr)	28.4	13.81

Table 3 displays the observed and expected counts (based on age-, race-, sex-, and calendar-year-specific general population incidence rates applied to corresponding strata of person-years for astronauts) of cancers by type, and their SIRs with 95% confidence intervals. Taking all cancers as a group, astronauts have an

incidence rate 12% greater than would be expected in the general population given the age and sex structure of the astronaut cohort and number of person-years of follow-up. With 65 tumors observed and 58.12 expected, this yielded modest increase in risk (SIR = 112) with a confidence interval that included 100 (95% CI = 86–143). Since the incidence and mortality rates from melanoma are known to be elevated among commercial and military pilots, we also computed composite risk estimates without melanoma included in the totals.[10-12] When melanoma is removed from consideration the SIR drops to 98 (95% CI = 73–128), implying no significant difference in cancer incidence rate between the astronaut cohort and the general population.

The most frequently diagnosed individual cancer in the astronaut cohort was prostate cancer. With 30 cases observed and only 16.07 expected, this is a statistically significant increase (SIR = 187; 95% CI = 126–266). The next most frequent cancer type was melanoma, with 11 cases observed while only 2.86 cases were expected; this gives a SIR of 385 (95% CI = 192–688), which was also statistically significant.

There were a number of SIRs greater than 100, but which were not statistically significant. The SIRs in these cases are based on 4 or fewer observed tumors and similarly small expected numbers. The cancers in these cases included cancers of the brain, breast, pancreas, and thyroid, as well as hematologic cancers, mesothelioma, and sarcomas.

There was only one type of cancer that had significantly lower incidence among astronauts than expected. There were 2 cases of lung cancer among astronauts while 9.11 were expected, leading to a statistically significant SIR of 22 (95% CI = 3–79). The number of observed colon cancers was lower than expected but not statistically significantly so. The SIR for this cancer was 26 (95% CI = 1–147). There were also slightly fewer head and neck cancers than expected and an insignificant reduction in kidney cancer.

Table 3. SIRs and SMRs for select cancers among astronauts.										
	Incidence					Mortality				
Cancer type	Obs. Tumors	Exp. tumors	SIR	LL	UL	Obs. deaths	Exp. deaths	SMR	LL	UL
Brain	3	0.76	399	81	1152	3	0.80	374	77	1092
Breast	1	0.13	750	19	4180	1	0.29	346	9	1930
Colon	1	3.78	26	1	147	1	1.92	52	1	290
Head & Neck	2	2.64	76	9	273	1	0.57	175	4	973
Hematologic	4	1.83	219	60	561	2	2.76	72	9	262
Kidney	1	2.3	44	1	242	0	0.77	0	0	389
Lung	2	9.11	22	3	79	1	8.71	11	0	64
Melanoma	11	2.86	385	192	688	3	0.59	508	105	1485
Mesothelioma	1	0.19	516	13	2876	1	0.16	644	16	3586
Pancreas	2	1.43	140	17	504	2	1.60	125	15	452
Prostate	30	16.07	187	126	266	3	1.80	166	34	486
Sarcoma	2	0.33	607	73	2191	0	0.16	0	0	1921
Thyroid	1	0.56	178	5	990	0	0.06	0	0	4675
All cancers	65	58.12	112	86	143	20	27.70	72	44	111
Non-skin cancers	54	55.26	98	73	128	17	27.11	63	37	100

Observed and expected numbers of cancer deaths and corresponding SMRs and 95% confidence intervals are also presented in Table 3. Whereas the composite incidence rate showed a nominal increase for astronauts in comparison to the US general population, the composite mortality rate shows a modest but insignificant reduction, with astronauts having only 72% the mortality risk in the general population for all cancers combined (95% CI = 44–111). When considering all non-skin cancers, the composite SMR was 63 and was on the boundary for statistical significance with a 95% confidence interval of 37–100.

As was the case for incidence rates, lung cancer was the only individual cancer type for which there was a statistically significant reduction in mortality rate for US astronauts in comparison to the general population. There was a single lung cancer death in the astronaut cohort when 8.7 would have been expected in the general population, leading to a SMR of 11 (95% CI = 0–64).

