DEPARTMENT OF THE AIR FORCE
711TH HUMAN PERFORMANCE WING (AFRL)
WRIGHT-PATTERSON AFB OHIO

26 May 2021

MEMORANDUM FOR USAF/SG

FROM: USAFSAM/PHR
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SUBJECT: Cancer Incidence and Mortality among Fighter Aviators who Served on Active Duty in the U.S. Air Force between 1970 and 2004: A Comparison to Other Officers and the General U.S. Population

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1. INTRODUCTION:

a. *Purpos*e: This is a study of cancer outcomes in active duty U.S. Air Force fighter aviators. Study ideas were discussed in the fall of 2019 by subject matter experts, the Red River Valley Fighter Pilots Association, and the Air Force Medical Readiness Agency. The Epidemiology Consult Service Division (USAFSAM/PHR) was officially consulted on 2 December 2019. The Air Force Research Laboratory Institutional Review Board (IRB) approved the study on 10 February 2020 (protocol #FWR20200049E).

b. *Background*: Most epidemiologic studies have found no significant difference in overall cancer rates or odds among aviators and their general population peers. Some have reported increased likelihood of select cancers—including brain, prostate, testicular, and melanoma skin cancers—but these findings have not been consistent across all investigations. In a previous cohort study of U.S. Air Force officers who served on active duty between 1986 and 2005, and were followed from 1995 through 2017, fighter pilots had statistically similar rates of all cancers and of site-specific cancers compared to their non-fighter pilot peers (Robbins 2020). Although methodologically solid, this study left three major issues unresolved. First, does this equivalency extend to cancer mortality? Second, do the results apply to fighter pilots who served before 1986 and to backseat aircrew? Third, how do fighter aviators compare with the general U.S. population?

c. *Study Personnel*:

(1) Lt Col Bryant Webber, MD, MPH, Preventive Medicine, USAFSAM/PHR
(2) Ms. Crystal Tacke, MPH, Epidemiologist, USAFSAM/PHRR
(3) Capt Ashley Rutherford, PhD, MPH, MA, Public Health Officer, USAFSAM/PHRR
(4) Mr. William Erwin, MS, Health Physicist, USAFSAM/OEC
(5) Mr. James Escobar, MPH, Database Manager, USAFSAM/PHRR
(6) Dr. Alisa Simon, DrPH, Biostatistician, USAFSAM/PHRR
(7) Col (ret) B. Hadley Reed, MD, MPH, Senior Flight Surgeon, USAFSAM/FESS
(8) Maj Justin Whitaker, MPH, Public Health Officer, USAFSAM/PHRR
(9) Mr. Greg Wolff, MPH, Senior Epidemiologist, USAFSAM/PHR
(10) Lt Col David Stuever, PhD, MPH, Branch Chief, USAFSAM/PHRR

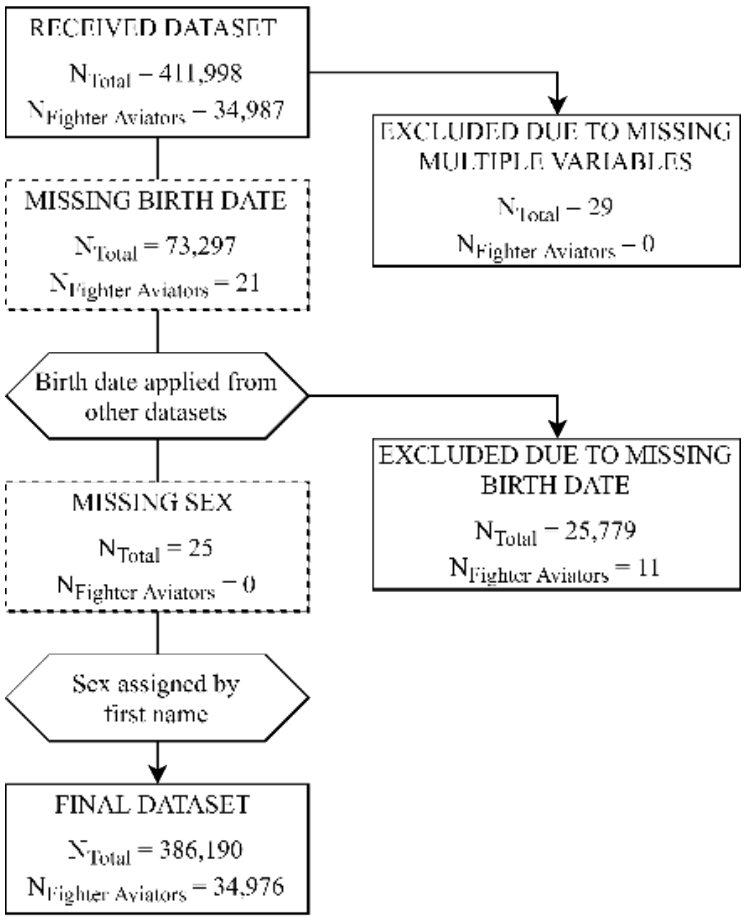
2. METHODOLOGY:

a. *Study Design and Population*: This is a retrospective cohort study that compares U.S. Air Force fighter aviators to other U.S. Air Force officers (an "internal" comparison group) and to the general U.S. population (an "external" comparison group). The term *fighter aviator* is used to designate both pilots proper and backseat aircrew. Fighter aviators and other officers were included if they served on active duty at any time between 1 June 1970 and 31 December 2004.

(1) *Classification of Fighter Aviators and Aircraft Flown*: All personnel data were received from the Air Force Personnel Center (AFPC). Data from June 1970 through December 1973 originated at the Air Force Research Laboratory; personnel data before June 1970 are unavailable. An AFPC analyst coded personnel as fighter aviators if they had at least 100 hours in any seat of any fighter airframe (n=34,679) or if they had a Rated Distribution and Training Management code or a Major Weapon System code consistent with fighter aviation (n=308). AFPC also provided the airframes flown by each fighter aviator.

(2) *Demographic Variables*: AFPC provided name and social security number for all U.S. Air Force officers who served on active duty for at least one day during the surveillance period (N=411,998), as required for merging with diagnostic and mortality data. When available, AFPC provided birth date, sex, race, ethnicity (i.e., Hispanic or non-Hispanic), and military entrance date. Twenty-nine (0.007%) officers were excluded due to multiple missing variables. Birth dates were missing for 73,297 (17.8%) officers in the AFPC dataset, but 47,518 (64.8%) were recovered by querying other available databases. Since age is a significant risk factor for cancer incidence and mortality, the remaining 25,779 (6.3%) officers with missing birth dates were excluded from the final dataset. The sex variable was missing for 25 officers and manually assigned according to first name. The final dataset had 386,190 officers, of whom 34,976 (9.1%) were fighter aviators (**Figure 1**). Demographics of fighter aviators and other officers were compared with Student's t-tests (for age) and chi-square tests (for sex and race/ethnicity), with statistical significance established at an alpha of 0.05. Since 99.4% of fighter aviators were male, and since two of the cancers exclusively afflict males, all results were stratified by sex.

Figure 1. Flow Diagram of Study Participants



(3) *Race and Ethnicity*: Race and ethnicity variables were merged and grouped into six categories: American Indian/Alaskan Native (AI/AN); Asian/Pacific Islander (PI); black; white; Hispanic; and other. Officers of Hispanic ethnicity were assigned to the Hispanic group, regardless of race. The 7,821 (2.0%) officers with multiple races were assigned using the rarest group method: AI/AN, then Asian/PI, then black. For example, someone reporting Asian and black races was assigned to the Asian/PI category. Those missing both race and ethnicity (n=27) were assigned to the *other* category.

(4) *Military Entrance Date*: A variety of military-related service dates were provided in the dataset, including date of service, pay date, entered active duty date, total active federal military service date, total active federal commissioned service date, separation or retirement date, and last ASOF ("as of") date. The last ASOF date is defined by AFPC as "either the date of separation or retirement, or, when missing, the date of the last snapshot at which the person has a record." It was determined with AFPC guidance that the entered active duty date was the single best date for capturing the start of an officer's career. For those missing this date (n=77), the total active federal commissioned service date was substituted.

b. *Cancer Types*: Based on previous research, theoretical risks, and anecdotal reports, ten cancers were selected for inclusion: colon and rectum; pancreas; melanoma skin; prostate; testis; urinary bladder; kidney and renal pelvis; brain and other nervous system; thyroid; and non-Hodgkin lymphoma. Pancreas was added in March 2021 after discussion with the Red River Valley Fighter Pilots Association, which had conducted a voluntary health survey of its members and found a surprising number of pancreatic cancer cases; a protocol amendment was approved by the Air Force Research Laboratory IRB on 29 March 2021.

c. *Cancer Incidence*: Fighter aviators were compared to other officers and to the general U.S. population in terms of cancer incidence, or new cancer diagnoses.

(1) *Data Sources*: The final personnel roster was merged with diagnostic data in the Automated Central Tumor Registry (ACTUR), the Veterans Affairs Central Cancer Registry (VACCR), and the Defense Medical Surveillance System (DMSS). ACTUR, which is managed by the Joint Pathology Center, is the central cancer registry for the Department of Defense and contains some but not all cancers diagnosed in service members since 1998. VACCR, which includes cases since 1995, is the equivalent registry for the Veterans Health Administration. DMSS is an archive of diagnostic codes received by service members and retirees and their dependents during inpatient visits and outpatient encounters at military treatment facilities and at outside facilities reimbursed by TRICARE since 1993. Cancer incidence was defined according to the Ninth and Tenth Revisions of the *International Classification of Diseases* (ICD-9 and ICD-10), using taxonomy from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (https://training.seer.cancer.gov/icd10cm/appendix-b/). All cases identified in ACTUR and VACCR were included. Cases identified only in DMSS had to meet the oncological case definition established by the Armed Forces Health Surveillance Branch (https://www.health.mil/Military-Health-Topics/Combat-Support/Armed-Forces-Health-Surveillance-Branch/Epidemiology-and-Analysis/Surveillance-Case-Definitions). Based on a previous study with chart confirmation, the case definition has high positive predictive values: for colon and rectum (93.9%); pancreas (94.7%); melanoma skin (97.9%); prostate (96.4%); testis (99.6%); urinary bladder (91.9%); kidney and renal pelvis (96.5%); brain and other nervous system (84.3%); thyroid (96.8%); and non-Hodgkin lymphoma (78.1%) (Webber 2019). All cancer deaths were captured as cases in ACTUR, VACCR, and/or DMSS. The incidence date was defined differently by source: the registry-assigned date for ACTUR and VACCR and the first date with a case-defining code for DMSS. An individual was counted once per cancer type.

(2) *Comparison to Other Officers*: As noted in the previous study and replicated here, fighter aviators and other officers are demographically dissimilar. To make the groups comparable, fighter aviators and other officers were assigned to buckets, each of which reflected a distinct combination of sex, age at active duty entrance (in six 5-year age groups), and age at incidence censoring (in sixteen 5-year age groups). Incidence censoring was based on either the incidence date, or, for those without cancer, the date of the last medical encounter in DMSS; for those without any encounters in DMSS, the last ASOF date was used. After matching, all 34,976 fighter aviators and 316,262 (90.0%) other officers were available for analysis; excluded were 34,952 (10.0%) other officers who did not match into a demographic bucket with at least one

fighter aviator. Multivariable logistic regression, adjusted for race/ethnicity and exact age at censoring, was used to calculate an odds ratio (OR) with 95% confidence intervals (CI) for each cancer. Given statistically significant differences in cancer diagnosis ages between the two groups, and the discovery of residual confounding during stepwise addition of variables, censoring age was added to the regression model *a posteriori*. Violations of the proportional hazards assumption precluded Cox analyses. Mean age at cancer diagnosis (with 95% CIs), stratified by sex and adjusted for race/ethnicity, was calculated for fighter aviators and other officers and, given non-violation of distribution and independence assumptions, compared with Student's t-test.

(3) *Comparison to the General Population*: Fighter aviators were assigned to one of 192 unique combinations of race/ethnicity, sex, and age group category (e.g., Hispanic males aged 60–64 years). Expected diagnosis counts of each cancer site were based on the experience of the general U.S. population, indirectly adjusted for race/ethnicity, sex, and age. Expected counts were retrieved from the Cancer Query System, the online portal to the National Cancer Institute's DevCan program (https://surveillance.cancer.gov/devcan/ canques.html), based on the SEER 21 Registries Incidence and Mortality database. DevCan computes the probability of being diagnosed with or dying from cancer between two ages, in 5-year increments. Probabilities are provided in 3-year intervals for the inclusive years of 2000–2017; these probabilities were weighted equally. Fighter aviators were assigned to the SEER 5-year increments based on their age at incidence censoring (see previous paragraph). Race/ethnicity was stratified as AI/AN, Asian/PI, black, white, Hispanic, and other, with expected deaths in the lattermost category based on overall risk. Expected counts were calculated for each sex-age-race/ethnicity category, with probability rounded to five decimal places (e.g., 0.00217 or 0.217%). The starting age was established at 20 years, rather than birth, because fighter aviators by definition would be at least 20 years-old at the start of their aeronautical rating. The ending age was established at both the beginning and end of each 5-year interval, with the expected diagnoses calculated as the mean of the two (e.g., for Hispanic males aged 60–64 years, the number of expected cases was defined as the mean of expected cases by ages 60 and 65). Standardized incidence ratios (SIR) with 95% CIs were calculated using exact Poisson regression (Liddell 1984).

d. *Cancer Mortality*: U.S. Air Force fighter aviators were compared to other U.S. Air Force officers and to the general U.S. population regarding cancer mortality.

(1) *Data Sources*: The final personnel roster was merged with death certificate data archived in the National Death Index (NDI) Plus, the central repository for deaths occurring in the United States since January 1979. At the time of request, death records were available through December 2018. NDI Plus was accessed through the Joint Department of Veterans Affairs and Department of Defense Suicide Data Repository. The data request was approved by the Defense Suicide Prevention Office on 1 April 2020. To maximize capture, the Air Force Mortality Registry (AFMR) was also queried. AFMR includes death certificate information for most Airmen who died while on active duty or on retired status, and some separated Airmen, beginning in 1970. Conditions on death certificates are coded in NDI Plus and AFMR according

to ICD-9 (before 1999) and ICD-10 (since 1999). Consistent with SEER methodology, deaths were coded according to the underlying cause of death recorded on the death certificate.

(2) *Comparison to Other Officers*: Male fighter aviators and other officers were assigned to buckets, each of which reflected a distinct combination of age at active duty entrance (in six 5-year age groups) and age at mortality censoring (in sixteen 5-year age groups). Mortality censoring was based on either the date of death (from any cause) or the last date of the outcome surveillance period (31 December 2018). After matching, all 34,760 male fighter aviators and 293,667 (99.9%) male other officers were available for analysis. Multivariable logistic regression, adjusted for race/ethnicity and exact age at mortality censoring, was used to calculate ORs with 95% CIs for each cancer type. Mean age at cancer death (with 95% CIs), adjusted for race/ethnicity, was calculated for fighter aviators and other officers and compared with Student's t-test. As with the incidence data, t-test assumptions were met.

(3) *Comparison to the General Population*: Male fighter aviators were assigned to one of 96 unique age-race/ethnicity categories. Expected deaths from each cancer were based on the experience of the general U.S. population, with indirect adjustment for race/ethnicity, sex, and age group, as described in paragraph 2c(3). Standardized mortality ratios (SMR) with 95% CIs were calculated using exact Poisson regression (Liddell 1984).

e. *Analysis of Aircraft*: The Red River Valley Fighter Pilots Association expressed concern about cancer outcomes in fighter aviators who served in the Vietnam War. Based on an unclassified document provided by the National Museum of the U.S. Air Force (McCrea 1976), the U.S. Armed Forces flew 2,605,094 combat and combat-support sorties over Southeast Asia between April 1965 and March 1973—of which 67.9% were conducted by the Air Force. The most prolific Air Force aircraft were the O-1/O-2 (n=636,362 sorties), F-4 (n=454,844), F-100 (n=344,619), F-105 (n=157,895), and RF-4 (n=93,164). A case-cohort approach was used to assess the relationship between flying these aircraft and subsequent cancer. For each of the ten cancer types, male fighter aviators who experienced the outcome (i.e., diagnosis of or death from the cancer) were compared with male fighter aviators who had not experienced the outcome with respect to aircraft flown. ORs, adjusted for age and race/ethnicity, were calculated to compare the odds of cases and non-cases having ever flown the F-4, RF-4, F-100, and F-105. These were the only Vietnam War era aircraft with sufficient statistical power for analysis, defined as having been flown by at least 1,000 fighter aviators in the AFPC dataset. Of note, O-1/O-2 were not classified as fighter platforms; their missions included reconnaissance, convoy escort, and forward air control. Given the large number of statistical tests (i.e., up to 80 tests, or 20 outcomes by four aircraft), 99% CIs were used to define statistically significant ORs.

f. *Sensitivity Analysis*: The results of the aircraft analysis, as described in paragraph 3e, prompted a sensitivity analysis. All of the primary analyses outlined above were repeated after excluding aviators who flew the F-100. The aim was to determine if the population findings were unduly influenced by the subpopulation of F-100 aviators.

g. *Data Sources and Software*: As described in detail above, personnel data were provided by AFPC, mortality data were provided by the Defense Suicide Prevention Office, diagnostic data were provided by the Armed Forces Health Surveillance Branch, and cancer registry data were provided by the Joint Pathology Center and Veterans Health Administration. DevCan v6.7.8 (via the Cancer Query System) was used to determine expected cancer diagnoses and cancer deaths. SAS version 9.4 was used to merge databases and perform all analyses. Statistically significant findings in tables are bolded for emphasis.

3. RESULTS: A total of 386,190 officers, of whom 34,976 (9.1%) were fighter aviators, served on active duty during the 35-year exposure period and had sufficient personnel data available for analysis. Compared to their officer peers, fighter aviators were approximately 24 months younger at active duty entrance, 93 months older at incidence censoring (i.e., age at diagnosis, last medical encounter, or last personnel record), and 51 months older at mortality censoring (i.e., age at death or, if living, age on the last day of the surveillance period) ($p<0.001$ for all). In other words, fighter aviators had a larger surveillance window than their officer peers. Fighter aviators were more likely than other officers to be male (99.4% vs. 83.7%) and white (80.6% vs. 74.1%) ($p<0.001$ for both) (**Table 1**).

Table 1. Demographic Characteristics, U.S. Air Force Fighter Aviators and Other Officers, June 1970 – December 2004 (N=386,190)

	Fighter Aviators (n=34,976)	Other Officers (n=351,214)	P Value
Age, mean (SD)			
At Active Duty Entrance	23.1 (3.4)	25.1 (4.5)	**<0.001**
At Incidence Censoring†	57.4 (17.7)	49.7 (19.7)	**<0.001**
At Mortality Censoring‡	64.1 (14.4)	59.8 (16.0)	**<0.001**
Sex, no. (%)			
Male	34,760 (99.4)	293,840 (83.7)	**<0.001**
Female	216 (0.6)	57,374 (16.3)	
Race/Ethnicity, no. (%)			
White	28,196 (80.6)	260,330 (74.1)	**<0.001**
Black	5,960 (17.0)	64,199 (18.3)	
Hispanic	193 (0.6)	6,483 (1.8)	
AI/AN	189 (0.5)	6,591 (1.9)	
Asian/PI	80 (0.2)	4,562 (1.3)	
Other§	358 (1.0)	9,049 (2.6)	

AI, American Indian; AN, Alaskan Native; PI, Pacific Islander; SD, standard deviation

†Age at first cancer diagnosis, or age at the last medical encounter in the Defense Medical Surveillance System, or age at the last "as of" date in the personnel record

‡Age at death or, if living, age on the last day of the surveillance period (31 December 2018)

§Includes those missing race and ethnicity variables (n=27)

a. *Cancer Incidence*: Of the studied cancers, the most frequent diagnosis among male fighter aviators was prostate cancer (n=2,124), followed distantly by melanoma skin cancer (n=416) and colon and rectum cancer (n=387). Compared to matched other officers and adjusted for race/ethnicity and age at incidence censoring, male fighter aviators had greater odds of being diagnosed with testicular cancer (by 29%), melanoma skin cancer (by 24%), and prostate cancer (by 23%), and similar odds of the seven other cancers. Compared to males in the general U.S. population, standardized for age group and race/ethnicity, male fighter aviators were more likely to be diagnosed with melanoma skin cancer (by 25%), prostate cancer (by 19%), and non-Hodgkin lymphoma (by 13%), and less likely to be diagnosed with kidney and renal pelvis cancer (by 69%), testicular cancer (by 62%), colon and rectum cancer (by 29%), thyroid cancer (by 29%), and urinary bladder cancer (by 15%). Three female fighter aviators were diagnosed with a cancer; their odds of each cancer was similar to matched female officers, and their standardized incidence was similar to females in the general U.S. population (**Table 2**).

Table 2. Adjusted Cancer Incidence, U.S. Air Force Fighter Aviators Compared to Other Officers and the U.S. Population, Exposure Period of June 1970 – December 2004, Followed through December 2018

	Fighter Aviators		Matched Other Officers[†]			General U.S. Population	
	No.	%	No.	%	aOR (95% CI)[‡]	Exp.	SIR (95% CI)[§]
Males	n=34,760		n=274,451				
Colon and Rectum	387	1.11	2,946	1.07	1.00 (0.89–1.12)	542.4	**0.71 (0.64–0.79)**
Pancreas	169	0.49	1,316	0.47	0.94 (0.76–1.11)	149.5	1.13 (0.97–1.31)
Melanoma Skin	416	1.20	2,375	0.87	**1.24 (1.11–1.38)**	332.2	**1.25 (1.13–1.38)**
Prostate	2,124	6.11	12,637	4.60	**1.23 (1.17–1.30)**	1,779	**1.19 (1.14–1.25)**
Testis	43	0.12	244	0.09	**1.29 (1.15–2.12)**	114.0	**0.38 (0.27–0.51)**
Urinary Bladder	305	0.88	2,204	0.80	1.04 (0.92–1.18)	357.7	**0.85 (0.76–0.95)**
Kidney and Renal Pelvis	78	0.22	657	0.24	0.87 (0.68–1.12)	254.6	**0.31 (0.24–0.38)**
Brain and Nervous System	104	0.30	861	0.31	0.88 (0.71–1.10)	98.0	1.06 (0.87–1.29)
Thyroid	72	0.21	463	0.17	1.12 (0.86–1.44)	101.1	**0.71 (0.56–0.90)**
Non-Hodgkin Lymphoma	309	0.89	1,963	0.72	1.15 (0.99–1.21)	273.1	**1.13 (1.01–1.27)**
Females	n=216		n=41,811				
Melanoma Skin	1	0.46	121	0.29	1.58 (0.35–18.2)	0.66	1.51 (0.04–8.43)
Thyroid	1	0.46	194	0.46	1.18 (0.29–10.5)	0.97	1.04 (0.03–5.77)
Non-Hodgkin Lymphoma	1	0.46	105	0.25	1.62 (0.55–37.2)	0.22	4.53 (0.11–25.2)

aOR, adjusted odds ratio; CI, confidence interval; Exp, expected; SIR, standardized incidence ratio

[†]Matched on sex, age group at active duty entrance, and age group at incidence censoring

[‡]Based on multivariable logistic regression, adjusted for race/ethnicity and exact age at incidence censoring

[§]Based on exact Poisson regression, standardized for sex, race/ethnicity, and age group

b. *Age at Cancer Diagnosis*: Male fighter aviators were diagnosed with six cancers at later ages than matched other officers, adjusted for race/ethnicity: for colon and rectum cancer, by a mean of 31 months ($p<0.001$); for pancreas cancer, by 74 months ($p<0.001$); for melanoma skin cancer, by 33 months ($p=0.012$); for kidney and pelvis cancer, by 93 months ($p<0.001$); for brain and nervous system cancer, by 59 months ($p=0.005$), and for non-Hodgkin lymphoma, by 41 months ($p<0.001$). No statistical differences were noted for female fighter aviators and matched other officers (**Table 3**). The findings reported in this table impelled the addition of exact age at incidence censoring to the regression model.

Table 3. Adjusted Age at Diagnosis, U.S. Air Force Fighter Aviators Compared to Matched Other Officers, Exposure Period of June 1970 – December 2004, Followed through December 2018

	Fighter Aviators		Matched Other Officers[†]		P Value[‡]
	Mean	95% CI	Mean	95% CI	
Male	n=34,760		n=274,451		
Colon and Rectum	62.93	61.89–64.67	60.32	59.68–60.94	**<0.001**
Pancreas	63.45	61.01–65.84	57.30	56.29–58.31	**<0.001**
Melanoma Skin	64.80	63.55–66.05	62.08	61.42–62.75	**0.012**
Prostate	68.09	67.74–68.43	67.26	67.07–68.45	0.086
Testis	41.79	37.43–46.15	39.26	37.57–40.96	0.267
Urinary Bladder	70.82	69.69–71.95	70.07	69.49–70.65	0.340
Kidney and Renal Pelvis	63.94	60.85–67.04	56.22	54.82–57.62	**<0.001**
Brain and Nervous System	54.69	51.09–57.64	49.77	48.61–50.93	**0.005**
Thyroid	54.26	50.96–57.55	53.34	52.35–55.02	0.635
Non-Hodgkin Lymphoma	65.19	63.63–66.74	61.75	60.02–63.50	**<0.001**
Female	n=216		n=41,811		
Melanoma Skin	47.00	--	50.10	47.33–52.87	0.843
Thyroid	32.00	--	41.93	40.25–43.60	0.411
Non-Hodgkin Lymphoma	29.00	--	51.96	48.76–55.17	0.172

CI, confidence interval

[†]Matched on age group at active duty entrance and age group at incidence censoring

[‡]Based on race/ethnicity-adjusted Student's t-test

c. *Cancer Mortality*: Of the studied cancers, the most frequent causes of death among fighter aviators were prostate cancer (n=197), colon and rectum cancer (n=168), pancreas cancer (n=166), and non-Hodgkin lymphoma (n=119). For all cancer types, male fighter aviators had similar race/ethnicity-adjusted mortality odds as compared to matched other officers. Compared to males in the general U.S. population, standardized for age group and race/ethnicity, male fighter aviators were 24% less likely to die from colon and rectum cancer, and more likely to die from melanoma skin cancer (by 64%), non-Hodgkin lymphoma (by 32%), and prostate cancer (by 23%) (**Table 4**). No female fighter aviators died from any of the studied cancers.

Table 4. Adjusted Cancer Mortality, Male U.S. Air Force Fighter Aviators Compared to Other Officers and the U.S. Population, Exposure Period of June 1970 – December 2004, Followed through December 2018

	Fighter Aviators (n=34,760)		Matched Other Officers† (n=293,667)			General U.S. Population	
	No.	%	No.	%	aOR (95% CI)‡	Exp.	SMR (95% CI)§
Colon and Rectum	168	0.48	1,480	0.50	0.92 (0.78–1.08)	222.1	**0.76 (0.65–0.88)**
Pancreas	166	0.48	1,311	0.45	0.97 (0.82–1.14)	157.2	1.06 (0.90–1.23)
Melanoma Skin	88	0.25	601	0.20	1.14 (0.91–1.44)	53.5	**1.64 (1.32–2.03)**
Prostate	197	0.57	1,750	0.60	0.89 (0.76–1.03)	160.5	**1.23 (1.06–1.41)**
Testis	3	0.01	21	0.01	1.58 (0.46–5.49)	4.7	0.63 (0.13–1.85)
Urinary Bladder	62	0.18	521	0.18	0.91 (0.69–1.19)	68.7	0.90 (0.69–1.16)
Kidney and Renal Pelvis	68	0.20	562	0.19	0.92 (0.71–1.18)	69.3	0.98 (0.76–1.24)
Brain and Nervous System	92	0.26	812	0.28	0.87 (0.70–1.09)	81.7	1.13 (0.91–1.38)
Thyroid	11	0.03	51	0.01	1.54 (0.79–2.99)	6.0	1.83 (0.91–3.27)
Non-Hodgkin Lymphoma	119	0.34	863	0.29	1.08 (0.88–1.31)	90.3	**1.32 (1.09–1.58)**

aOR, adjusted odds ratio; CI, confidence interval; Exp, expected; SMR, standardized mortality ratio

†Matched on sex, age group at active duty entrance, and age group at mortality censoring

‡Based on multivariable logistic regression, adjusted for race/ethnicity and exact age at mortality censoring

§Based on exact Poisson regression, standardized for race/ethnicity and age group

d. *Age at Cancer Death*: The race/ethnicity-adjusted mean age at death was similar between male fighter aviators and matched other officers for all cancers except colon and rectum. Of males who died from colon and rectum cancer, mean age at death was 27 months earlier in fighter aviators than their officer peers (p=0.022) (**Table 5**).

Table 5. Adjusted Age at Death, Male U.S. Air Force Fighter Aviators Compared to Matched Other Officers, Exposure Period of June 1970 – December 2004, Followed through December 2018

	Fighter Aviators (n=34,760)		Matched Other Officers† (n=293,667)		P Value‡
	Mean	95% CI	Mean	95% CI	
Colon and Rectum	64.39	62.67–66.11	66.63	66.01–67.25	**0.022**
Pancreas	69.83	68.21–71.46	69.41	68.85–69.97	0.649
Melanoma Skin	64.67	61.99–67.35	63.86	62.75–64.98	0.610
Prostate	75.01	73.80–76.20	75.69	75.23–76.14	0.292
Testis	55.33	34.22–77.56	46.71	39.08–53.62	0.402
Urinary Bladder	72.43	69.90–74.96	74.74	73.84–75.64	0.098
Kidney and Renal Pelvis	67.42	64.74–70.10	67.38	66.39–68.38	0.980
Brain and Nervous System	62.08	59.65–64.52	62.61	61.77–63.44	0.693
Thyroid	67.63	58.63–76.64	67.84	64.94–70.74	0.954
Non-Hodgkin Lymphoma	68.85	66.24–71.47	68.50	67.65–69.35	0.779

CI, confidence interval

†Matched on age group at active duty entrance and age group at mortality censoring

‡Based on race/ethnicity-adjusted Student's t-test

e. *Cancer Incidence and Mortality by Vietnam War Era Aircraft*: Large numbers of male aviators in this cohort flew the F-4 (n=10,634), RF-4 (n=2,750), F-100 (n=2,285), and F-105 (n=1,271). Compared to fighter aviators who never flew the F-100, adjusted for race/ethnicity and age at censoring, male fighter aviators who flew the F-100 had greater odds of being diagnosed and dying from colon and rectum cancer, pancreas cancer, melanoma skin cancer, prostate cancer, and brain cancer. They also had greater odds of dying from thyroid cancer and non-Hodgkin lymphoma, despite similar odds of diagnosis (**Table 16**).

Table 6. Adjusted Cancer Incidence and Mortality, Male U.S. Air Force Fighter Aviators Who Ever Flew the Vietnam War Era Aircraft Compared to Male Fighter Aviators Who Never Flew the Aircraft, Exposure Period of June 1970 – December 2004, Followed through December 2018

	F-4 (n=10,634)		RF-4 (n=2,750)		F-100 (n=2,285)		F-105 (n=1,271)	
	No.	aOR (99% CI)†	No.	aOR (99% CI)†	No.	aOR (99% CI)†	No.	aOR (99% CI)†
Diagnosis								
Colon and rectum	154	**1.34 (1.01–1.77)**	39	1.20 (0.76–1.85)	69	**2.56 (1.77–3.70)**	27	1.53 (0.90–2.61)
Pancreas	77	**1.64 (1.08–2.48)**	17	1.15 (0.59–2.25)	28	**2.18 (1.24–3.83)**	13	1.64 (0.76–3.52)
Melanoma skin	162	1.19 (0.91–1.56)	46	1.26 (0.83–1.89)	55	**1.53 (1.04–2.27)**	26	1.22 (0.71–2.09)
Prostate	935	**1.36 (1.21–1.54)**	256	**1.31 (1.08–1.57)**	298	**1.41 (1.17–1.69)**	129	1.02 (0.80–1.32)
Testis	4	0.31 (0.08–1.19)	1	0.35 (0.03–4.80)	0	--	0	--
Urinary bladder	132	1.23 (0.90–1.68)	48	**1.70 (1.27–2.58)**	44	1.26 (0.81–1.96)	27	1.37 (0.80–2.34)
Kidney	41	**2.24 (1.21–4.13)**	14	**2.30 (1.06–4.97)**	9	1.34 (0.52–3.50)	6	1.60 (0.52–4.94)
Brain	34	1.26 (0.72–2.23)	11	1.55 (0.67–3.56)	13	**2.55 (1.13–5.77)**	7	2.30 (0.81–6.54)
Thyroid	26	1.58 (0.81–3.08)	4	0.76 (0.20–2.89)	7	2.02 (0.69–5.95)	3	1.45 (0.31–6.84)
Non-Hodgkin lymphoma	119	1.21 (0.89–1.65)	33	1.23 (0.76–1.99)	40	1.51 (0.95–2.39)	25	1.66 (0.95–2.90)
Death								
Colon and rectum	67	1.52 (0.97–2.36)	20	1.58 (0.84–2.95)	39	**4.97 (2.92–8.44)**	10	1.61 (0.68–3.81)
Pancreas	77	1.52 (0.99–2.32)	17	1.08 (0.56–2.11)	28	**2.04 (1.15–3.60)**	13	1.54 (0.72–3.33)
Melanoma skin	34	1.42 (0.77–2.61)	14	**2.22 (1.03–4.79)**	14	**2.76 (1.22–6.24)**	6	1.85 (0.60–5.72)
Prostate	70	0.77 (0.52–1.13)	25	1.19 (0.68–2.08)	39	**1.70 (1.04–2.76)**	22	1.66 (0.91–3.02)
Testis	2	12.42 (0.38–399)	1	10.4 (0.35–309)	0	--	0	--
Urinary bladder	31	1.51 (0.77–2.97)	11	1.90 (0.79–4.52)	11	1.71 (0.69–4.20)	7	1.93 (0.67–5.60)
Kidney	36	**2.34 (1.39–3.92)**	12	2.26 (0.97–5.27)	8	1.50 (0.54–4.15)	5	1.67 (0.49–5.72)
Brain	30	1.22 (0.65–2.27)	11	1.74 (0.75–4.08)	12	**2.57 (1.09–6.07)**	7	2.51 (0.87–7.22)
Thyroid	6	2.69 (0.49–14.8)	1	1.02 (0.07–15.6)	4	**9.49 (1.43–63.0)**	1	2.25 (0.14–37.2)
Non-Hodgkin lymphoma	44	1.03 (0.62–1.73)	13	1.21 (0.56–2.59)	21	**2.31 (1.19–4.49)**	13	**2.43 (1.10–5.34)**

aOR, adjusted odds ratio; CI, confidence interval

†Odds ratio comparing ever versus never flown, adjusted for race/ethnicity and exact age at incidence or mortality censoring

f. *Sensitivity Analysis*: Exclusion of F-100 aviators from the exposed group reduced nearly all ratios comparing fighter aviators to other officers and to the general U.S. population. In terms of incidence, adjusted ORs comparing non-F-100 fighter aviators and other officers were similar, with melanoma skin, prostate, and testis cancers being statistically higher in fighter aviators. The SIR for non-Hodgkin lymphoma was not statistically significant in the sensitivity analysis (SIR=1.12; 95% CI: 0.99–1.27) (**Table 7**). Mortality comparisons were also largely similar in the sensitivity analysis, with a few notable exceptions. Compared with other officers, non-F-100 fighter aviators had lower adjusted odds of mortality from colon and rectum cancer (aOR=0.76; 95% CI: 0.63–0.91) and prostate cancer (aOR=0.81; 95% CI: 0.69–0.96). The SMR for prostate cancer was not statistically significant (SMR=1.16; 95% CI: 0.98–1.35). (**Table 8**).

Table 7. Adjusted Cancer Incidence, Male U.S. Air Force Fighter Aviators (with F-100 Aviators Excluded) Compared to Other Officers and the U.S. Population, Exposure Period of June 1970 – December 2004, Followed through December 2018

	Fighter Aviators (n=32,475)		Matched Other Officers[†] (n=274,396)			General U.S. Population	
	No.	%	No.	%	aOR (95% CI)[‡]	Exp.	SIR (95% CI)[§]
Colon and Rectum	318	0.97	2,946	1.07	0.91 (0.81–1.03)	474.8	**0.67 (0.60–0.75)**
Pancreas	141	0.43	1,316	0.47	0.90 (0.72–1.11)	130.1	1.08 (0.91–1.28)
Melanoma Skin	361	1.11	2,375	0.87	**1.21 (1.08–1.35)**	288.0	**1.25 (1.13–1.39)**
Prostate	1,826	5.62	12,637	4.60	**1.15 (1.09–1.22)**	1,560	**1.17 (1.12–1.23)**
Testis	43	0.13	244	0.09	**1.30 (1.14–2.14)**	103.8	**0.41 (0.30–0.56)**
Urinary Bladder	261	0.80	2,204	0.80	1.01 (0.91–1.20)	305.2	**0.86 (0.75–0.97)**
Kidney and Renal Pelvis	69	0.21	657	0.24	0.84 (0.64–1.08)	224.1	**0.31 (0.24–0.39)**
Brain and Nervous System	91	0.28	861	0.31	0.84 (0.64–1.10)	86.6	1.05 (0.85–1.29)
Thyroid	65	0.20	463	0.17	1.08 (0.82–1.41)	90.0	**0.72 (0.56–0.92)**
Non-Hodgkin Lymphoma	269	0.82	1,963	0.72	1.11 (0.97–1.27)	239.5	1.12 (0.99–1.27)

aOR, adjusted odds ratio; CI, confidence interval; Exp, expected; SIR, standardized incidence ratio

[†]Matched on sex, age group at active duty entrance, and age group at incidence censoring

[‡]Based on multivariable logistic regression, adjusted for race/ethnicity and exact age at incidence censoring

[§]Based on exact Poisson regression, standardized for race/ethnicity and age group

Table 8. Adjusted Cancer Mortality, Male U.S. Air Force Fighter Aviators (with F-100 Aviators Excluded) Compared to Other Officers and the U.S. Population, Exposure Period of June 1970 – December 2004, Followed through December 2018

	Fighter Aviators (n=32,475)		Matched Other Officers† (n=293,643)			General U.S. Population	
	No.	%	No.	%	aOR (95% CI)‡	Exp.	SMR (95% CI)§
Colon and Rectum	129	0.40	1,480	0.50	**0.76 (0.63–0.91)**	194.8	**0.66 (0.55–0.79)**
Pancreas	138	0.42	1,311	0.45	0.87 (0.73–1.05)	137.5	1.00 (0.84–1.19)
Melanoma Skin	74	0.23	601	0.20	1.03 (0.81–1.32)	46.6	**1.59 (1.25–1.99)**
Prostate	158	0.48	1,750	0.60	**0.81 (0.69–0.96)**	136.5	1.16 (0.98–1.35)
Testis	3	0.01	21	0.01	1.58 (0.46–5.49)	4.3	0.69 (0.14–2.03)
Urinary Bladder	51	0.16	521	0.18	0.86 (0.64–1.15)	58.4	0.87 (0.65–1.15)
Kidney and Renal Pelvis	60	0.18	562	0.19	0.90 (0.67–1.15)	60.7	0.99 (0.75–1.27)
Brain and Nervous System	80	0.24	812	0.28	0.80 (0.64–1.02)	72.3	1.11 (0.88–1.38)
Thyroid	7	0.01	51	0.01	1.05 (0.47–2.33)	5.2	1.33 (0.54–2.75)
Non-Hodgkin Lymphoma	98	0.30	863	0.29	0.98 (0.78–1.20)	78.4	**1.25 (1.01–1.52)**

aOR, adjusted odds ratio; CI, confidence interval; Exp, expected; SMR, standardized mortality ratio

†Matched on sex, age group at active duty entrance, and age group at mortality censoring

‡Based on multivariable logistic regression, adjusted for race/ethnicity and exact age at mortality censoring

§Based on exact Poisson regression, standardized for race/ethnicity and age group

g. *Cancer Types*: The previous paragraphs provided results by outcome type. This section presents the same information arranged by cancer type. Data in italics represent the sensitivity analysis with F-100 aviators excluded. All outcomes are for males only.

Table 9. Colon and Rectum Cancer Diagnoses (n=387) and Deaths (n=168), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	aOR=1.00 (95% CI: 0.89–1.12) *aOR=0.91 (95% CI: 0.81–1.03)*	aOR=0.92 (95% CI: 0.78–1.08) ***aOR=0.76 (95% CI: 0.63–0.91)***
	General Population	**SIR=0.71 (95% CI: 0.64–0.79)** ***SIR=0.67 (95% CI: 0.60–0.75)***	**SMR=0.76 (95% CI: 0.65–0.88)** ***SMR=0.66 (95% CI: 0.55–0.79)***

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 10. Pancreatic Cancer Diagnoses (n=169) and Deaths (n=166), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	aOR=0.94 (95% CI: 0.76–1.11) *aOR=0.90 (95% CI: 0.72–1.11)*	aOR=0.97 (95% CI: 0.82–1.14) *aOR=0.87 (95% CI: 0.73–1.05)*
	General Population	SIR=1.13 (95% CI: 0.97–1.31) *SIR=1.08 (95% CI: 0.91–1.28)*	SMR=1.06 (95% CI: 0.90–1.23) *SMR=1.00 (95% CI: 0.84–1.19)*

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 11. Melanoma Skin Cancer Diagnoses (n=416) and Deaths (n=88), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	**aOR=1.24 (95% CI: 1.11–1.38)** ***aOR=1.21 (95% CI: 1.08–1.35)***	aOR=1.14 (95% CI: 0.91–1.44) *aOR=1.03 (95% CI: 0.81–1.32)*
	General Population	**SIR=1.25 (95% CI: 1.13–1.38)** ***SIR=1.25 (95% CI: 1.13–1.39)***	**SMR=1.64 (95% CI: 1.32–2.03)** ***SMR=1.59 (95% CI: 1.25–1.99)***

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 12. Prostate Cancer Diagnoses (n=2,124) and Deaths (n=197), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	**aOR=1.23 (95% CI: 1.17–1.30)** ***aOR=1.15 (95% CI: 1.09–1.22)***	aOR=0.89 (95% CI: 0.76–1.03) ***aOR=0.81 (95% CI: 0.69–0.96)***
	General Population	**SIR=1.19 (95% CI: 1.14–1.25)** ***SIR=1.17 (95% CI: 1.12–1.23)***	**SMR=1.23 (95% CI: 1.06–1.41)** *SMR=1.16 (95% CI: 0.98–1.35)*

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 13. Testicular Cancer Diagnoses (n=43) and Deaths (n=3), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	**aOR=1.29 (95% CI: 1.15–2.12)** ***aOR=1.30 (95% CI: 1.14–2.14)***	aOR=1.58 (95% CI: 0.46–5.49) *aOR=1.58 (95% CI: 0.46–5.49)*
	General Population	**SIR=0.38 (95% CI: 0.27–0.51)** ***SIR=0.41 (95% CI: 0.30–0.56)***	SMR=0.63 (95% CI: 0.13–1.85) *SMR=0.69 (95% CI: 0.14–2.03)*

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 14. Urinary Bladder Cancer Diagnoses (n=305) and Deaths (n=62), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	aOR=1.04 (95% CI: 0.92–1.18) *aOR=1.01 (95% CI: 0.91–1.20)*	aOR=0.91 (95% CI: 0.69–1.19) *aOR=0.86 (95% CI: 0.64–1.15)*
	General Population	**SIR=0.85 (95% CI: 0.76–0.95)** ***SIR=0.86 (95% CI: 0.75–0.97)***	SMR=0.90 (95% CI: 0.69–1.16) *SMR=0.87 (95% CI: 0.65–1.15)*

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 15. Kidney and Renal Pelvis Cancer Diagnoses (n=78) and Deaths (n=68), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	aOR=0.87 (95% CI: 0.68–1.12) *aOR=0.84 (95% CI: 0.64–1.08)*	aOR=0.92 (95% CI: 0.71–1.18) *aOR=0.90 (95% CI: 0.67–1.15)*
	General Population	**SIR=0.31 (95% CI: 0.24–0.38)** ***SIR=0.31 (95% CI: 0.24–0.39)***	SMR=0.98 (95% CI: 0.76–1.24) *SMR=0.99 (95% CI: 0.75–1.27)*

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 16. Brain and Other Nervous System Cancer Diagnoses (n=104) and Deaths (n=92), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	aOR=0.88 (95% CI: 0.71–1.10) *aOR=0.84 (95% CI: 0.64–1.10)*	aOR=0.87 (95% CI: 0.70–1.09) *aOR=0.80 (95% CI: 0.64–1.02)*
	General Population	SIR=1.06 (95% CI: 0.87–1.29) *SIR=1.05 (95% CI: 0.85–1.29)*	SMR=1.13 (95% CI: 0.91–1.38) *SMR=1.11 (95% CI: 0.88–1.38)*

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 17. Thyroid Cancer Diagnoses (n=72) and Deaths (n=11), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	aOR=1.12 (95% CI: 0.86–1.44) *aOR=1.08 (95% CI: 0.82–1.41)*	aOR=1.54 (95% CI: 0.79–2.99) *aOR=1.05 (95% CI: 0.47–2.33)*
	General Population	**SIR=0.71 (95% CI: 0.56–0.90)** ***SIR=0.72 (95% CI: 0.56–0.92)***	SMR=1.83 (95% CI: 0.91–3.27) *SMR=1.33 (95% CI: 0.54–2.75)*

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

Table 18. Non-Hodgkin Lymphoma Diagnoses (n=309) and Deaths (n=119), Male U.S. Air Force Fighter Aviators, June 1970 – December 2004, Followed through December 2018

		Outcome Type	
		Incidence	Mortality
Comparison Group	Other Officers	aOR=1.15 (95% CI: 0.99–1.21) *aOR=1.11 (95% CI: 0.97–1.27)*	aOR=1.08 (95% CI: 0.88–1.31) *aOR=0.98 (95% CI: 0.78–1.20)*
	General Population	**SIR=1.13 (95% CI: 1.01–1.27)** *SIR=1.12 (95% CI: 0.99–1.27)*	**SMR=1.32 (95% CI: 1.09–1.58)** ***SMR=1.25 (95% CI: 1.01–1.52)***

aOR, adjusted odds ratio; CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Note: italicized font represents a sensitivity analysis that excludes F-100 aviators

h. *Carcinogenic Exposures*: This section highlights novel and extant evidence on potentially carcinogenic exposures associated with fighter aviation.

(1) *Galactic Cosmic Radiation*: The effect of ionizing radiation on cancer development is stochastic and tissue-specific. For radiosensitive tissue types, the probability of carcinogenesis increases with the absorbed dose, without a clear threshold between safe and unsafe. While airborne, aviators are exposed to greater amounts of ionizing radiation from galactic cosmic radiation (GCR) and other ambient sources. An early modeling study suggested that GCR modestly increases cancer mortality in aircrew (Friedberg 1989), but real-world observational evidence has not substantiated this conclusion. A study of male European pilots (N=19,184) found no association between GCR and cancer mortality (Langer 2004). A study of German cockpit crew members (N=6,000) described a positive but non-significant correlation between GCR dose and cancer mortality risk; nonetheless, crew members with the highest cumulative effective dose (≥25 mSv) had significantly lower cancer mortality than their peers in the general German population (SMR=0.58; 95% CI: 0.36–0.92) (Hammer 2012). A dose-response relationship between GCR exposure and skin cancer incidence has been documented in some epidemiologic studies, but this finding is contentious given the impact of confounding variables (e.g., skin tone, family history, and ultraviolet radiation exposure) and potential bias from the healthy worker effect (Sigurdson 2004).

According to a British study of occupational radiation, the lowest cumulative chronic radiation dose range associated with a statistically significant increase in cancer risk is 200–500 mSv (Muirhead 2009). Although the cumulative GCR dose absorbed by U.S. Air Force fighter aviators who served in the Vietnam War is unknown, it is possible to estimate their per-hour absorbed dose. Using the CARI-7 program developed by the Federal Aviation Administration (https://www.faa.gov/data_research/research/med_humanfacs/aeromedical/radiobiology/cari7/), we simulated a flight from Saigon to Hanoi at 25,000 feet in 1965. The simulation accounts for 1965-level solar activity and applies the maximum altitude of fighter aircraft from that era (Hopkins 1979)—thus providing an upper approximation of exposure. The average calculated dose rate was 0.79 µSv/hr. Dividing the low-side cumulative estimate of 200 mSv by the high-side dose rate estimate of 0.79 µSv/hr, we find that aircrew would require 28 years of continuous flight operations at 25,000 feet over Vietnam to absorb sufficient GCR to increase cancer risk.

During an overlapping 8-year period in the 1960s, Strategic Air Command conducted Operation Chrome Dome, a series of around-the-clock airborne alert missions to deter nuclear escalation with the Soviet Union. The B-52s, which had similar radiation shielding as fighter aircraft, would fly in and around the Arctic Circle at a cruising altitude between 32,000 and 35,000 feet (Potter 2013). A CARI-7 simulation of these sorties, assuming a mean altitude of 33,500 feet, yielded an average dose rate of 2.87 µSv/hr—3.6 times higher than the previous simulation. Crews flew the missions weekly, in addition to training flights. If GCR increased cancer rates among Vietnam War fighter aviators, we would expect a more pronounced effect in the Chrome Dome bomber crews; no such effect has been documented.

While GCR, in and of itself, did not constitute a carcinogenic threat to fighter aviators who served in the Vietnam War, other sources of natural radiation cannot be excluded by mathematical modeling. Solar particle events (Anderson 2014) and terrestrial gamma flashes from lightning strikes (Dwyer 2012) can generate considerable doses of ionizing radiation that may imperil aviators. These risks are not unique to Vietnam War fighter aviators. All aircrew are threatened by these phenomena, but since they are rare and chrono-geographically random, the degree of threat across eras and theaters is unpredictable.

(2) *Radium and Other Radioisotopes*: Some legacy aircraft used radioactive radium in dial and instrument paints to facilitate nighttime operations. Radium paint was manufactured by mixing a small amount of a radium salt, a much larger amount of luminescent material, and a binding glue. Workers who applied these paints suffered from well-documented health effects. Although radium paint application was discontinued in the 1960s, fighter aviators who served in the Vietnam War likely flew aircraft with radium-painted dials and instruments. Radium-226, a naturally-occurring radioactive material extracted from uranium ore, decays to Radon-222 by emitting an alpha particle; this decay generates some gamma and beta radiation. Alpha and beta radiation, but not gamma radiation, would be blocked by the glass enclosure in the cockpit. Ingestion or inhalation of radioactive particles in paint dust cannot be ruled out, but it is highly unlikely given cockpit ventilation (Norquest 2015).

As with GCR, radium exposure for Vietnam War era fighter aviators is unknown but can be estimated. We reviewed photographs of the F-4C, F-100D, and F-100F cockpits, available in the public domain from the National Museum of the U.S. Air Force, and determined that each aircraft had fewer than 30 dials and instruments that may have contained radium paint. A recent measurement at the Smithsonian National Air and Space Museum, just beyond the acrylic surface of a display case containing 60 legacy radium instruments with the highest radioactivity, found a radiation dose rate below 0.02 mSv/hr, the public dose limit (Norquest 2015). Given the half-life of radium (1,600 years), these instruments are 97.4% as radioactive as they were in 1960. Using the low-side cumulative dose of 200 mSv and dividing by the high-side estimate of 0.02 mSv/hr, aircrew would require 10,000 hours in an unventilated cockpit to encounter an increased cancer risk. This may explain why no studies have demonstrated detrimental effects from radium paint on aviators, although the absence of evidence is not synonymous with evidence of an absent effect.

Some Vietnam War era fighter jets used radioisotopes elsewhere on the airframe. The F-4 used Caesium-137 in its engine ignition system, for example, and the F-111 used Cobalt-60 in electron tubes of some electronic components. Among the aircraft of interest in our study, none had a documented radiation risk within the cockpit (Emmer 1992).

(3) *Ultraviolet Radiation*: Ultraviolet radiation is an established risk factor for melanomatous and non-melanomatous skin cancers (Narayanan 2010), although it is difficult to distinguish occupational from recreational exposures (Nicholas 2009). A study of 322 commercial flights in Europe found that monthly intra-cockpit exposure experienced by pilots was significantly less than weekend recreational exposure experienced by office workers in the

United Kingdom (Baczynska 2020). Some studies have documented an inverse relationship between ultraviolet radiation and risk of non-Hodgkin lymphoma and cancers of the colon, breast, and prostate—a relationship that may be mediated by endogenous synthesis of vitamin D3 following cutaneous exposure to ultraviolet radiation (Holick 2016).

(4) *Radar Radiation*: Non-ionizing radiation from radar is not a known carcinogen. A recent meta-analysis concluded that occupational exposure to radar conveys no significant cancer risk if proper preventive measures are followed (Variani 2019). A large military cohort study found that French Navy personnel who worked in close proximity to radar systems had similar all-cause and cancer-specific mortality as their unexposed peers (Dabouis 2016). We are not aware of any studies assessing the health impact of intra-cockpit radar exposure.

(5) *Jet Fuel*: Chronic jet fuel exposure has been linked to immune dysfunction, which could impair tumor suppression (Harris 1997). Unprotected exposure to benzene, a ubiquitous air pollutant found in jet fuel, is associated with an increased risk of acute myeloid leukemia (Johnson 2009). To date, occupational studies of jet fuel exposure have been restricted to aircraft maintainers (Carlton 2000; Smith 1997), who can negate their cancer risk by diligent use of personal protective equipment and frequent handwashing (Tunsaringkarn 2012). While jet fuel combustion releases volatile organic compounds, which could theoretically increase intra-cockpit health risks, ambient air quality near airfields is no worse than air quality in standard urban environments (Tesseraux 2004).

(6) *Mechanical Forces*: No information is available regarding cancer risk associated with physiological stressors of flight, such as gravitational forces, vibration, and hypobaria. We cannot conceive of any mechanisms by which these forces could trigger carcinogenesis.

4. LIMITATIONS: Several limitations should be considered when interpreting these results.

a. *Under-capture of Outcomes*: Our study likely did not capture all cancer diagnoses and deaths among fighter aviators and other officers. This limitation differentially affects each of the four comparison/outcome combinations. Our inability to capture diagnoses outside the Military Health System and Veterans Health Administration could affect, in either direction, the incidence comparison of fighter aviators to other officers. We applied statistical techniques to abate unequal visibility of diagnostic histories between these groups, but we cannot certify equal case capture success between fighter aviators and other officers. Under-capture of diagnoses in fighter aviators would falsely underestimate SIRs, making fighter aviators look less susceptible to cancer than the general population. Reassuringly, all 8,946 cancer deaths in NDI Plus were also in the cancer registries or DMSS data. Future military cancer studies may benefit from the Virtual Pooled Registry Cancer Linkage System, a nascent service of the North American Association of Cancer Registries, which will offer investigators a fee-based portal to multiple civilian jurisdiction cancer registries. Failure to capture deaths is less concerning. We obtained death certificate data from NDI Plus, a compendious archive that outperforms even the Death Master File maintained by the Social Security Administration (Lash 2001). Since our ability to

capture deaths surpassed our ability to capture diagnoses, mortality results may have greater internal validity than incidence results.

b. *Latency Period*: The previous section addresses under-capture of outcomes that have already occurred. For indolent conditions like cancer, however, we should also consider under-capture of outcomes that have *not yet* occurred. The duration between carcinogenic exposure and cancer diagnosis, and between carcinogenic exposure and cancer death, can span decades. The minimum follow-up period in our study, for someone who entered active duty on the last day of the exposure period, is 14 years. Relative to other military aviation cancer studies, this is a robust interval between the closure of the exposure and outcome windows. For comparisons of fighter aviators and other officers, and comparisons based on aircraft, differences in follow-up time were addressed by upfront matching and backend statistical adjustment.

c. *Missing Data*: Of the 411,998 officers who served at least one day on active duty during the surveillance period, 25,808 (6.3%) with missing birth dates were excluded. Although missing variables can be imputed using various techniques, we avoided birth date imputation for three reasons: (1) it would introduce statistical liability throughout the study, since age is a principal confounder in cancer epidemiology; (2) only 11 fighter aviators were missing birth dates; and (3) given the large population, we could retain robust statistical power even after these exclusions. Other missing data elements, such as race/ethnicity and sex, were less consequential. The 27 members missing both race and ethnicity variables were assigned to the *other* category, and the 25 missing sex were manually assigned using first name.

d. *Assumptions*: First, and most consequential, was the assumption that AFPC correctly distinguished fighter aviators from non-fighter aviators. To verify, we cross-matched the AFPC assignments with those from the previous cancer study, in which we assigned fighter pilot status based on duty Air Force Specialty Codes. For the overlapping period of 1986 through 2004 (n=88,260), the overall concordance was 97.9%. Of the 4,949 officers we had classified as *fighter pilots* in the previous study, only 47 (0.9%) were not classified as *fighter aviators* by AFPC; occupational assignment using Air Force Specialty Codes may have imperfect specificity, especially before the coding overhaul in 1993. Of the 83,311 we had previously classified as *other officers*, AFPC classified 1,844 (2.2%) as *fighter aviators*; this likely reflects backseat aircrew, who were not included in the exposed group in the prior study. In other words, AFPC classifications were likely accurate. Second, we assumed that anyone not found in NDI Plus or AFMR was still alive on 31 December 2018; for reasons outlined above, under-captured deaths were likely negligible. Third, we assumed that cases identified solely through the Armed Forces Health Surveillance Branch oncological case definition, which relies on diagnostic codes and not on cancer registries, reflect true cancers; this assumption is tolerable given prior research (Webber 2019). Fourth, we assumed that AFPC correctly identified the aircraft flown by each aviator, and we assumed that any amount of flight time in the aircraft constituted an exposure. It may be epidemiologically preferable to subdivide exposure intensity by duration in the cockpit, but this was deemed inadvisable after comparing AFPC-provided flight hours with the official flight records in the Automated Records Management System. Among a random sample of 21 aviators, total flight time in the latter differed from the AFPC figures by a mean of 940 hours

(range: 346–1407). The Automated Record Management System is an operational database and is not positioned for research involving historic cohorts or voluminous sample sizes.

e. *Multiple Comparisons*: This study featured nearly 70 unique tests of association: for males, ten cancer types by six outcome/comparison combinations; and for females, three cancer types by three combinations. The alpha level for all tests was established at 0.05, meaning that each test carries a 5% false positive (or false discovery) risk. Had we adjusted the alpha level for multiple comparisons, we may have obtained fewer "statistically significant" results but at the expense of increasing the false negative (or missed discovery) risk. In our judgment, false positives would be less concerning than false negatives. Whereas the former might reveal fallacious associations, the latter might conceal genuine associations. For the case-cohort study of Vietnam War era aircraft, which featured 90 interconnected regressions, we selected a significance threshold of 0.01 in order to minimize the familywise error rate.

f. *Residual Confounding by Year*: Cancer incidence and mortality in the general population, and presumably in the fighter aviator population, has varied over time. The incidence of some cancers (e.g., colon and rectum cancer) has decreased, while that of others (e.g., pancreas) has increased. Mortality from many cancers, particularly prostate cancer and colon and rectum cancer, has declined precipitously (Siegel 2020). Because of these fluctuations and the outcome surveillance period of our study, we calculated SIRs and SMRs based on an average of the U.S. population data from 2000 through 2017. This accounts for some but not all of the period effect associated with cancer data vacillation, leaving residual confounding by year.

g. *Residual Confounding by Age*: For both comparison groups in this study—the internal comparison of other officers and the external comparison of the general population—we mitigated demographic confounding by accounting for sex, age, and race/ethnicity. For the external comparison, we adjusted indirectly by applying the specific sex-age-race/ethnicity cancer incidence and mortality rates from the general population to the demographic composition of the fighter aviator cohort. Ideally, the exact probability of cancer incidence and mortality for each fighter aviator would be known. Cancer data for the U.S. population, however, are arranged in 5-year intervals. Fighter aviators were thus assigned to 5-year buckets and the mean probability of diagnosis and death was determined at each terminus. This leaves residual confounding by age that could modestly bias results in either direction. For example, a 60 year-old black male would be assigned the same probability of cancer death as a 64 year-old black male—despite the *de facto* higher probability for the latter. For the comparison of fighter aviators with other officers, we blunted residual confounding by adjusting for exact age at incidence or mortality censoring.

h. *Other Confounding*: Lastly, and most importantly, this study could not account for other factors associated with cancer incidence and mortality, including personal health behaviors, socioeconomic status, and genetic predilection. In high-income countries, 37% of all cancer deaths can be attributed to eight modifiable risk factors: smoking; alcohol use; overweight and obesity; low fruit and vegetable consumption; physical inactivity; urban air pollution; unsafe sex; and contaminated injections in healthcare settings. Smoking alone accounts for 41% of urinary

bladder cancer deaths, while physical inactivity and overweight/obesity account for 26% of colon and rectum cancer deaths (Danaei 2005). Socioeconomic status has a particularly strong impact on cancers detectable by screening, likely due to inequalities in healthcare access and in screening uptake—described in some epidemiologic studies as "screening detection bias." As a general rule, socioeconomic status is inversely related with mortality from screen-detectable cancers because lower income persons are more likely to be diagnosed at advanced stages of disease (Ward 2003). These phenomena may explain the colon and rectum cancer findings: fighter aviators had similar incidence and mortality as other officers (given similar health behaviors and socioeconomics), but they had significantly lower incidence and mortality compared to the general population (as fighter aviators presumably maintain healthier body weights, engage in more physical activity, and have a higher socioeconomic profile). Some cancers evaluated in this study are affected by genetics. Men with a first-degree relative with prostate cancer, for example, have twice the risk of developing prostate cancer (Bruner 2003). Although we included race/ethnicity data, we had no visibility on family history or genetic risk.

Between-group differences in any of these behavioral, socioeconomic, and genetic factors would introduce confounding. Although the precise impact of such unmeasured confounding is elusive, the *potential* impact can be assessed with an E-value, which quantifies the evidence for causality in observational studies (VanderWeele 2017). The E-value associated with the comparison of prostate cancer incidence in fighter aviators and other officers (OR=1.23; 95% CI: 1.17–1.30) is 1.76 (https://www.evalue-calculator.com/). This means that an unmeasured confounder would need to be associated with both fighter aviation and prostate cancer incidence by ORs of at least 1.76, above and beyond the measured demographic confounders, to explain away the observed effect. The respective E-values for incidence of melanoma skin and testicular cancers are 1.79 and 1.90. These are small E-values, suggesting that the observed effects could be explained by relatively modest confounding, to include residual confounding.

5. DISCUSSION: In the internal comparison to other officers, male fighter aviators had slightly increased odds of being diagnosed with melanoma skin, prostate, and testis cancers, and equivalent odds of being diagnosed with the other seven cancers. Male fighter aviators and other officers had equivalent mortality odds for all ten cancers. In the external comparison to the general U.S. population, male fighter aviators had a higher standardized incidence of melanoma skin and prostate cancers and non-Hodgkin lymphoma; a lower standardized incidence of colon and rectum, testis, urinary bladder, kidney and renal pelvis, and thyroid cancers; and an equivalent standardized incidence of pancreas and brain and other nervous system cancers. Male fighter aviators had a higher standardized mortality of melanoma skin and prostate cancers and non-Hodgkin lymphoma, a lower standardized mortality of colon and rectum cancer, and equivalent standardized mortality for the remaining six cancers. Female fighter aviators had similar cancer incidence as other officers and equivalent standardized incidence compared to the general U.S. population; none had died from any of the studied cancers. The volume of these findings can be distracting. Statistical noise can obscure true signals, and even "statistically significant" associations can mislead when interpreted myopically. Assessing the evidence panoramically, we encounter four patterns that deserve further consideration.

(a) *First Pattern*: Melanoma skin and prostate cancers are potential concerns. Male fighter aviators were more likely than their fellow officers to be diagnosed with each of these cancers (by respective odds of 24% and 23%), and, when standardized to the U.S. population, they experienced greater incidence (by 25% and 19%) and mortality (by 64% and 23%). While none of the six individual effect sizes is especially salient—each would be considered epidemiologically "small" (Chen 2010), and their E-values raise serious concerns of unmeasured confounding (VanderWeele 2017)—their uniformity is suggestive. In absolute terms, for every 1,000 fighter aviators, compared to other officers, there were 15 additional lifetime cases of prostate cancer and three additional lifetime cases of melanoma skin cancer.

A unifying explanation is elusive. While both cancers are screen-detectable, the constellation of findings does not reflect common biases associated with screening. Differential uptake is unlikely because the pattern does not extend to colon and rectum cancer, which is likewise detectable by screening. Lead time and length time biases—i.e., detection of less advanced and less aggressive cancers—would not explain concomitant elevations of SIRs and SMRs. It is also unclear why fighter aviators were more likely than other officers to be diagnosed with these two cancers but not more likely to die from them. Insufficient follow-up time for progression to mortality might explain this finding, as could differential access to specialty care, such as dermatologists and urologists.

Having largely ruled out screening biases, we turn to other explanations. Apart from age, which was accounted for in all analyses, the two cancers share no established risk factors. Ultraviolet radiation increases the risk of melanoma skin cancer (Narayanan 2010), but its relationship with prostate cancer is, if anything, protective (Holick 2016). Ionizing radiation does not constitute an important risk factor for either cancer (National Research Council 2006). Some other aspect of military aviation could be a common causal factor, but observational studies have produced heterogeneous results. When compared to the general British and Welsh population, Royal Air Force and Navy service members who served abroad in the 1950s and 1960s had an elevated SMR for prostate cancer, but the investigators regarded the cause as unknown (Darby 1990). More recent studies in the U.S. Air Force have found no difference in prostate cancer rates between aviators and non-aviators (Rogers 2011; Robbins 2020).

In the sensitivity analysis, which excluded F-100 aviators, the findings for melanoma skin cancer were only modestly attenuated. The findings for prostate cancer, on the other hand, were more dramatically altered. With F-100 aviators excluded, fighter aviators had a 19% *lower* odds of prostate cancer mortality compared to other officers, and the SMR transitioned from significantly elevated to statistically insignificant. Adjusted odds of diagnosis and the SIR moved toward the null but remained statistically elevated. These findings suggest that fighter aviation writ large may not predispose to aggressive or severe prostate cancer. However, results from sensitivity analyses should always be considered hypothesis-generating. More research is needed to understand the differential impact of fighter airframes.

Because of contradictory evidence in the literature, the tenuous associations in this study that could be explained by unmeasured confounding, and the potential for medical interventions to

cause harm (e.g., screening exams leading to unnecessary biopsies), our results do not justify new universal cancer screening recommendations for fighter aviators. *Individual* fighter aviators, however, may wish to reduce their potential morbidity and mortality from these two cancers. To that end, we outline primary and secondary prevention strategies that current and former fighter aviators may wish to consider in the context of shared clinical decision-making (**Table 19**). Primary prevention aims to inhibit cancer initiation, while secondary prevention aims to expedite cancer detection, when treatment is more likely to succeed. This findings of our study may or may not apply to fighter aviators in the reserve component and in the sister services, or to those who have served more recently than 2004. Generalizing to aviators of bombers, tankers, transports, and other aircraft types is more questionable, and extrapolating to remotely piloted aircraft aviators is inadvisable.

Table 19. Potential Strategies† to Reduce Morbidity and Mortality from Melanoma Skin Cancer and Prostate Cancer in U.S. Air Force Fighter Aviators Who Served from 1970–2004

	Melanoma Skin Cancer	Prostate Cancer
Primary Prevention	• Minimize in-flight and recreational exposure to ultraviolet radiation by protective clothing and sunscreen • Understand impact on serum 25(OH)D level and consider supplementation with vitamin D3	• Consume a whole-food and low-glycemic diet, with a focus on vegetables, fruits, seafood, whole grains, and Brazil nuts • Minimize alcohol consumption • Ensure adequate sleep
Secondary Prevention	• Conduct periodic skin examination, especially if fair-skinned • Obtain referral to dermatology for evaluation of pigmented lesions	• Initiate prostate specific antigen screening at an earlier age • Shorten intervals between prostate specific antigen screening

†These strategies are not risk-free. Patients should discuss with their flight surgeon or primary care provider.

Chung WS and Lin CL, "Sleep Disorders Associated with Risk of Prostate Cancer: A Population-Based Cohort Study," *BMC Cancer* 19, no. 1 (February 2019): 146.

Fenton JJ et al., "Prostate-Specific Antigen–Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force," *JAMA* 319, no. 18 (May 2018): 1914–1931.

Ghiasvand R et al., "Sunscreen Use and Subsequent Melanoma Risk: A Population-Based Cohort Study," *Journal of Clinical Oncology* 34, no. 33 (November 2016): 3976–3983.

Henrikson NB et al., "Behavioral Counseling for Skin Cancer Prevention: Evidence Report and Systematic Review for the US Preventive Services Task Force," *JAMA* 319, no. 11 (March 2018): 1143–1157.

Oczkowski M et al., "Dietary Factors and Prostate Cancer Development, Progression, and Reduction," *Nutrients* 13, no. 2 (February 2021): 496.

Zhao J et al., "Is Alcohol Consumption a Risk Factor for Prostate Cancer? A Systematic Review and Meta-Analysis," *BMC Cancer* 16, no. 1 (November 2016): 845.

(b) *Second Pattern*: Standardized to the general population, male fighter aviators were more likely to develop and die from non-Hodgkin lymphoma, by 13% and 32%. In addition, the adjusted odds of non-Hodgkin lymphoma diagnosis among male fighter aviators was 15% higher than that in matched other officers, although the ratio fell shy of statistical significance (OR=1.15; 95% CI: 0.99–1.21). Like prostate cancer mortality, these ratios were attenuated

when F-100 aviators were excluded. Since ultraviolet radiation is a potential risk factor for non-Hodgkin lymphoma (Zhang 2007), this second broad finding reinforces the recommendation that fighter aviators minimize occupational and recreational exposure to ultraviolet radiation by use of sun-protective clothing and sunscreen.

(c) *Third Pattern*: Male fighter aviators were less likely than their peers in the general population to be diagnosed with or die from colon and rectum cancer, by 29% and 24%, although they had equivalent incidence and mortality as their officer peers. Fighter aviators likely engage in more physical activity and maintained lower body fat percentage than their peers in the broader population, but these health behaviors are probably similar to their peers in the narrower population of U.S. Air Force officers. In other words, the data suggest a healthy worker (or healthy airman) effect, not a healthy aviator effect. Current and former fighter aviators should follow national guidelines regarding colon and rectum cancer screening (Lin 2016). Note: these guidelines are currently under revision (https://uspreventiveservicestaskforce.org/uspstf/draft-update-summary/colorectal-cancer-screening3).

(d) *Fourth Pattern*: Male fighter aviators had greater odds of testicular cancer diagnosis than their officer peers. As a rarer cancer in both groups, however, the absolute difference is small: For every 10,000 fighter aviators, compared to other officers, there were three additional lifetime cases of testis cancer. A case-control study of U.S. Air Force officers hospitalized between 1988 and 1999 also found an increased odds of testicular cancer among aviators. Unable to establish a biologically plausible mechanism, the study investigators encouraged testicular self-examination (Yamane 2003). Despite our similar finding, we cannot endorse this recommendation because testicular cancer screening has well-described harms (U.S. Preventive Services Task Force 2011), and the similar mortality odds between fighter aviators and other officers suggests that enhanced detection does not necessarily reduce mortality.

Embedded in this investigation was a case-cohort study that compared cancer outcomes between fighter aviators who ever and never flew each of four Vietnam War era aircraft. This methodology controls for possible confounding differences between fighter aviators and other officers by excluding the latter altogether, but it introduces other limitations. Two noteworthy concerns are the cohort and period effects, neither of which could be addressed by demographic adjustment. The cohort effect occurs when the probability of an outcome varies by birth year, regardless of age and period effects. The historic trend in smoking prevalence presents a potential cohort effect: Among white males in the United States, over 60% of those born in the 1940s ever smoked, compared to fewer than 40% of those born in the 1970s (Anderson 2012). This alone could explain a tremendous discrepancy in future cancer outcomes among fighter aviators who served in different eras—for example, during the Vietnam and Persian Gulf Wars.

The period effect occurs when the probability of an outcome changes across an entire population simultaneously, regardless of age and birth cohort. National cancer rates have fluctuated dramatically, even after accounting for changes in mean population age and life expectancy. The incidence and mortality of prostate cancer, for instance, rose significantly between 1975 and 1992; during the period of 1988 and 1992, annual incidence increased by an astounding 16.1

percent—a pattern repeated across demographic strata (black: 22.0%; white: 16.0%; age <50: 19.2%; age 50–64: 23.4%; age ≥65: 14.9%). Despite this influx of diagnoses, the mortality rate inverted thereafter, having now declined for black and white Americans every year since 1993. This intense period effect can be traced to the enthusiastic reception of prostate specific antigen screening in the early 1990s. Among all cancer types explored in this study, only brain and urinary bladder cancer have trended monotonically since 1975. Period effects for the other cancers may reflect introduction of enhanced diagnostics and therapeutics and inauguration of environmental regulations. (Trends in U.S. cancer incidence and mortality can be examined on SEER*Explorer, available at https://seer.cancer.gov/explorer/.)

In light of these cohort and period effects, and given the surveillance inception of June 1970, it is irresponsible to derive conclusions from individual odds ratios in the case-cohort study. The conspicuous findings for one aircraft, however, deserve attention. Of the 2,285 aviators who flew the F-100, 176 (7.7%) have died from a cancer investigated in this study, exceeding the exposure fatality ratio associated with the F-4 (3.7%), RF-4 (4.5%), and F-105 (6.6%). The true difference may be even greater, as the categories were not mutually exclusive; for example, some F-100 aviators also flew the F-4 (n=42), RF-4 (n=4), and F-105 (n=31). F-100 aviators had elevated incidence ORs for five cancers, and they had particularly large mortality ORs (adjusted for age and race/ethnicity) for cancers of radiosensitive tissue, including the thyroid and colon (National Research Council 2006). This finding may be related to the airframe proper, its in-garrison or deployment locations, or mission contextual factors, or it may be the result of statistical chance. Further investigation is warranted.

Agent Orange is a perennial concern of service members who participated in Operation Ranch Hand, the decade-long effort to apply herbicides across millions of acres of Vietnam and Laos. According to an Office of Air Force History monograph, F-100s provided fighter cover for some spraying missions in the mid-1960s, and F-4s were modified to spray for a brief period in 1969; the RF-4 and F-105 were not involved in Ranch Hand (Buckingham 1982). In response to Public Law 102-4, the National Academy of Sciences formed the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. In a 2002 update to their initial report, the Committee adjudicated associations between Agent Orange exposure and several cancers. Among the cancers evaluated in this study, the Committee reported sufficient evidence of an association for non-Hodgkin lymphoma; limited evidence for prostate cancer; limited or sufficient evidence of no association for colon and rectum cancer, pancreas cancer, and brain cancer; and inadequate evidence for the remaining cancers (Institute of Medicine 2002). In our case-cohort study, ever flying the F-100 was associated with increased odds of mortality from seven cancers, representing cancers with and without an established Agent Orange relationship. Lacking granularity about exposure for individual fighter aviators, our study cannot implicate or exculpate Agent Orange as a causal factor for any of the cancers.

This study supplies new information regarding fighter aviator exposure to GCR. The CARI-7 flight simulations, interpreted alongside published research, suggest that fighter aviators did not sustain cancer-inducing doses of GCR during the Vietnam War. However, these simulations do not incorporate rarer and more random sources of natural ionizing radiation, such as solar

particle events and terrestrial gamma flashes, nor do they include artificial occupational sources like radium-painted instruments, or non-occupational sources like computerized tomography scans. Because the relationship between ionizing radiation and carcinogenesis is stochastic and based on the cumulative absorbed dose from all sources, the flight simulations do not absolve radiation as a carcinogenic hazard for fighter aviators.

6. CONCLUSION: This is the largest study ever conducted on military aviation and cancer. It provides three key insights. First, U.S. Air Force fighter aviators who served between 1970 and 2004 had similar cancer outcomes as their fellow officers, with the exception of greater incidence of melanoma skin and prostate cancers, and a suggestive association with non-Hodgkin lymphoma. These are the same three cancers—the *only* three cancers—for which the standardized incidence and mortality ratios were statistically elevated. Compared to the general population, fighter aviators were less likely to be diagnosed with several cancers (i.e., colon and rectum, testis, urinary bladder, kidney and renal pelvis, and thyroid) and less likely to die from colon and rectum cancer. This juxtaposition, in which an apparent healthy worker effect extends to most but not all cancers, suggests that fighter aviators were indeed more susceptible to melanoma skin cancer, prostate cancer, and potentially non-Hodgkin lymphoma. Second, F-100 aviators may be more vulnerable than other fighter aviators to several cancers, especially of radiosensitive tissue. A sensitivity analysis excluding F-100 aviators suggested that particular fighter airframes, not the occupation of fighter aviation, may be more predictive of certain cancer outcomes. Further studies are recommended to elicit airframe factors that may contribute to these differences in cancer incidence and mortality. Third, galactic cosmic radiation is an unlikely *de novo* carcinogen in fighter aviators, but other sources of ionizing radiation have not been exonerated.

In summary, the findings of this study do not justify wholesale changes to cancer prevention recommendations for U.S. Air Force fighter aviators. Current and former fighter aviators are encouraged to discuss this report with their flight surgeon or primary care provider. Topics may include ultraviolet radiation protection and its impact on vitamin D, lifestyle approaches to cancer prevention, and screening for melanoma skin and prostate cancers.

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