An Exploratory Study of the Frequency of Central Nervous System Tumors by Type in the Central Texas Military and Civilian Populations

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Abstract

Background: The types of central nervous system (CNS) tumors in a patient population with a history of military service were compared to the types of CNS tumors in a similar patient population without a military service history to determine if a relationship exists between military service and CNS tumor type.

Methods: This study analyzed data for adult patients diagnosed with an intra- or extra-axial CNS tumor from January 2016 to July 2019. One cohort was constructed of patients who had a history of military service (MIL), and the other cohort was made of patients who did not have a history of military service (NMIL). Appropriate parametric and non-parametric analyses were used to compare frequencies of tumor types between cohorts adjusting for potential confounders.

Results: We identified 2001 patients (MIL, n = 190; NMIL, n = 1811). In the MIL cohort, most patients were males, younger, and more racially diverse. In the primary analysis, the MIL cohort showed higher diagnoses of metastatic tumors compared with the NMIL cohort (X^2(1)= 3.71, p=.05). The MIL cohort also showed lower diagnoses of meningioma compared to the NMIL cohort. There was no statically significant difference between cohorts or tumors after adjusting for primary source by gender.

Conclusions: MIL experience was associated with lower diagnoses of meningioma but higher diagnoses of metastatic tumors compared with the NMIL cohort. There was no statically significant difference in the incidence of brain cancer between patients with a history of military service and those without military history regarding primary CNS tumor frequency.

Introduction

In the past decades, studies comparing the incidence rates of central nervous system (CNS) tumors between patients with a history of military service and those without have delivered conflicting results. One well-studied example involves veterans of the Persian Gulf War. The Persian Gulf War linked exposure to nerve agents released during the March 1991 weapons demolition in Khamisiyah, Iraq, with an increased risk of death from brain cancer [1]. The relative risk of brain cancer deaths in veterans exposed to two or more days of these toxins (RR=5.26; 95% CI=1.53, 7.96) increased significantly when compared to veterans exposed to only one day (RR=1.72; 95% CI=0.95, 3.10) [2-3]. In addition to nerve agents, Gulf War veterans who were exposed to oil well fire smoke had an increased risk of brain cancer mortality (RR=1.81; 95% CI=1.00, 3.00) when compared to veterans who were not exposed [2]. However, a later study about this same military population found that there was no increase in brain cancer incidence when compared to non-Gulf War veterans [4]. Other studies, such as those reviewed by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, have demonstrated insufficient evidence to definitively link veteran exposure to Agent Orange with increased incidence of CNS tumors, despite the fact that it is a unique chemical to which the civilian population was largely not exposed [5]. Additionally, a different study evaluated active duty United States Air Force personnel from 1989-2002 and found that there was a statistically significant decrease in the incidence of brain neuroepithelial cancer in the military population compared to standardized incidence ratios in the general population [6].

In an Italian study, a case-control analysis performed for newly diagnosed brain tumors from 1990-1999 revealed a statistically significant association between military occupation and two of the most common brain tumors, gliomas and meningiomas [7]. Additional studies have shown a correlation between general military exposures (radiation, chemical carcinogens, etc.) and CNS tumor growth. There is some evidence...
that exposure to low frequency/microwave electromagnetic fields is associated with an increased risk of developing CNS tumors [6,8]. A retrospective cohort study comparing Canadian military members to the general population found that while Canadian military members who served any time between January 1, 1976, and May 31, 2015, overall had lower incidences of cancer, males were found to have a statistically significant increased risk of developing brain cancer [9]. Another study in Iowa looking at occupational and risk for histologically confirmed brain gliomas reported a statistically significant higher odds ratio for developing a brain glioma in men who had served in an unspecified role in the military [10].