There were 3 deaths in the astronaut cohort from prostate cancer, which yields a moderate (but insignificant) increase in comparative mortality risk (SMR = 166; 95% CI = 34–486).

The only cancer for which mortality risk was significantly elevated was melanoma. US astronauts were found to have approximately five times the expected number of deaths due to melanoma (SMR = 508; 95% CI = 105–1485), with 3 deaths observed compared to only 0.59 expected. All other tumor types had statistically non-significant SMRs.

Table 4 presents the observed and expected counts of deaths, ECFRs, and RCFRs for the various cancer types (recall that here the expected number of deaths is calculated as the product of the corresponding ECFR and the number of observed cases in the astronaut cohort). A few of the ECFRs exceeded 1.0, suggesting that based on general population cancer-specific mortality and incidence rates applied to exposure time among astronauts, we would expect to see more deaths from these tumors than we would incident cases. This seemingly paradoxical result is attributable to prevalent cases in the general population, present prior to the start of follow-up for astronauts. Some tumors have many prevalent cases at any given time in the general population (breast) or have a combination of moderate levels of both lethality and prevalence (lung). In a few cases, ECFRs were close to or equal to 1.0. These corresponded to tumors with high lethality (brain and pancreatic cancers).

The overall RCFR for astronauts in comparison to the general population was 0.63 (95% CI = 0.41–0.88). Removing melanoma from the RCFR calculation did not change the point estimate of the RCFR and had only a minimal impact on the confidence interval (RCFR = 0.63; 95% CI = 0.37–0.89). This indicates that, overall, with or without the inclusion of melanomas, cancers tend to be less fatal for astronauts than would be expected (based on the corresponding case fatality ratios in the general population). These two composite estimates were the only estimates that reached statistical significance.

Table 4. RCFRs for cancers in the astronaut cohort.								
Cancer type	**Exp. deaths**	**Exp. Tumors**	**ECFR**	**Obs. Cases**	**Exp. case deaths**	**Obs. case deaths**	**RCFR**	**p-value***
Brain	0.80	0.76	1.05	3	3.0	3	1.00	1.0000
Breast	0.29	0.13	2.23	1	1.0	1	1.00	1.0000
Colon	1.92	3.78	0.51	1	0.5	1	2.00	0.5079
Head & Neck	0.57	2.64	0.22	2	0.4	1	2.00	–
Hematologic	2.76	1.83	1.51	4	4.0	2	0.50	–
Kidney	0.77	2.30	0.33	1	0.3	0	0.00	–
Lung	8.71	9.11	0.96	2	1.9	1	0.53	1.0000
Melanoma	0.59	2.86	0.21	11	2.3	3	1.30	0.7074
Mesothelioma	0.16	0.19	0.84	1	0.8	1	1.25	1.0000
Pancreas	1.60	1.43	1.12	1	2.0	2	1.00	1.0000
Prostate	1.80	16.07	0.11	30	3.4	3	0.88	1.0000
Sarcoma	0.16	0.33	0.48	2	1.0	0	0.00	0.5005
Thyroid	0.06	0.56	0.11	1	0.1	0	0.00	–
All cancers	27.7	58.12	0.48	67	31.9	20	0.63	0.0071
All non-skin	27.11	55.26	0.49	55	27.5	17	0.62	0.0070
* Two-tailed binomial probability of obtaining the observed number of deaths with the observed number of cases when the probability of death for cases is equal to the ratio of observed to expected number of deaths.								

Of the 13 individual cancer RCFRs, 6 of them had values of 1.0, signifying cancers that had lethality on par with the general population. This group included brain, breast, colon, pancreas, and prostate cancers, as well as mesothelioma.

Hematologic and lung cancers both had RCFRs of 0.5, indicating that there were half the number of expected deaths among astronauts as would be expected with the observed case counts. In contrast, the RCFR for melanoma was 1.5, suggesting that there were 50% more deaths among astronauts than would be expected given the number of melanoma cases.

