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ANALYSIS OF BRAIN CANCER RISK AMONG AFSOC AND CONVENTIONAL C-130 AIRCREW

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14. ABSTRACT

Between 2006 and 2009, seven cases of primary brain cancer, including two deaths, were reported among Air Force Special Operations Command (AFSOC) C-130 crewmembers. Of particular concern was crew status on the MC-130 models (particularly the MC-130P) as an apparent common factor among the cases. This prompted AFSOC to request that the USAF Epidemiology Consult Service evaluate the potential risk posed by C-130s or by modified AFSOC-specific C-130s on the development of brain cancer. Brain cancer is a very rare event and has few known risk factors. The only known environmental risk for developing brain cancer is exposure to extremely high doses of ionizing radiation, as seen with atomic bomb detonations and with extreme doses of therapeutic radiation used to treat childhood cancers several decades ago. The vast majority of brain cancers are random occurrences with no identifiable cause. Some earlier studies suggest a higher incidence of brain cancer among career aviators, although more recent studies have not found an increased incidence. Studies of military aviators specifically have not found an increase in brain cancer attributable to flying. The cases reported from AFSOC appear to be related to chance and not to any particular exposure risk. Population-based evaluation of tumor registry and mortality data revealed no increased risk for brain cancer associated with flying or with C-130 models specifically. Formal assessment of nonionizing radiation exposure levels in selected C-130 model cockpits may be considered, although the results of such an evaluation would not alter the conclusions of this investigation.

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1.0 EXECUTIVE SUMMARY

Between 2006 and 2009, a perceived elevation in the number of brain cancer cases was reported among Air Force Special Operations Command (AFSOC) C-130 crewmembers. This prompted AFSOC to request that the USAF Epidemiology Consult Service evaluate the potential risk posed by C-130s or by modified AFSOC-specific C-130s on the development of brain cancer.

Brain cancer is a very rare event, occurring in approximately 6.5 out of every 100,000 people in the United States annually. (Note: This is corrected from an erroneous figure in the October 2009 preliminary report.) The demographics of the active duty population, readily available access to health care, frequent periodic hands-on medical evaluations, and a low threshold for providers to initiate comprehensive medical evaluations for rated aircrew make detection of brain cancer more likely among this population than among the general population. However, the small size of this population and the rarity of brain cancer make any group of cases appear to be unusual. Brain cancer has few known risk factors. Risk appears to increase with higher socioeconomic status, which would lead to a truly higher incidence among active duty Air Force (ADAF) rated aircrew than the general population. Some earlier studies suggested a higher incidence of brain cancer among career aviators, although more recent studies have not found an increased incidence. Studies of military aviators specifically have not found an increase in brain cancer attributable to flying. The only known environmental risk for developing brain cancer is exposure to extremely high doses of ionizing radiation, as seen with atomic bomb detonations or with extreme doses of therapeutic radiation such as those used to treat childhood cancers several decades ago. The vast majority of brain cancers are random occurrences with no identifiable cause.

The cases reported from AFSOC appear to be related to chance and not to any particular exposure risk. In particular, no specific airframe, crew position, or deployment location was found that could account for all cases. Population-based evaluation of tumor registry data from the Armed Forces Institute of Pathology’s Automated Central Tumor Registry (ACTUR) from 1987 to 2008 and mortality data from the Air Force Mortality Registry (AFMR) from 1992 to 2009 revealed no increased risk for brain cancer associated with flying or with C-130 models specifically. Formal assessment of nonionizing radiation exposure levels in selected C-130 model cockpits may be considered, although the results of such an evaluation would not alter the conclusions of this investigation.

2.0 BACKGROUND

On 8 Sep 2009, the Epidemiology Consult Service at the United States Air Force School of Aerospace Medicine (USAFSAM/PHR) at Brooks City-Base, TX, was notified of a possible cluster of brain cancer cases among C-130 crewmembers within the Air Force Special Operations Command. Over the preceding 3 years, seven cases of primary brain cancer were reported by flight surgeons among AFSOC C-130 crewmembers, including two deaths. Via personal communication with one base-level flight surgeon, of particular concern was crew status on the MC-130 models (particularly the MC-130P) as an apparent common factor among the cases. Following this notification and request from HQ AFSOC/SG, the Consult Service initiated a formal evaluation to assess the nature of the apparent cluster and the risk of primary brain cancer among AFSOC C-130 crewmembers.

To provide HQ AFSOC/SG with timely information and recommendations for senior leadership, USAFSAM/PHR produced a rapid-turnaround preliminary report on 21 October 2009 with the caveat that more comprehensive data were not yet available. USAFSAM/PHR continued the process of obtaining and analyzing relevant data for preparation of the current report.

2.1 Prior Studies

Investigations of potential causes of brain cancer are particularly complicated because there are few known risk factors. One noteworthy exposure is extremely high doses of ionizing radiation. This refers to levels experienced by atomic bomb survivors or by individuals exposed to high-dose radiation therapies for childhood cancer (Ref 1, 2). It does not include radiofrequency such as radar units or mobile telephones (Ref 3). The other known risk factor is the presence of certain rare genetic syndromes that generally exhibit other characteristic features (Ref 2). Finally, brain cancer incidence is positively associated with socioeconomic status (Ref 4), a factor that would be expected to lead to higher incidence among Air Force officers and professional aviators relative to the general population.

Prior studies in the published medical literature have attempted to evaluate the risk of brain cancer in aircrew members (Ref 1, 4-9). The findings of these studies have been mixed: some studies have demonstrated a higher incidence of brain cancer among career aviators versus the general population (Ref 1, 4, 7-8), but these findings were not all statistically significant. Other studies have not replicated those findings (Ref 1, 5-6, 9). Perhaps most relevant to the current study, Grayson et al. (Ref 4) found that the odds of brain cancer for career USAF aircrew in the 1970s and 1980s were significantly higher than for nonflying USAF members; however, this association was not seen after adjusting for socioeconomic status, a previously established risk factor for brain cancer. When comparing the incidence of brain cancer with nervous system cancer, they found no difference in the standardized incidence ratio versus that seen in general population data from the National Cancer Institute (Ref 6). A meta-analysis (Ref 5), which showed an overall higher incidence of brain cancer among aviators versus the general population (albeit with notable heterogeneity among the studies), specifically excluded the USAF data in its analysis. Similarly, more recent European studies of aircrew using cohorts dating from 1960 to 1997 have not shown an increased risk of brain cancer (Ref 7-9), with some of the pooled analyses still forthcoming (Ref 1). It is also important to note that both military and civil aviation aircrews typically receive closer and more frequent medical assessment than the general population, which can result in greater detection of cancer cases and seemingly higher incidence than the general population (Ref 5).

2.2 Review of Case Series

There were six cases of primary brain cancer among AFSOC C-130 crewmembers initially reported to USAFSAM/PHR; this was later updated to seven cases: three pilots, two flight engineers, one loadmaster, and one navigator (Table 1). Of the seven members, five were assigned to the MC-130P Shadow, one to the AC-130U Gunship, and one to the MC-130H Talon. The mean age at diagnosis was 39 years (median 39.5, range 31-46). At diagnosis, four individuals were assigned to either Eglin AFB or Hurlburt Field (although one had only recently transferred to the area) and one each to Kadena AB, Kirtland AFB, and RAF Mildenhall.

Consideration of the clinical diagnoses is limited by lack of detailed information in the Armed Forces Health Longitudinal Technology Application (AHLTA) clinical records, as the majority of specialty care for these individuals is likely to have been delivered in the civilian purchased care network rather than within military treatment facilities. Two individuals had available biopsy results confirming malignant lesions: both were high-grade astrocytomas. Imaging studies, most commonly magnetic resonance imaging (MRI), were documented for six of the seven cases. Specific diagnoses were assigned in AHLTA for four of the seven; the remaining three were categorized simply as “brain tumor,” “neoplasm,” and “mass lesions.” Most of the specific pathology information was collected in good faith by the base-level tumor registrars, although in three of the cases neither they nor USAFSAM/PHR could independently verify the results.

Table 1. Initial AFSOC-Reported Cases

Age Range at Diagnosis	Diagnosis Date	Crew Position	Airframes	Total Flying Hours	Confirmed by Pathology?
30-39	2009	Pilot	C-130E MC-130P[a]	1600	Referenced in medical record, no report available
30-39	2009	Pilot	AC-130U[a] EC-130H[a]	3500	Yes
40-49	2008	Navigator	C-130E KC-135A[b] KC-135Q[a] MC-130E[a] MC-130P[b]	3400	Cannot determine
40-49	2009	Flight Engineer	C-130E HC-130N HC-130P[a] MC-130P	2200	Yes
40-49	2009	Loadmaster	MC-130E[b] MC-130H[c]	2800	Cannot determine
30-39	2006	Pilot	C-130E MC-130P[a]	2100	Yes
30-39	2009	Flight Engineer	C-130E[a] MC-130P	2400	Cannot determine

[a]>1,000 hr
[b]<100 hr
[c]>2,500 hr

All seven individuals logged rated flying hours on at least one conventional and one modified C-130 airframe, most commonly the C-130E (five persons) and the MC-130P (five persons). No single model was common to all cases. The mean total flying hours was 2,569.9 (range 1,629.2-3,532.4). Only one individual had more than 200 hours in the C-130E.

Review of deployment information from 2001-2008 revealed no deployed locations or timing common to all. The most common deployment locations were Iraq (four cases) and Kuwait (four cases, although not the same four individuals). The deployments for one individual during that period were solely within the Pacific Rim. The remainder deployed to various locations in southwest and central Asia and the Horn of Africa.

We did not find compelling evidence to categorize these cases as a true epidemiologic cluster linked by person, place, and time. Conclusive evidence is lacking that all cases represent the same form of cancer, or even that they all represent cancer. Not all of the reported cases have official pathology (biopsy or necropsy) reports confirming the presence of a primary brain-derived malignancy. Some did not have biopsies performed or documented but were apparently diagnosed and treated based on clinical and radiologic findings. This is important since noncancerous masses can exist in the brain with identical clinical features and consequences to cancer but with entirely different sources and causes (Ref 10). Additionally, brain cancers are not uniformly alike and, in fact, arise from different cell types within the brain.

2.3 Review of Preliminary Investigation

This section reviews the findings as reported in the preliminary investigation of October 2009. The initial epidemiologic analysis to investigate the association between flying history and brain cancer was performed using data from the Air Force Mortality Registry due to lack of timely access to current tumor registry information. Consequently, the preliminary findings were based on individuals who had already died of brain cancer. We did find a slightly higher risk of death from brain cancer (opposed to other causes of death) among rated aircrew versus nonaviators (risk ratio (RR) 1.51, 95% confidence interval (CI) 1.05, 2.18). However, this did not account for socioeconomic status, a factor that has accounted for artificially elevated brain cancer incidence among rated aircrew in prior studies (Ref 4, 6), nor were age or gender considered. Detailed analysis of the cohort of rated aircrew who died of brain cancer revealed only two who had logged any C-130 flying hours, one of whom had only 2 hours in the C-130.

3.0 EXPANDED ANALYSIS

3.1 Methods

For the expanded analysis, we used a case-control approach. A case was defined as a diagnosis of primary brain cancer (International Classification of Disease (ICD)-9 codes 191-191.9 or ICD-10 codes C71-C71.9) in an active duty Air Force member diagnosed between 1 Jan 1987 and 31 Dec 2008 as recorded in ACTUR or a death directly or indirectly attributable to primary brain cancer (ICD-10 code C71, malignant neoplasm of brain) in an active duty or retired Air Force member as recorded in the AFMR. For deaths recorded in the AFMR, we included individuals with a retirement date of 1 Jan 1987 or later and a recorded date of death 1 Jan 1992 or later, chosen to reflect the minimum 5-year latency period reported between exposure to ionizing radiation and development of brain cancer (Ref 11).

Cases were assessed for flying status, defined as either (1) logged flying hours on current or archived data from the Aviation Resource Management System (ARMS); (2) presence of an AF Form 1042, Medical Recommendation for Flying or Special Operational Duty; or (3) presence of a flying-associated Air Force Specialty Code (AFSC) on archived data from the Air

Force Personnel Center (AFPC). We also conducted a retrospective cohort analysis of all rated aircrew identified by ARMS. In this analysis, we considered the exposure variable of C-130 flying, defined as flying hours logged in ARMS on any C-130 model or variant. (Note: The terms "aviators" and "rated aircrew" in this report refer to individuals who have ever logged flying hours on an aircraft, whether currently or in the past.)

Availability of ACTUR data was made possible through an amendment to the protocol of a study on urogenital cancers, melanoma, and leukemia in USAF aviators (Col Marc Goldhagen, Principal Investigator) and approval by the investigational review boards (IRBs) of the Armed Forces Institute of Pathology and the 711th Human Performance Wing. The data were analyzed using Microsoft SQL Server 2005 and Microsoft Access 2007, and 2x2 tables and statistics were performed using OpenEpi, version 2.3 (http://www.openepi.com/Menu/OpenEpiMenu.htm).

3.2 Findings

As reported in the preliminary report, the AFMR data search yielded 7,391 ADAF persons who served on or after 1 Jan 1987 and with a date of death 1 Jan 1992 or later, including 291 with primary brain cancer listed among the causes of death. The ACTUR data yielded 1,402 cases of primary brain cancer among all military health care beneficiaries diagnosed from 1 Jan 1987 to 31 Dec 2008. After filtering for current or former ADAF status, merging and de-duplicating the datasets, 621 cases of primary brain cancer were identified among active duty and retired USAF members. Of these, 39 (6.3%) were rated aircrew. This number does not include the cases initially reported by AFSOC that were diagnosed in 2009. If these additional cases were included and assumed to be the only additional cases of brain cancer in the entire eligible population, the proportion of rated aircrew among all brain cancer cases would increase to 44/625 (7.0%). By contrast, flying AFSCs (11X, 12X, 13X, 48X, 1AX, 1CX) account for approximately 12.3% of the total active duty force (40,570 of 330,159) (Ref 12).

ARMS data revealed 80,582 individuals who logged flying hours, including 17,752 (22%) with C-130 flying hours. Among the 39 rated aircrew with a diagnosis of primary brain cancer, 6 (15.4%) had ARMS-logged flying hours in at least one variety of C-130 (Table 2a-c). For C-130 aviators, the risk of brain cancer was 36% lower than for other aviators for the period 1987 through 2008 [risk ratio (RR) 0.64 (95% CI 0.27, 1.54)] (Table 2a-c). However, as the confidence interval crosses zero, there is no statistical association between C-130 flying and brain cancer. If we include the five additional cases identified from 2009 and assume no additional cases of brain cancer among non-C130 aviators, we would see an 18% higher risk of brain cancer for C-130 aviators versus other aviators [RR 1.18 (95% CI 0.60, 2.33)] (Table 3a-c), although again the confidence interval crosses zero, indicating no statistical association. The contrasting findings between the two results further illustrate the lack of significant association between C-130 exposure and brain cancer.

Table 2a. Brain Cancer in C-130 vs. Non-C-130 Aviators (Single Table Analysis) [from OpenEpi v.2]

Airframe	No. of Aviators-- With Brain Cancer	Without Brain Cancer	Total
C-130	6	17,746	17,752
Non-C-130	33	62,797	62,830
Total	39	80,543	80,582

Table 2b. Brain Cancer in C-130 vs. Non-C-130 Aviators (Chi Square[a] and Exact Measures of Association) [from OpenEpi v.2]

Test	Value	p-Value (1-Tail)	p-Value (2-Tail)
Uncorrected Chi Square	1.003	0.1594	0.3187
Mid-P Exact		0.1627[b]	0.3253

[a]All expected values (row total*column total/ grand total) are >=5. OK to use chi square.
[b]Indicates a 1-tail p-value for protective or negative association; otherwise 1-tail exact p-values are for a positive association.

Table 2c. Brain Cancer in C-130 vs. Non-C-130 Aviators (Risk-Based Estimates and 95% Confidence Intervals) [from OpenEpi v.2]

Type of Point Estimate	Value	Confidence Limits Lower	Upper	Type
Risk in Exposed	0.0338%	0.01355	0.07566	Taylor series
Risk in Unexposed	0.05252%	0.03715	0.074	Taylor series
Overall Risk	0.0484%	0.03523	0.06633	Taylor series
Risk Ratio	0.6435	0.2697	1.535[a]	Taylor series
Risk Difference	-0.01872%	-0.05116	0.01371[b]	Taylor series
Prevented Fraction in Population (pfp)	7.853%	-6.38	18.73	
Prevented Fraction in Exposed (pfe)	35.65%	-53.55	73.03	

[a]95% confidence limits testing exclusion of 1.
[b]95% confidence limits testing exclusion of 0.

Table 3a. Brain Cancer in C-130 vs. Non-C-130 Aviators (2009 Cases Included) (Single Table Analysis) [from OpenEpi v.2]

Airframe	No. of Aviators--		
	With Brain Cancer	Without Brain Cancer	Total
C-130	11	17,746	17,757
Non-C-130	33	62,797	62,830
Total	44	80,543	80,587

Table 3b. Brain Cancer in C-130 vs. Non-C-130 Aviators (2009 Cases Included) (Chi Square[a] and Exact Measures of Association) [from OpenEpi v.2]

Test	Value	p-Value (1-Tail)	p-Value (2-Tail)
Uncorrected Chi Square	0.2254	0.3175	0.6350
Mid-P Exact		0.3114	0.6228

[a]All expected values (row total*column total/ grand total) are >=5. OK to use chi square.

Table 3c. Brain Cancer in C-130 vs. Non-C-130 Aviators (2009 Cases Included) (Risk-Based Estimates and 95% Confidence Intervals) [from OpenEpi v.2]

Type of Point Estimate	Value	Confidence Limits		Type
		Lower	Upper	
Risk in Exposed	0.06195%	0.0331	0.1124	Taylor series
Risk in Unexposed	0.05252%	0.03715	0.074	Taylor series
Overall Risk	0.0546%	0.04051	0.07345	Taylor series
Risk Ratio	1.179	0.5963	2.333[a]	Taylor series
Risk Difference	0.009425%	-0.03132	0.05017[b]	Taylor series
Prevented Fraction in Population (pfp)	3.804%	-12.6	20.21	
Prevented Fraction in Exposed (pfe)	15.21%	-67.71	57.14	

[a]95% confidence limits testing exclusion of 1.
[b]95% confidence limits testing exclusion of 0.

4.0 DISCUSSION

The principal focus of this report is the updated epidemiologic analysis described above. With regard to the initial case series brought to the attention of AFSOC, our findings remain unchanged from the preliminary report. The initial report found no significant difference in odds of flying among brain cancer deaths relative to deaths from other causes (odds ratio 0.95, 95% CI 0.51-1.76). There was a slightly elevated relative risk for having brain cancer among the causes of death for decedent rated aircrew relative to nonaviator deaths in the AFMR (1.51, 95% CI 1.05-2.18), although this was not adjusted for socioeconomic status, age, or gender. These findings were consistent with those in previous studies (Ref 4). AFMR-alone analysis yielded only two individuals who had flown on C-130s, one of whom had just over 2 hours. The resulting volatility of the statistical analysis precluded any meaningful interpretation.

Few factors are common to all of the cases. The timing of diagnosis is spread over a 39-month period (June 2006 – August 2009). The variable and often slow growth of brain tumors poses considerable difficulty in determining whether the timing of these cases more accurately reflects incidence (i.e., when the cancers actually developed) or prevalence (i.e., when existing cancers either reached the point of causing symptoms or simply happened to be discovered). We found no geographic linkage to these cases, with diagnoses being made at four separate locations (counting Eglin and Hurlburt as a single site). It is plausible that the common assignment of these individuals to AFSOC provides for the possibility of a shared duty station. However, investigation at an installation-specific level is beyond the scope of the current phase of this study. Deployment histories are similarly unrevealing. Although some individuals did deploy to some of the same locations as others over the course of their careers, generally in support of Operation Enduring Freedom/Operation Iraqi Freedom, there was no location common to all that could be implicated as a potential exposure source to link all cases.

With regard to airframe exposures, the most important finding is that no one airframe was common to all reported cases, beyond the shared exposure to some modification of the C-130. Additionally, the variety of crew positions represented suggests no particular location or physical feature of the aircraft that would convey excess risk.

The addition of ACTUR data on living persons with primary brain cancer increased the sensitivity of detecting brain cancer cases, allowing for a more robust analysis. The proportion of rated aircrew among all brain cancer cases was markedly lower than the expected proportion of rated aircrew in the ADAF population. This contrast remains, even when including the cases known to have occurred after 2008.

Retrospective cohort analysis of rated aircrew showed no significant association with primary brain cancer, even with the additional cases identified via ACTUR. Including the additional cases identified in 2009 (outside the 1987-2008 collection period) still produced a nonsignificant risk ratio that is almost certainly an overestimate of true risk, as it would be unreasonable to assume that no cases of brain cancer occurred among non-C130 aviators in 2009.

The results of this and all studies depend greatly on the accuracy of the original data. While we have no cause to believe the information analyzed is somehow extraordinary in its degree of accuracy, it should be noted that the lack of definitive, laboratory-confirmed diagnoses, whether by clinical decision or through lack of access to complete medical records, in several of the initially reported cases might have resulted in an overestimate of the true risk.

The size of the total eligible population could not be accurately determined given the dynamic nature of the ADAF population and the absence of reliable data on total numbers and identities of all retired and separated members. In particular, accurate numbers of nonaviators among controls were not available. This prevents any further statistical analysis of association between flying status and brain cancer beyond the findings described in the preliminary report. We were unable to obtain tumor registry information on cases of brain cancer among nonaviators, thus precluding the calculation of odds or risk ratios. Finally, reliance on AFSC and ARMS data would not account for nonrated personnel who may have flown frequently on these aircraft.

5.0 CONCLUSIONS AND RECOMMENDATION

This report updates the analysis of primary brain cancer among C-130 crewmembers initially released in October 2009. The preliminary report was able to assess only mortality data; this report expands the analysis to include as-yet nonfatal cases of brain cancer. In both reports, no significant association is seen between brain cancer and flying in C-130 aircraft versus other airframes. Additionally, there does not appear to be an increased risk of brain cancer among rated aircrew versus nonaviators, although neither risk nor odds can be calculated in the expanded analysis due to lack of accurate denominator data for nonflying controls. In fact, the raw numbers suggest the incidence of brain cancer may, in fact, be lower among rated aircrew than among nonaviators.

As reported previously, analysis of the brain cancer cases initially reported by AFSOC does not reveal any factors that suggest a common exposure or etiology that would constitute a true disease cluster. Rather, the overall consideration of the case series and epidemiologic calculations suggest that the apparent clustering may be more likely attributable to chance occurrence.

One particular caveat to these findings is that analysis of cancers dating back to 1987 does not consider the possibility of a before/after difference relative to the introduction of radar modifications to certain AFSOC C-130 models such as the MC-130 series. Although nonionizing, radiofrequency radiation does not have a proven association with brain cancer, the possibility of increased incidence post-modification suggests an analysis by a health physicist of radiofrequency radiation exposure in crew areas of AFSOC C-130s may be informative. It should be particularly clear, however, that none of the findings from such an assessment can be directly linked to existing cases of brain cancer without independent establishment of a causal association, which to date does not exist.

5.1 Summary

- Analysis of the AFSOC-reported brain cancer cases does not suggest presence of a true disease cluster.
- Epidemiologic assessment of brain cancer cases dating from 1987 does not suggest increased risk of brain cancer among rated aircrew in general or among C-130 rated aircrew in particular.

5.2 **Recommendation**

The authors recommend that AFSOC/SG consider requesting a radiation exposure assessment by the USAFSAM Radiation Assessment Consult Service (USAFSAM/OEHHH).

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LIST OF ACRONYMS

ACTUR	Automated Central Tumor Registry
ADAF	active duty Air Force
AFMR	Air Force Mortality Registry
AFPC	Air Force Personnel Center
AFSC	Air Force specialty code
AFSOC	Air Force Special Operations Command
AHLTA	Armed Forces Health Longitudinal Technology Application
ARMS	Aviation Resource Management System
CI	confidence interval
ICD	International Classification of Disease
MRI	magnetic resonance imaging
RR	risk ratio
USAFSAM/PHR	United States Air Force School of Aerospace Medicine/Epidemiology Consult Service