Many prior studies had limitations that were similar in nature. In some of the studies, the statistics were underpowered due to limited number of military CNS tumor cases analyzed [5,9-11]. Study design was also a limitation, such as a hospital-based case-control design which may not accurately reflect the general population [11]. One other potential issue in some of the studies was reporting. Military personnel have the option of seeking medical care through a military healthcare system or through another healthcare system, which could underestimate the true burden of CNS tumors in military personnel [12]. Likewise, confounding factors such as relative health may have impacted the results since Gulf War veterans were slightly younger and possibly healthier compared to non-Gulf War veterans [4]. Limitations in the other studies included not having data for pre- and post-environmental and occupational exposures as well as a comprehensive list of chemicals for which military personnel may have been exposed [1]. In those with Gulf War exposure to chemicals that may have caused brain cancer, air samples were not taken and computer models were used to determine areas of exposure to sarin [2]. In some studies, family history of brain cancer was not addressed [2]. Other factors such as behavioral risk factors were not taken into account because of lack of data [2].

This study aims to compare the frequency of primary and secondary CNS tumor types in those with a history of military service against those without a military history in the Central Texas region. Secondly, this study aims to explore how demographic differences may relate to different patterns of nervous system tumor development in Central Texas. Bell County and the adjacent areas within Central Texas are ideal for studying our population of interest. As a state, Texas is second only to California regarding total veteran population, with the Bell County area specifically having a veteran population density of 13.5%, which is more than twice the state average [13-14]. Although we are unable to provide exact numbers, the Baylor Scott and White System serves as a primary referral site for management of CNS tumors and other serious neurological conditions for Veterans Healthcare Facilities in the region, as the Central Texas Veterans Health Care System does not provide neuro-oncology services. Baylor Scott and White is the only major medical system in the region providing comprehensive neurological and neurosurgical care with the Baylor Scott & Medical Center itself being located just one mile west of the Olin E. Teague Veterans’ Medical Center in Temple, Texas.

Materials And Methods
Study design and data source

This was a retrospective cohort study using patients’ information from our electronic medical record (EMR) with specific International Classification of Diseases (ICD)-10 codes (Table 1) which were dated January 1, 2016, to July 1, 2019. We extracted these data and reviewed encounters at the Baylor Scott & White Medical Centers in Temple, TX; Waco, TX; Round Rock, TX; and Temple Cancer Center.

| Description                                                                 | ICD 10     |
|-----------------------------------------------------------------------------|------------|
| Neuroendocrine carcinoma                                                    | C7A.1      |
| Leptomeningeal disease                                                      | C70.1      |
| Cerebrum, except lobes and ventricles, includes basal ganglia, unspecified   | C71.0      |
| lobe of cerebral cortex, corpus striatum, globus pallidus, hypothalamus,    |            |
| and thalamus                                                                |            |
| Frontal lobe                                                                | C71.1      |
| Temporal lobe, which includes hippocampus and uncus                          | C71.2      |
| Parietal lobe                                                               | C71.3      |
| Occipital lobe                                                              | C71.4      |
| Ventricles, which includes choroids plexus and ventricle floor               | C71.5      |
| Cerebellum, not otherwise specified, which includes cerebellopontine angle   | C71.6      |
| Brain stem, which includes cerebral peduncle, medulla oblongata, midbrain,   | C71.7      |
| and pons                                                                    |            |
| Other parts of brain, which includes corpus callosum and tapetum. This code  | C71.8      |
| also includes a malignant neoplasm of contiguous or overlapping sites of    |            |
| brain whose point of origin cannot be determined                             |            |
| Condition                                                                 | ICD Code  |
|--------------------------------------------------------------------------|-----------|
| Brain unspecified and cranial fossa unspecified                          | C71.9     |
| Glioma: malignant neoplasm of brain not otherwise specified              | C71.9     |
| Oligodendroglia                                                         | C71.9     |
| Astrocytoma (also known as glioma) includes anaplastic and glioblastoma | C71.9     |
| Ependymoma                                                              | C71.9     |
| Medulloblastoma                                                          | C71.6     |
| Benign neoplasms of the brain                                           | D33.2     |
| Secondary brain tumors AKA metastasis/unknown origin                     | C79.31, C80.1 |
| Germinoma                                                               | C80.1     |
| Acoustic neuroma (schwannoma) — Malignant                               | D36.10    |
| Acoustic neuroma (schwannoma) — Benign                                  | D36.10    |
| Meningioma                                                              | D32.0     |
| CNS lymphoma                                                             | C85.89    |
| Hemangioblastoma CNS                                                    | D18.02    |
| Craniotharyngioma                                                        | D44.4     |
| Ganglioglioma                                                            | D48.9     |
| Adenoma                                                                 | D35.2     |
| Mass of brain, extra axial in left temporal region                       | G93.9     |
| Neurofibromatosis                                                        | Q85.00    |
| Neurofibromatosis I                                                      | Q85.01    |
| Neurofibromatosis II                                                     | Q85.02    |
| Neurofibromatosis III                                                    | Q85.09    |
| Neoplasm of brain                                                        | D49.6     |
| Neurocytoma                                                              | D33.2     |
| Leptomeningeal metastases                                                | C79.49    |
| Schwannomatosis                                                          | Q85.03    |
| Neoplasm of pituitary gland                                              | D49.7     |
| Neoplasm of uncertain behavior of brain                                  | D43.2     |
| Neoplasm of uncertain behavior of brainstem/infratentorial/cerebellum    | D43.1     |
| Neoplasm of uncertain behavior of brain, supratentorial                  | D43.2     |
| Neoplasm of uncertain behavior of cerebral meninges                      | D42.0     |
| Neoplasm of uncertain behavior of cerebral ventricle/cerebrum/frontal lobe/occipital/parietal/temporal | D43.0 |
| Bladder cancer metastasized to brain                                     | C67.9     |
| Breast cancer metastasized to brain                                      | C50.919,  |
|                                                                          | C50.912,  |
|                                                                          | C50.911   |
| Colon cancer metastasized to brain                                       | C18.9     |

### TABLE 1: ICD-10 Codes for primary and secondary CNS Tumors

ICD: International Classification of Diseases, CNS: central nervous system
Case selection
From the EMR, we identified a cohort of 110 patients ≥18 years of age, with a primary or secondary CNS nervous system tumor diagnosis who had a recorded history of military payor information and had "self" as relationship in that payor information. Patients missing information on veteran status or who did not have a defined tumor type identified via chart review were excluded. Patient demographics were obtained from the EMR data. Data collected included age, gender, and race. The records were stratified by gender for each cohort.

Defining military group membership
Two cohorts were constructed based on military service history payor type listed at any time as Tricare, Veterans’ Administration, and/or TriWest Healthcare Alliance and also had the relationship of self were placed into the military cohort (MIL). Another cohort comprised patients who had previous payor information as listed with relationship being spouse, child, or other and all other patients extracted that did not have the previously named payor information was labeled as the non-military (NMIL) cohort.

Statistical analysis
In this exploratory study, we examined the frequency of tumor diagnoses over the same period in veteran and civilian samples. The Student’s t-test was used to compare age between cohorts while potential confounding nonparametric variables (gender, race, and ethnicity) were compared via Chi-Squared testing. Distribution of tumor type between the NMIL and MIL cohort was compared via Chi-Squared analysis and was repeated exclusively on males. Primary source of metastatic disease was also compared via Chi-Squared testing with repeat analyses to compare metastatic disease incidence in NMIL and MIL males given the differing incidence of cancer type between sexes. All statistics were conducted using JASP (JASP Team, 2019).

Results
In total, 2782 charts were initially reviewed. After case-by-case evaluation by the primary author, 781 charts were omitted because of diagnostic errors in the chart (i.e. non-nervous system cancer). This left a total of 2001 cases included in the current study with 190 (9.45%) being in the MIL cohort. Tumor types with less than 10 reported cases were merged into the “Other” category.

The MIL cohort (age 55.19 years [sd=15.99]) was slightly younger than the NMIL cohort (58.74 years [sd=17.23]; t(1999)=2.723, p < .007). Further demographic descriptions of the patients are found in Table 2. The MIL cohort tended to be more racially diverse than the civilian sample and disproportionately male.

| Variable                  | MIL (N=190) | NMIL (N=1811) | Contrast     |
|---------------------------|-------------|---------------|--------------|
| Gender Male (%)           | 86.32       | 37.94         | X²(1)=164.68, p<.0001 |
| Age Years                 | 55.19       | 58.74         | t = 2.72, p < .007 |
| Race American Indian      | 2.11        | .28           | X²(4)=42.25, p<.0001 |
| or Alaska Native          |             |               |              |
| Asian (%)                 | 1.05        | 1.55          |              |
| Black or African American | 24.74       | 12.54         |              |
| White or Caucasian (%)    | 60.00       | 77.64         |              |
| Ethnicity Other/Unknown (%)| 12.1       | 7.99          |              |
| Hispanic (%)              | 6.32        | 11.82         | X²(2)=21.39, p<.0001 |
| Not Hispanic (%)          | 85.79       | 85.70         |              |
| Other/Unknown (%)         | 7.89        | 2.48          |              |

TABLE 2: Demographic and Descriptive Data from Military Service (MIL) and Non-Military Service (MIL) Cohorts

The distribution of tumor type differed by cohort (Table 3) to a statistically significant degree
When our population was analyzed as a whole, the MIL cohort had a higher proportion of metastases ($X^2(1)=3.71, p=.05$) and a lower proportion of meningioma cases in comparison to the NMIL cohort ($X^2(1)=10.39, p<.01$). There was no significant difference in percentage of glioblastoma multiforme (GBM) diagnoses between the cohorts.

| Tumor Type             | MIL (N=190) | NML (N=1811) |
|------------------------|-------------|--------------|
| mets                   | 33.68%      | 27.11%       |
| pituitary adenoma      | 19.47%      | 16.90%       |
| meningioma             | 16.32%      | 22.64%       |
| GBM                    | 5.79%       | 9.39%        |
| neurofibromatosis      | 3.68%       | 4.58%        |
| schwannoma             | 3.68%       | 3.70%        |
| spinal cord lesion     | 3.16%       | 0.66%        |
| oligodendroglioma      | 2.63%       | 1.77%        |
| ependymoma             | 2.63%       | 0.99%        |
| OTHER                  | 2.11%       | 2.82%        |
| cyst                   | 2.11%       | 1.71%        |
| astrocytoma            | 1.58%       | 2.26%        |
| lymphoma               | 1.58%       | 0.50%        |
| craniopharyngioma      | 1.05%       | 0.88%        |
| DNET                   | 0.53%       | 0.00%        |
| unknown brain lesion   | 0.00%       | 2.82%        |
| hemangioma             | 0.00%       | 1.2%         |

**TABLE 3: Percentage of Tumor Type by Cohort**

MIL: Military Service, NMIL: Non-Military Service, GBM: glioblastoma multiforme, DNET: dysembryoplastic neuroepithelial tumors

Follow-up analysis of the source of metastatic disease is presented in Table 4. Overall, the distribution of metastatic source differed between the cohorts ($X^2(4)=11.15, p=.02$), with more breast cancer in the NMIL cohort and more lung cancer in the MIL cohort. However, given the fact that primary sources of metastatic tumors differ between genders, we re-ran the analyses looking only at NMIL versus MIL males and explored differences in primary tumor type [15]. When genders were compared directly, no statistically significant differences were observed ($X^2(3)=5.54, p=.32$).
| Tumor Type          | Males + Females MIL (N=190) | NMIL (N=1811) | