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

12 FEB 2024

MEMORANDUM FOR AFSOC/SG

ATTN: AFSOC/SGP

FROM: USAFSAM/PHR
Epidemiology Consult Service Division
USAF School of Aerospace Medicine
2510 5th Street, Building 840
Wright Patterson AFB, OH 45433

SUBJECT: Evaluation of Pediatric Brain Cancer Risk at Cannon Air Force Base

References: (a) Pachocki CJ, Hol EM. Current perspectives on diffuse midline glioma and a different role for the immune microenvironment compared to glioblastoma. J Neuroinflammation. 2022 Nov 19;19(1):276.
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EXECUTIVE SUMMARY: At the request of the Air Force Special Operations Command Surgeon (AFSOC/SGP), the United States Air Force School of Aerospace Medicine Epidemiology Consult Service Division (USAFSAM/PHR) assessed the incidence of Diffuse Intrinsic Pontine Glioma (DIPG) and Diffuse Midline Glioma (DMG) from 2010-2020 among children of Active Duty Department of the Air Force (ADDAF) parents who had an assignment at Cannon AFB during this time period and compared that incidence to other ADDAF children and to the U.S. civilian child population. Given the small number of DIPG/DMG cases, USAFSAM also evaluated the incidence of all pediatric brain cancers in the three study populations.

This evaluation found no statistically significant increase in overall brain cancer among the pediatric population whose sponsor was stationed at Cannon AFB when compared to the rest of the AF pediatric population and when compared to the U.S. civilian population from 2011-2020. When considering only the rare diagnosis DIPG/DMG, children with a Cannon AFB affiliation had a statistically higher incidence of DIPG/DMG compared to the non-Cannon AFB pediatric population and when compared to the U.S. civilian pediatric population. However, these differences were based on very low counts at Cannon AFB (n=3). Findings with extremely low counts are statistically unstable and have low reliability, making it difficult to rule out the effect of random variability and chance. This means that despite the observed statistically significant increase in rates, the role of chance cannot be dismissed as an explanation for this observation. In addition, these results should be interpreted in the context of what is known about the causes of DIPG/DMG, especially the fact that there are no known environmental exposures or risk factors linked to DIPG/DMG incidence. Regarding Cannon AFB specifically, there are no data that would suggest a relationship between environmental conditions on the base and DIPG/DMG rates.

It is reassuring that, when comparing rates of pediatric brain cancer and DIPG/DMG in the Department of the Air Force (DAF) to civilian rates, the DAF pediatric population actually has a significantly lower rate of pediatric brain cancer overall and the rate of DIPG/DMG is statistically similar. Using larger populations provides better statistical stability and paints a more accurate epidemiologic picture.

Study Personnel:

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(10) Mr. Gregory Wolff, MPH, Senior Epidemiologist, USAFSAM/PHR

1. INTRODUCTION:

Purpose: In general, brain cancer is the most common pediatric solid tumor within the US. DIPG/DMG is a rare pediatric brain cancer subtype (approximately 300 cases in the entire U.S. pediatric population per year). Though radiation therapy can be of some benefit, DIPG/DMG is almost always fatal; the median survival time is less than 12 months (a). This study addresses a population level concern among a select number of service members and beneficiaries whose families suffered a devastating medical episode from the highly fatal pediatric brain cancer, DIPG/DMG. On 19 Sept 2022, USAFSAM leadership alerted the Epidemiology Consult Service of concern for a possible pediatric brain cancer cluster within AFSOC, reported across social media in the local community. The originator of the query, who was assigned to Cannon AFB when his child developed DIPG, gathered information relevant to his own family's tragedy. He discovered three additional families that were assigned to Cannon AFB prior to or at the time their children were diagnosed with DMG: two cases diagnosed in 2020 and one in 2022. Considering the very low expected frequency of this diagnosis, there was concern for elevated cancer rates, given the small population size of Cannon AFB.

The number of DIPG/DMG cases that were reported to USAFSAM was small and there was concern that it would be difficult to make any meaningful statistical conclusions. When small numbers of cases are used to calculate rates and trends, findings may be the result of chance, confounding, misclassification, or other factors rather than from exposures specific to Cannon AFB. Investigations that include large numbers of cases minimize these effects. Per the National Cancer Institute (b), having fewer than 16 cases of the same or etiologically related cancers results in unstable statistics and unreliable results, as evidenced by wide confidence intervals. Based on the current scientific literature, there is no evidence that DIPG/DMG is caused by environmental factors or specific inherited genetic variations. Despite these limitations, USAFSAM/PHR agreed to pursue a preliminary cancer cluster assessment specifically investigating whether DIPG/DMG cases were statistically higher among the pediatric population whose parents were ever stationed at Cannon AFB compared to DIPG/DMG cancer rates among children whose parents were never stationed at Cannon AFB. Due to the small count of DIPG/DMG cases, the scope of the study was expanded to include all brain cancers.

2. METHODOLOGY:

a. *Study Design and Population:* A retrospective cohort study examining the incidence of malignant brain tumor cases, including cases of DIPG/DMG, was conducted among all dependents of ADDAF (<20 years old) from 01 January 2010—31 December 2020. The end date of the study was determined by the availability of civilian data and so the study was not able to include the case diagnosed after this date. Malignant brain tumor incidence was compared among dependents whose sponsor was ever stationed at Cannon AFB, to children whose sponsor was never stationed at Cannon AFB, during the study period. Incidence for dependents of ADDAF were also compared to U.S. incidence (<20 years old). The same methodology and datasets were used to identify DIPG/DMG incidence, which were also compared to the U.S. population.

Primary malignant brain tumors were identified using methodology published by the Armed Forces Health Surveillance Division (AFHSD) (Appendix A). Chart review was conducted to confirm malignant brain cancer cases. The case definition for chart review was confirmation of a malignant brain cancer (tumor grades 3 and 4) by a trained reviewer. An analysis of malignant brain tumors was done to identify DIPG/DMG in dependents of ADDAF and compare them to rates in the U.S. population. DIPG/DMG are malignant brain tumors, and therefore were captured utilizing the AFHSD incidence rules for malignant brain cancer. DIPG/DMG cases were also confirmed by chart review; similarly, the case definition for DIPG/DMG included confirmation of "diffuse intrinsic pontine glioma (DIPG)" or "diffuse midline glioma (DMG)" by a trained reviewer.

b. *Outcomes and Analyses:* Cumulative incidence (CuI) over the 11-year study timeframe at Cannon AFB, other AFBs (never stationed at Cannon AFB), and all AFBs (including Cannon) was calculated by dividing cumulative case counts from the study period by the specific ADDAF dependent population of the same 2010-2020 period. Malignant brain cancer incidence among Dependents of ADDAF was compared to malignant brain cancer incidence in the general U.S. pediatric population (<20 years old) from 2010-2020 from Central Brain Tumor Registry in the United States (CBTRUS) (Appendix B). DIPG/DMG incidence among dependents of ADDAF was compared to DIPG/DMG incidence in the general U.S. population (<20 years old) from 2010-2020 via CBTRUS high-grade gliomas in the brain stem case counts. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were calculated by dividing incidence of Cannon AFB by incidence of other AFBs, and 95% CIs were calculated to compare Cannon AFB, other AFBs, and all AFBs' incidence to those of the U.S. pediatric population using the 2000 U.S. Census Standard Population.

c. *Data Sources:* Cancer diagnosis data were retrieved from the Military Health System Management Analysis and Reporting Tool (MHS MART)/M2 medical database. Both hospitalization and ambulatory data were utilized from DoD military treatment facilities and non-DoD facilities (direct care and purchased care). Sponsor information was obtained via the Air Force Personnel Center (AFPC) database. Dependent demographic information was obtained via the Defense Eligibility Enrollment System (DEERS).

3. RESULTS:

a. Chart Confirmed primary malignant brain cancer: There were 179 cases identified using the AFHSD incidence rules for malignant brain cancer. Chart review found that while 133 (74%) patients had brain tumors, only 89 (49.7%) had primary malignant brain cancer (**Table 2**). Additionally, 41 out of the 179 cases were not able to be investigated due to the lack of information in their electronic health records (22.9%). During chart review, it was found that many patients being evaluated for brain cancer were seen at specialty referral centers and the records were not available to the USAFSAM team to review.

i. Primary Malignant brain cancer at All AFB vs U.S.: There were 89 cases of primary malignant brain cancer in dependents at all AFB (including Cannon AFB) (Cul =15.26 per 100,000). The number of primary brain cancer cases

observed in dependents at all AFB was significantly lower than the expected number of cases given U.S. civilian (US CuI = 40.31; SIR = 0.38; 95% CI = 0.30, 0.47; p<0.001) (**Table 3**).

ii. *Primary malignant brain cancer at Cannon AFB vs Other AFBs:* There were no significant differences in the incidence of primary malignant brain cancers in children whose sponsor was ever stationed at Cannon AFB (CuI = 36.95) compared to the IR of children whose sponsor was stationed at other AFBs (never at Cannon AFB) (CuI = 14.85; IRR=2.49, 95% CI = 0.78, 6.19; p=0.110) (**Table 4**).

iii. *Primary malignant brain cancer at Cannon AFB vs U.S.*: The number of primary malignant brain cancer cases observed among children whose sponsor was ever stationed at Cannon AFB was not significantly different than the expected number of cases given the incidence among the general U.S. population (SIR = 0.92; 95% CI = 0.25, 2.35; p=0.881) (**Table 5**).

iv. *Primary malignant brain cancer at Other AFB vs U.S.:* There were significantly less primary malignant brain cancer cases than expected among children whose sponsor was never stationed at Cannon AFB (Other AFB) compared to U.S. civilians (SIR = 0.37; 95% CI =0.30, 0.46; p<0.001) (**Table 6**).

v. *High-end estimate for primary malignant brain cancer*: A high-end estimate was generated by adding the 41 not found/unable to determine cases to the 89 chart-confirmed cases to create an estimate of 130 cases (**Table 7**). Hypothetically, if the 41 cases were considered chart confirmed, the all AFB population would still have a significantly lower observed case count of primary malignant brain cancer compared to the U.S. civilian population (SIR = 0.55; 95% CI = 0.46, 0.66; p<0.001).

b. *Chart Confirmed DIPG/DMG brain cancer:* Of the 89 primary malignant brain cancer cases identified in the total DAF dependent population, 15 were chart confirmed DIPG/DMG tumors (CuI = 2.57) (**Table 8**).

i. *DIPG/DMG at all AFB vs U.*S.: There was no significant difference in the incidence of DIPG/DMG tumors in all AF dependents compared to the U.S. population CuI = 4.11) (SIR = 0.63; 95% CI = 0.35, 1.03; p=0.070).

ii. *DIPG/DMG at Cannon AFB vs Other AFB*: Children whose sponsor was ever stationed at Cannon AFB had 13 times the incidence of DIPG/DMG compared to children whose sponsor was never stationed at Cannon AFB (other AFBs) (IRR=13.22; 95% CI=2.99, 43.88; p=0.003). This difference was statistically significant (**Table 9**), however, the 95% confidence interval ranges from 2.99 to 43.88 given the small numbers of cases of this rare brain cancer.

iii. *DIPG/DMG at Cannon AFB vs U.S.*: Of the 15 DIPG/DMG cases identified in all AFB dependents, 3 were among children whose sponsor was ever stationed at Cannon AFB (CuI = 27.7) (**Table 10**). The incidence of DIPG/DMG tumors in children whose sponsor was ever stationed at Cannon AFB was significantly

higher than expected, compared to the U.S. population (SIR = 6.82; 95% CI = 1.37,19.92; p=0.024).

iv. *DIPG/DMG in at Other AFB vs U.S.*: There were 12 DIPG/DMG cases identified in dependents whose sponsor was never stationed at Cannon AFB (CuI = 2.10) (**Table 11**). Compared to the U.S. population, the incidence of DIPG/DMG cases was significantly less than expected in the Other AFB population (SIR = 0.51; 95% CI = 0.26,0.89; p=0.014).

4. LIMITATIONS:

This study has many limitations that are common to cancer cluster investigations. For cancer incidence and mortality reporting, the NCI does not report cancer cases and deaths if there are fewer than 16 cases or death since these rates have poor reliability (b). Our statistically significant finding among DIPG/DMG cases from the pediatric population ever stationed at Cannon AFB compared to children stationed at other DAFB consisted of three cases. The small number of DIPG/DMG cases in the Cannon AFB population has produced a wide confidence interval, and low statistical reliability. This means that the reported SIR was likely elevated by chance. Moreover, the wide confidence intervals further support the unreliability of the SIR. Even if we ignore the limitations of our results and the required number of cases for meaningful interpretation of incidence rates, determining a specific cancer-causing substance from a cluster investigation is extremely rare. A 20-year review of 576 cancer clusters found only three clusters could be linked to a possible exposure, and of these, only one cluster had a clearly identified cause (c).

In the context of epidemiologic studies, dependent and child outcomes are rarely studied within service branches. Incomplete follow-up is common in dependents and children, especially considering studies spanning longer timeframes. Follow-up issues such as this bias this study toward a null result—meaning that it makes it less likely to find a difference in the rates between populations if one truly exists. The transient nature of military assignments further convolutes prenatal, perinatal and pediatric exposures, as child dependents frequently move and therefore have more varied environmental exposures.

There are several significant limitations with the civilian cancer data. These data have a three-year time lag to be released, thus elongating the completion timeline of the study. Additionally, the U.S. civilian data is based on the rate of all high-grade malignant gliomas in the brain stem—experts predict that 80% of these are assumed to be DIPG/DMG. However, this subtle difference makes a perfect comparison of the rates impossible.

5. DISCUSSION: There is a statistically significant elevation of DIPG/DMG cases among children of those who were ever stationed at Cannon AFB when compared to the rest of the DAF population and to the U.S. civilian population through 2020. It is the opinion of experts and the USAFSAM team that this increase in rates is likely due to chance or confounding factors. These are the reasons why:

1) Based on a review of the cases and of the published scientific literature, there is no evidence that DIPG/DMG is caused by any environmental factor, such as exposure to

chemicals or radiation. Additionally, no evidence exists that specific inherited genetic mutations contribute to DIPG/DMG. Most DIPG/DMG cases are associated with an epigenetic phenomenon resulting in a histone mutation known as H3K27M which aggressively facilitates the development and growth of glioma within the midbrain and brainstem. This is a random mutation without any known upstream cause (e). While ionizing radiation is associated with increased rates of pediatric brain cancer in general, there was no note of excessive ionizing radiation exposure among the cases. New Mexico is not known to have areas with environmental ionizing radiation and has a cancer rate, including pediatric brain cancer, below the national average, according to a representative with the New Mexico Department of Health.

2) The diagnosis and coding of DIPG/DMG has changed over time which may have differentially changed the rate of diagnosis in different populations. DIPG is a radiographic diagnosis whereas DMG diagnosis requires a biopsy of brain tissue. This revised classification occurred in 2016 during the middle of our study time period. In addition, the rate of diagnoses in a specific location can be influenced by the local availability/expertise of pediatric neurosurgeons and radiologists.

3) The incidence rate of DIPG/DMG at Cannon AFB was also likely influenced by the timeline of cases in the investigation period. Our years of analysis (2010-2020) were bookmarked by cases of DIPG/DMG, including 2 cases in 2020. This had the likely effect of artificially increasing the incidence rate at Cannon AFB.

4) The USAFSAM team thoroughly reviewed the charts of the confirmed DIPG/DMG cases whose parents were ever stationed at Cannon AFB to ascertain any commonality in timing or potential exposure that could be associated with the base. There was nothing found that would support a biologically plausible link to a potential environmental contaminant at Cannon AFB (f). One of the children was at Cannon AFB less than 1 year before developing DIPG/DMG. Even though DIPG/DMG is a rapidly growing tumor, it is highly unlikely that any environmental condition at Cannon AFB would have contributed to this particular child's diagnosis in such a short time.

5) With the small number of DIPG/DMG cases at Cannon AFB during the study period (n=3), the addition of 1-2 cases had a profound impact on the observed rates. Therefore, these rates should be interpreted with caution. When considering pediatric brain cancer overall, Cannon AFB rates were statistically similar to the rest of DAF bases and to the overall U.S. pediatric population.

Therefore, the investigators at USAFSAM do not recommend additional investigation into environmental conditions at Cannon AFB. With DIPG/DMG, there are no known environmental exposures to investigate, and the small number of cases makes identification of new causative factors impossible. The best way to identify any potential causative factors is through participation in the International DIPG/DMG Registry.

Overall malignant brain cancer incidence did not differ between children whose parents were previously assigned to Cannon AFB when compared to children assigned to the rest of the DAF and to the U.S. civilian pediatric population. Malignant brain cancer incidence was significantly lower in the DAF pediatric population compared to the civilian pediatric population.

The USAFSAM team recommends that AFSOC consider the following actions:

a. Thoroughly educate medical providers regarding signs and symptoms of pediatric brain cancer, including DIPG/DMG.
b. Encourage enrollment of children diagnosed with DIPG/DMG in tumor registries and referral to regional specialty sites to optimize care, better understand these rare cancers, and build knowledge for targeted treatments that can lead to a cure.
c. Active monitoring of pediatric brain cancer by Cannon AFB, specifically cases of DIPG/DMG. Ensure all cases of DIPG/DMG are referred to the International DIPG/DMG Registry.
d. Refer study findings to appropriate authorities (including the AFHSD) so that they may monitor and perform additional investigations as indicated.

6. For questions or concerns, my POC is Lt Col Keith T. Beam, MD, MPH, FACP. The investigative team can be reached at usafsam.phrepiservic@us.af.mil.

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Table 1. Dependents (<20 years of age) of ADDAF ever stationed at Cannon AFB or Other AFBs, by Gender, 01 Jan 2010—31 Dec 2020 (N=583,244)

	Cannon AFB	Other AFBs	Total
Overall	10,824 (1.9%)	572,420 (98.1%)	**583,244**
Gender			
Male	5,526 (51.1%)	291,489 (50.9%)	**297,015 (50.9%)**
Female	5,298 (48.9%)	280,926 (49.1%)	**286,224 (49.1%)**
Unknown	-	5 (0.0%)	**5 (0.0%)**

Table 2. DIPG/DMG and primary malignant brain cancer case counts among dependents (<20 years of age) of ADDAF ever stationed at Cannon AFB or Other AFBs, by year of diagnosis, 01 Jan 2010—31 Dec 2020 (N=89)

	Cannon			Other AFBs			Total		
	DIPG/ DMG	Malignant Brain Cancer	**Total**	DIPG/ DMG	Malignant Brain Cancer	**Total**	DIPG/ DMG	Malignant Brain Cancer	**Total**
Overall	**3**	**1**	**4**	**12**	**73**	**85**	**15**	**74**	**89**
Year		-							
2010	1	-	1	1	10	11	2	10	**12**
2011	-	-	-	-	4	4	-	4	**4**
2012	-	1	1	1	7	8	1	8	**9**
2013	-	-	-	1	9	10	1	9	**10**
2014	-	-	-	1	2	3	1	2	**3**
2015	-	-	-	2	12	14	2	12	**14**
2016	-	-	-	1	4	5	1	4	**5**
2017	-	-	-	-	7	7	-	7	**7**
2018	-	-	-	4	7	11	4	7	**11**
2019	-	-	-	-	7	7	-	7	**7**
2020	2	-	2	1	4	5	3	4	**7**

Table 3. Eleven-year Cumulative Incidence (CuI) and Standardized Incidence Ratio (SIR) of pediatric brain cancer cases among children <20 of ADDAF sponsors compared to the U.S. civilian population, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old[†]	Cumulative Incidence (CuI)[†]	Standardized Incidence Ratio (SIR) (95% CI)[‡]	p-value (95%CI)
All AFB	89	583,244	15.26	0.38 (0.30, 0.47)	p<0.001
U.S. Civilians[*]	31,760	78,782,657	40.31	-----	-----

[*] Incidence in the U.S. population provided by the Central Brain Tumor Registry of the United States (CBTRUS).
[†] 11-year incidence per 100,000 children <20 years old.
[‡] SIR = observed case count (89) for All AFB divided by expected case count (235.11) for All AFB (based on IR for U.S. from 01 January 2010—31 December 2020). Confidence intervals (CI) and p values were calculated with Byar's approximation of the exact Poisson distribution which is extremely accurate even with small numbers (Breslow and Day, 1987).

Table 4. Eleven-year CuI and IRR of pediatric brain cancer cases among children < 20 years old whose ADDAF sponsor was ever stationed at Cannon AFB compared to children whose sponsor was not stationed at Cannon AFB, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old	Cumulative Incidence (CuI)[†]	Incidence Rate Ratio (IRR) (95% CI)[‡]	p-value (95%CI)
Cannon AFB	4	10,824	36.95	2.49 (0.78, 6.19)	p=0.110
Other AFB	85	572,420	14.85	--	--

[†] 11-year incidence rate per 100,000 children <20 years old.
[‡] IRR = Cannon IR (36.95) divided by Other AF IR (14.85). Confidence intervals were calculated with Byar's approximation of the exact Poisson distribution and p-value calculated using Mid-P exact test using Miettinen's modification.

Table 5. Eleven-year CuI and SIR of pediatric brain cancer cases among children < 20 years old whose ADDAF sponsor was ever stationed at Cannon AFB compared to the U.S. civilian population, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old	Cumulative Incidence (CuI)[†]	Standardized Incidence Ratio (SIR) (95% CI)[‡]	p-value (95%CI)
Cannon AFB	4	10,824	36.95	0.92 (0.25, 2.35)	P=0.881
U.S. Civilians[*]	31,760	78,782,657	40.31	-----	-----

[*] Incidence in the U.S. population provided by the Central Brain Tumor Registry of the United States (CBTRUS).
[†] 11-year cumulative incidence per 100,000 children <20 years old.
[‡] SIR = observed case count (4) for Cannon AFB divided by expected case count (4.36) for Cannon AFB (based on IR for U.S. from 01 January 2010—31 December 2020). Confidence intervals and p values were calculated with Byar's approximation of the exact Poisson distribution which is extremely accurate even with small numbers (Breslow and Day, 1987).

Table 6. Eleven-year CuI and SIR of pediatric brain cancer cases among children < 20 years old of ADDAF sponsors were not stationed at Cannon AFB compared to the U.S. civilian population, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old	Cumulative Incidence (CuI)[†]	Standardized Incidence Ratio (SIR) (95% CI)[‡]	p-value (95%CI)
Other AFB (excludes Cannon AFB)	85	572,420	14.85	0.37 (0.30, 0.46)	p<0.001
U.S. Civilians[*]	31,760	78,782,657	40.31	-----	-----

[*] Incidence in the U.S. population provided by the Central Brain Tumor Registry of the United States (CBTRUS)
[†] 11-year cumulative incidence per 100,000 children <20 years old
[‡] SIR = observed case count (85) for Other AFB divided by expected case count (230.74) for Other AFB (based on IR for U.S. from 01 January 2010—31 December 2020). Confidence intervals and p values were calculated with Byar's approximation of the exact Poisson distribution which is extremely accurate even with small numbers (Breslow and Day, 1987).

Table 7. "High-end estimate" for the eleven-year CuI and SIR for pediatric brain cancer cases among children < 20 of ADDAF sponsors compared to the U.S. civilian population, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old	Cumulative Incidence (CuI)†	Standardized Incidence Ratio (SIR) (95% CuI)‡	p-value (95%CI)
All AFB (high-end estimate)	130	583,244	22.29	0.55 (0.46, 0.66)	p<0.001
U.S. Civilians*	31,760	78,782,657	40.31	-----	-----

* Incidence in the U.S. population provided by the Central Brain Tumor Registry of the United States (CBTRUS)
† 11-year cumulative incidence per 100,000 children <20 years old
‡ SIR = high-end estimate for observed case count (89+41=130) for All AFB divided by expected case count (235.11) for All AFB (based on IR for U.S. from 01 January 2010—31 December 2020). Confidence intervals and p values were calculated with Byar's approximation of the exact Poisson distribution which is extremely accurate even with small numbers (Breslow and Day, 1987).

Table 8. Eleven-year CuI and Standardized Incidence Ratio (SIR) of cases of DIPG/DMG among children <20 years old of ADDAF sponsors compared to the U.S. civilian population, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old	Cumulative Incidence (CuI)†	Standardized Incidence Ratio (SIR) (95% CI)‡	p-value (95%CI)
All AFB	15	583,244	2.57	0.63 (0.35, 1.03)	p=0.070
U.S. Civilians*	3,238	78,782,657	4.11	-----	-----

* Incidence in the U.S. population provided by the Central Brain Tumor Registry of the United States (CBTRUS)
† 11-year cumulative incidence per 100,000 children <20 years old
‡ SIR = observed case count (15) for All AFB divided by expected case count (23.97) for All AFB (based on IR for US from 01 January 2010—31 December 2020). Confidence intervals and p values were calculated with Byar's approximation of the exact Poisson distribution which is extremely accurate even with small numbers (Breslow and Day, 1987).

Table 9. Eleven-year Incidence and Incidence Ratio (IR) of cases DIPG/DMG among children < 20 years old whose ADDAF sponsor was stationed at Cannon AFB compared to children whose sponsor was not stationed at Cannon (other AFB) population, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old	Incidence*	Incidence Ratio (IR) (95% CI) †	p-value (95%CI)
Cannon AFB	3	10,824	27.72	13.22 (2.99, 43.88)	p=0.003
Other AFB	12	572,420	2.10	-----	-----

* 11-year cumulative incidence per 100,000 children <20 years old.
† IR = Cannon IR (27.72) divided by other AF IR (2.10). Confidence intervals were calculated with Byar's approximation of the exact Poisson distribution and p-value calculated using Mid-P exact test using Miettinen's modification.

Table 10. Eleven-year Incidence and Standardized Incidence Ratio (SIR) of cases of DIPG/DMG among children < 20 years old whose ADDAF sponsor was ever stationed at Cannon AFB compared to the U.S. civilian population, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old	Incidence†	Standardized Incidence Ratio (SIR) (95% CI)‡	p-value (95%CI)
Cannon AFB	3	10,824	27.72	6.82 (1.37, 19.92)	p=0.024
U.S. Civilians*	3,238	78,782,657	4.11	-----	-----

* Incidence in the U.S. population provided by the Central Brain Tumor Registry of the United States (CBTRUS).
† 11-year cumulative incidence rate per 100,000 children <20 years old.
‡ SIR = observed case count (3) for Cannon AFB divided by expected case count (0.44) for Cannon AFB (based on IR for US from 01 January 2010—31 December 2020). Confidence intervals and p values were calculated with Byar's approximation of the exact Poisson distribution which is extremely accurate even with small numbers (Breslow and Day, 1987).

Table 11. Eleven-year Incidence and Incidence Rate Ratio (IRR) of cases of DIPG/DMG among children < 20 years old whose ADDAF sponsor was not stationed at Cannon AFB (Other AFB) compared to the U.S. civilian population, 01 January 2010—31 December 2020.

	Total Case Count	Population <20 years old	Incidence[†]	Standardized Incidence Ratio (SIR) (95% CI)[‡]	p-value (95%CI)
Other AFB (excludes Cannon AFB)	12	572,420	2.10	0.51 (0.26, 0.89)	p=0.014
U.S. Civilians[*]	3,238	78,782,657	4.11	-----	-----

[*] Incidence in the U.S. population provided by the Central Brain Tumor Registry of the United States (CBTRUS)
[†] 11-year cumulative incidence rate per 100,000 children <20 years old
[‡] SIR = observed case count (12) for Other AFB divided by expected case count (23.53) for Cannon AFB (based on IR for US from 01 January 2010—31 December 2020). Confidence intervals and p values were calculated with Byar's approximation of the exact Poisson distribution which is extremely accurate even with small numbers (Breslow and Day, 1987).

Appendix A

Armed Forces Health Surveillance Division: Malignant Brain Cancer Case Definition
Source: https://health.mil/Reference-Center/Publications/2019/08/01/Malignant-Brain-Tumor

Case Definition and Incidence Rules

For surveillance purposes, a case of a malignant brain tumor is defined as:

- *One hospitalization* with a case defining diagnosis of a malignant brain tumor (see ICD9 and ICD10 code lists below) in the *first* diagnostic position; or
- *One hospitalization with a V or Z-code* indicating a radiotherapy, chemotherapy, or immunotherapy treatment procedure (see ICD9 and ICD10 code lists below) in the *first* diagnostic position; AND any case defining diagnosis of a malignant brain tumor (see ICD9 and ICD10 code lists below) in the *second* diagnostic position; or
- *Three or more outpatient medical encounters*, occurring *within a 90-day period*, with any case defining diagnoses of a malignant brain tumor (see ICD9 and ICD10 code lists below) in the *first or second* diagnostic position.

Incidence rules:

For individuals who meet the case definition:

(continued on next page)

Case Definition and Incidence Rules *(continued)*

- The incidence date is considered the date of the first hospitalization or the first of the three or more outpatient medical encounters occurring within a 90-day period that includes a case defining diagnosis of a malignant brain tumor (see *Case Definition and Incidence Rule Rationale*).
- An individual is considered an incident case only *once per lifetime*.

Exclusions:

- None

Codes

The following ICD9 and ICD10 codes are included in the case definition:

Condition	ICD-10-CM Codes	ICD-9-CM Codes
Malignant brain tumor	*C71 (malignant neoplasm of brain)*	*191 (malignant neoplasm of brain)*
	C71.0 (malignant neoplasm of cerebrum, except lobes and ventricles)	191.0 (malignant neoplasm of cerebrum, except lobes and ventricles)
	C71.1 (malignant neoplasm of frontal lobe)	191.1 (malignant neoplasm of frontal lobe)
	C71.2 (malignant neoplasm of temporal lobe)	191.2 (malignant neoplasm temporal lobe)
	C71.3 (malignant neoplasm of parietal lobe)	191.3 (malignant neoplasm of parietal lobe)
	C71.4 (malignant neoplasm of occipital lobe)	191.4 (malignant neoplasm of occipital lobe)
	C71.5 (malignant neoplasm of cerebral ventricle)	191.5 (malignant neoplasm of ventricles)
	C71.6 (malignant neoplasm of cerebellum)	191.6 (malignant neoplasm of cerebellum, not otherwise specified)
	C71.7 (malignant neoplasm of brain stem)	191.7 (malignant neoplasm of brain stem)
	C71.8 (malignant neoplasm of overlapping sites of brain)	191.8 (malignant neoplasm of other parts of brain)
	C71.9 (malignant neoplasm of brain, unspecified)	191.9 (malignant neoplasm of brain unspecified)

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Procedures	ICD-10-CM Codes	ICD-9-CM Codes
Related treatment procedures *(Radiotherapy, chemotherapy, immunotherapy)*	Z51.0 (encounter for antineoplastic radiation therapy)	V58.0 (radiotherapy)
	Z51.1 (encounter for antineoplastic chemotherapy and immunotherapy)	V58.1 (encounter for chemotherapy and immunotherapy for neoplastic conditions)
	- Z51.11 (encounter for antineoplastic chemotherapy)	V58.11 (encounter for antineoplastic chemotherapy)
	- Z51.12 (encounter for antineoplastic immunotherapy)	V58.12 (encounter for antineoplastic immunotherapy)

Appendix B

Central Brain Tumor Registry of the United States (CBTRUS)	
	Case Definition
Malignant Brain Tumors	Please see Table 2 in recent report (reference i) for ICD-O-3 malignant histopathology and behavior codes.
Malignant High-Grade Glioma in the brainstem	Only includes histologies coded with malignant International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) behavior code. Brainstem tumors were defined as tumors occurring at ICD-O-3 site code C71.7. The specific histologies included under HGG for this analysis were ICD-O-3 codes: 9380 (Site C71.7 only), 9385/3, 9401, 9440, 9441, 9442, 9451, 9460, 9400 (Site C71.7 only).