Discussion

Though the observed and expected case counts in this cohort are small, the results presented here nevertheless provide intriguing and potentially important information about cancer incidence and mortality among

astronauts. Of the three cancers that displayed statistically significant differences in incidence rates compared to those of the general population, we believe there was one real increase (melanoma), one real decrease (lung), and one increase due, at least in part, to detection bias (prostate). Additionally, though their differences in incidence were not statistically significant, two other tumor types showed evidence of detection bias as well (colon and hematologic).

In general, detection bias refers to a change in event rates that results solely from more frequent or more intense screening in a target population. In the context of cancer, this bias will most often lead to an increase in age-specific incidence, as tumors are discovered at younger ages than they might otherwise be in the absence of regular screening. Simultaneously, detection bias will often lead to better survival (i.e. lower age-specific mortality rates), since tumors are generally caught at less advanced stages than they otherwise would be, making them more amenable to treatment. Depending on the tumor type, this increase in survival can also be reflected in lower case fatality ratios over a fixed period. In this study we saw some evidence of detection bias, as discussed below.

Prostate cancer is one cancer type that we believe should demonstrate detection bias in the astronaut cohort. Prostate cancer screening is performed by testing for levels of prostate-specific antigen in the blood. In the general population, this screening is recommended to begin at age 50 for men at average risk, but for astronauts, it begins at age 40.[8,13-15] Since prostate cancer can be asymptomatic and is most often slow-growing, many such tumors are never detected for patients in the general population.[16] In this analysis, we saw a nearly two-fold increase in the incidence of prostate cancer for astronauts. If this increase were indeed due to detection bias, then the SMR should be close to 100 (there should be little to no difference in the mortality rate for this cancer in astronauts and in the general population), but the case fatality rate should be lower. The SMR shows a range between 0 and 166, representing either no risk of death from this cause in the observation period or a 66% increase in risk compared to the general population, with none of the estimates statistically significant. The RCFR for prostate cancer in this cohort is 1.0, suggesting exactly as many deaths occurred for the number of astronaut cases as we would expect given the general population case fatality ratio. This would seem to argue against detection bias for prostate cancer.

Another way to gauge the possible impact of detection bias on incidence rates is to consider historical cases when screening guidelines have changed. In the early 1990's incidence rates for prostate cancer nearly doubled in the general population, and this trend has been attributed to increases in screening with newly available prostate-specific antigen tests.[17] This confirms that detection bias may be expected given the reality of early and consistent prostate cancer screening among astronauts.

Hematologic cancers are of concern to space exploration because these malignancies are known to be among the most radio-sensitive both in childhood and in adulthood.[18-20] We observed 4 hematologic cancers in the astronaut cohort when fewer than 2 were expected, for an SIR of approximately 200. While the 2 observed deaths from this cancer type represented an insignificant reduction in the mortality rate, the expected number of deaths from this cancer exceeded the expected number of cases, making interpretation of the SMR difficult. The RCFR brings clarity, since the ECFR suggests that all four cases of hematologic cancers would have been expected to die over the observation period, but only 2 did.

The increased incidence of hematologic cancers among astronauts may be attributable to radiation exposure while in outer space. If so, this would be true for astronauts who have flown on the International Space Station (ISS) in the last approximately 15 years; before this time, doses of radiation exposure during space flight were below levels at which we would expect to see radiation-induced increases in cancer incidence. However, the high lethality of these tumors (as evidenced by its ECFR of 1.51) suggests that no matter the number of cases observed, all of them should have died in the observation period. The hematologic cancer SMR below 100 and the RCFR of 0.5 suggest lower mortality than expected. Unless space radiation leads to more frequent yet less lethal forms of hematologic cancers, the decrease in mortality lessens the plausibility of a true increase in incidence, including the possibility of a true increase from space radiation doses.

A possible explanation for the reduced case fatality of hematologic cancers reflected in the RCFR may have to do with the timing of cases among astronauts. The case fatality ratio for hematologic cancers may have declined over time, and if the diagnoses of hematologic cancers among astronauts were limited to only recent years, then the whole-period general population ECFR would be too high (it is 1.51 in the current analysis, Table 4). Under these circumstances, the OCFR would be lower than expected (i.e., the RCFR would be less than 1.0, which it is here, at 0.50). One way to explore this possibility is to assume that all astronaut cases and deaths occurred in a recent period, and re-compute the ECFR using general population data from the same recent period. We did this using only data from 1999 to 2017, and the ECFR was reduced to 1.15. This means that even if all the hematologic cancer cases among astronauts were diagnosed in 1999 or later, we still would have expected all 4 cases to die, and thus the RCFR would remain at 0.5.

Instead, the observed increase in incidence coupled with the decrease in mortality could, again, be suggestive of detection bias, especially since hematologic cancers as a category could be susceptible to detection bias depending on the specific cancers observed in the group. Myelodysplastic cancers are slower growing than leukemia and lymphoma and could therefore be detected via blood screening before any symptoms were apparent.[21] Of the 4 cases of hematologic cancer among astronauts, 1 was a case of myelodysplastic syndrome, lending some credibility to this explanation. However, with the small case count and resulting wide confidence intervals, these results may be due to chance. No matter the explanation for this combination of incidence and mortality, we conclude that there is no strong evidence of an *increase* in either the incidence of, or mortality from, hematologic cancers in the astronaut cohort at this time.

Another tumor that may be susceptible to detection bias is colon cancer, where screening has historically been more frequent in the astronaut cohort than in the general population.[8] However, the pattern of detection bias in colon cancer is different from that of other tumor types, since the screening technique (colonoscopy) is also a preventative intervention by way of routine removal of precancerous colon polyps during the procedure. Under these circumstances, detection bias should *lower* incidence and mortality, but the effect on the CFR is unclear.

Even if screening has a consistent effect on the SIR, SMR, and CFR for colon cancer, inconsistent screening practices over time could obscure or nullify these effects. In 2003, NASA reduced the frequency of colonoscopy among active-duty astronauts, leading to statistically significant increases in average time between screenings, average severity of polyps, and average age at screening – all known risk factors for colon cancer mortality.[22] While the data used here are not sufficiently detailed to address the effect of the change in screening practices, a more complete data set, with diagnosis and mortality information linked to individuals, could do so. Such

analyses may find differences in the SIRs, SMRs, and potentially the CFRs for colon cancer by time period, before and after this change in screening practice.

The lack of statistical significance in the reduction in incidence of colon cancer may reflect several factors. First, the expected case count for colon cancer was just under 4, making even 75% reductions in the observed number of cases insignificant. Under these conditions, only a total absence of colon cancer cases would have reached statistical significance (results not shown in Table 4). While we might indeed expect a stronger effect on incidence with intense screening, it is important to note that the average age of retirement from the Astronaut Corps is approximately 48 years of age, meaning that any colon cancer screening performed on active duty astronauts likely occurs before the period of greatest risk for colon cancer, age 50 and older.[23,24] The changes in colon cancer screening in 2003 may again be a factor.

The data for lung cancer suggest that astronauts have experienced a real (and marked) reduction in lung cancer incidence and mortality rates. This is likely the result of healthy lifestyle, especially resulting from low rates of smoking in contemporary astronauts.[25] Consistent with this hypothesis, prior studies of cardiovascular disease among astronauts show reductions in both incidence and mortality in comparison to the general population.[4-5,26] Large differences in incidence and mortality rates between a largely never-smoker population and the US population as shown in table 4 are to be expected. However, due to changing smoking patterns in the US population over time, determining whether this difference in lung cancer is entirely due to healthy behavior or whether spaceflight exposures are contributing to a cancer risk would require a more detailed analysis.[27]

The low SMR for lung cancer indicates a substantial reduction in mortality. However, this reduction is complicated by the low incidence since more lung cancer deaths were expected than there were actual cases of lung cancer among astronauts. Using the RCFR, which indexes mortality within the subset of observed cases, we see that astronauts had only one death when 2 would have been expected. Though the small number of lung cancer cases precludes meaningful significance testing for the RCFR, it nevertheless suggests that the observed reduction in the SMR may be more than just an artifact of the low incidence rates. As never-smokers have improved survival among lung cancer cases, this may again be due to the generally low rate of smoking among astronauts.[25,28]

It is possible that the relative increase in the incidence of malignant melanoma among astronauts is also due to detection bias. However, we believe that the SIR observed here represents a real increase in incidence, even if its magnitude may be overestimated to some extent. In the case of melanoma, detection bias should manifest as increased incidence and either decreased or unchanged case fatality. This effect on mortality occurs when regular screening leads not only to early detection of true cancers, but also the misdiagnosis of benign lesions as melanomas (false positives) or minor cancers that might otherwise resolve without treatment.[29] Since the SMR and RCFR both show *increased* mortality for astronauts in comparison to the US general population, we conclude that the increase in incidence is not merely a result of detection bias.

Another factor that would tend to increase the case count is the large percentage of pilots in the Astronaut Corps. Airline pilots are known to have greater rates of melanoma, with recent meta-analyses estimating the SIR and SMR for commercial airline pilots to both be approximately 200 compared to the general populations

of various nations.[10-12] While exposure to galactic cosmic rays (GCR) has been suggested as a risk factor for melanoma among airline pilots, this is unlikely since melanoma is not known to be strongly radiogenic.[18] The literature suggests that the more likely source of this excess risk is the amount of ultraviolet (UV) radiation pilots receive at typical flight altitudes, as well as lifestyle factors independent of profession.[30] UVA radiation is of particular relevance to melanoma incidence and mortality in pilots, because the exposure at typical commercial flight altitudes can be at least twice that of ground levels.[10] Table 3 shows that 70% of the astronaut cohort are licensed pilots. The RCFR also suggests that the astronaut cases may be more severe than those in the general population, which could be consistent with intense UVA exposure. In total, the evidence presented here fails to suggest any extra or unique risk of melanoma due to being an astronaut, as the results of the SIR and SMR are statistically indistinguishable from what we might expect from pilots who are not astronauts. More detailed research specifically investigating the role of hours of atmospheric flight time, time in space, and subsequent radiation exposure is forthcoming.

The HWE is a phenomenon that is composed of both a healthy worker selection effect and a healthy worker survival bias. The former is the bias created by healthy people entering the workforce and unhealthy ones being unable to, while the latter is the bias generated by only healthy people remaining in the workforce.[1] As an occupational cohort of highly selected individuals with good health behaviors, access to high-quality medical care via NASA, and relative affluence, the HWE predicts that astronauts should have lower age-specific incidence rates of disease and thus, lower mortality rates in comparison to the US general population.[31] While the reductions in overall mortality risk reported here are consistent with those observed in other populations, the composite results show no difference in the overall incidence of cancer among astronauts in comparison to the US general population.[6] This result held true even when melanoma was removed from consideration. However, these results are difficult to interpret in light of the evidence of detection bias in several cancer types among astronauts. If we believe that, by comparison with what might be expected under rates from the general population, some cancers have artificially high incidence while others have artificially low incidence, the composite effect becomes intelligible only as the total effect of a unique blend of observed biases, rather than as the true and generalizable experience with cancer applicable to the long term health of current and future astronauts. The matter is further complicated by evidence of detection bias in 2 of the most common cancers observed in the general population, prostate and colon.

When we use a sensitivity analysis to quantify the effects of detection bias in the composite estimates, the SIRs shrink away from parity toward results that are more consistent with the HWE (see Appendix for details). However, it should be noted that the corrections made for detection bias are conservative in that they only assume that astronauts have, at best, incidence equal to that of the general population. If instead the detection bias is large enough to obscure true rates of tumor development that are actually lower than the general population, the composite SIR estimates would be even lower and may in fact reach statistical significance.

However, the possible positive influence of the HWE on astronauts' risk of cancer over their lifetimes may be counterbalanced by unique occupational exposures such as increased exposure to UVA radiation and space radiation. Given this, levels of risk for cancers may be no different for astronauts and the general population. The best course of action for interpretation then may be to carefully scrutinize individual cancer types rather than relying on composite estimates. In addition, advances in molecular analysis of tumors may provide ability

to decipher contribution of these various environmental hazards based on their unique mutational signatures.[32]

The study conducted here uses aggregate counts of observed tumors and deaths against aggregated person-years of follow-up, stratified by calendar year, age, sex, and race. While this allows us to compute the overall trends in incidence and mortality, it does not allow for more detailed analysis of which demographic groups may be more or less likely to develop or die from each cancer type. However, given that even in aggregate form the numbers of tumors and deaths in most categories is quite small, the value of a more detailed analysis of incidence and mortality may be limited for all but the most frequently diagnosed tumors. In addition, some tumors are already demographically specific to some extent (female breast cancer and prostate cancer). Nevertheless, the ability analyze the data in terms of years or decades and the ability to test the association between time in space and flight time in aircraft may prove enlightening. Future research will examine incidence and mortality in these ways, with data that link tumors and deaths to individuals.

The use of 1999 incidence rates for all years prior to 1999 will likely bias the SIRs upwards, since the incidence of many cancers have declined in the general population for many years. This means that the expected counts generated for follow-up time before 1999 are likely too low, as higher rates in earlier periods would have led to greater expected cancer counts. This would in turn somewhat elevate all the SIRs presented in Table 4 but would not change the overall pattern of results. Even if we were to increase the expected case counts in Table 4 by 25%, no currently insignificant individual tumor result would become significant and no significant results would lose significance. The change resulting from applying higher historical incidence rates would almost certainly be less than a 25% increase in tumor counts, since the person-years affected would be from comparatively early periods when the Astronaut Corps was smaller, and the members were on average younger and thus at lower risk of developing cancers. This suggests that the impact of using these rates on our conclusions is minimal. This reasoning holds for SMRs as well, since the period where rates were unavailable (1958 to 1967) is smaller, and the astronaut person-years from this time are even fewer and younger than average.

The statistical power of the study is low, as highlighted also by the power analysis conducted by Elgart et al. (2018) in a subset of this cohort. Thus, the usefulness of SIR and SMR analysis in a small and highly selected occupational cohort is limited. However, the fact that some cancers appear to be in excess suggests that these increases are more likely to be real, as discussed above. This paper calculates the difference between the astronaut and general US population as an initial step in trying to determine potential risks from space flight exposures. While the low statistical power makes it unlikely to establish increased risk in terms of conventional thresholds for statistical significance in the near future, such information can still be useful in constraining possible risks. Future work extending this initial effort will look specifically at the upper bounds of risk estimates from the astronaut cohort in order to place such constraints on current NASA models that calculate space radiation risks.

The work presented here is useful in understanding the trends in cancer incidence and mortality among US astronauts. The results are constrained primarily by the limited pool of observation time and events (cancer diagnoses and deaths) that have accumulated to date. However, the framework presented here can easily be revised to include additional data as they are collected and will provide greater insights as such data

accumulates. More detailed research looking at occupational exposures is needed to determine if aircraft flight time or time in space have contributed to the risk of developing and/or dying from various cancers. Such efforts will need to be repeated over time, as more data accrue and newer classes of astronauts prepare to spend greater amounts of time outside of low Earth orbit, where space radiation dose-rates are more intense and spaceflight exposures may be prolonged.

As humans continue to master the immediate dangers of living and working in space, the post-mission, long-term health risks become more important; cancers are but one of many such dangers. Through continued occupational surveillance, targeted cohort studies, and ongoing basic and translational research, we can gain a better understanding of these long-term health risks for astronauts. This understanding will be key to continued space exploration as humans return to the Moon and expand out to Mars and beyond.

List Of Abbreviations

CDC Centers for Disease Control

CI Confidence Interval

ECFR Expected Case Fatality Ratio

HWE Healthy Worker Effect

ISS International Space Station

LSAH Lifetime Surveillance of Astronaut Health

NASA National Aeronautics and Space Administration

OCFR Observed Case Fatality Ratio

RCFR Relative Case Fatality Ratio

SD Standard Deviation

SIR Standardized Incidence Ratio

SMR Standardized Mortality Ratio

UV Ultraviolet

WONDER Wide-ranging ONline Data for Epidemiologic Research

yr year

Declarations

- Ethics approval and consent to participate: all data used in this study were publicly available from NASA sources on the internet. As such, this research was exempt from institutional review.

- Consent for publication: Not applicable
- Availability of data and materials: Not applicable
- Competing interests: The authors have no competing interests to report.
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- Authors' contributions: RJR conceived the study and collected the data; RJR, MPL and SMD designed and performed the statistical analysis; all authors contributed to the writing and editing of the manuscript.
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Figures

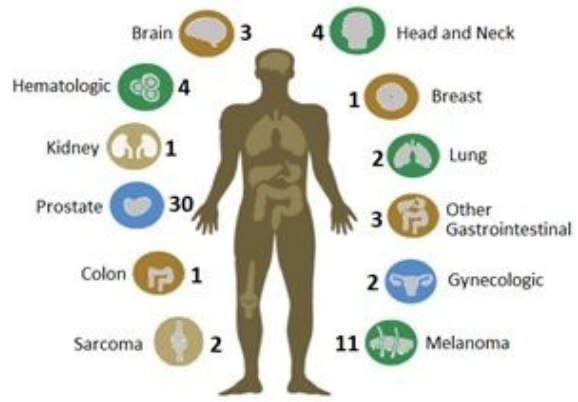

Figure 1

Cancer counts by body site

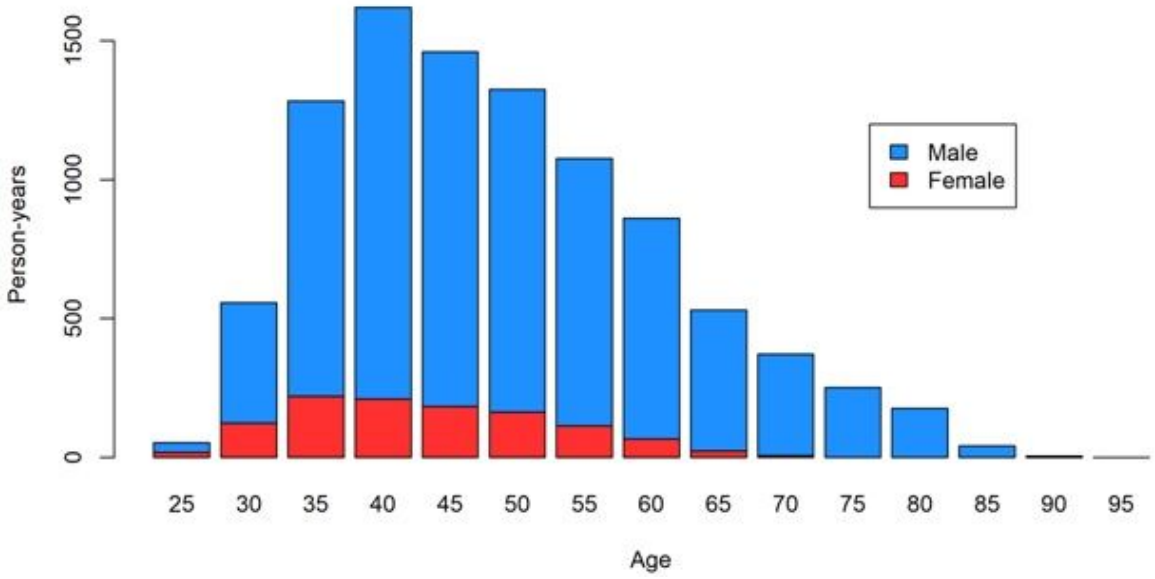

Figure 2

Person-years of follow-up by sex and age

Supplementary Files

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- APPENDIX.docx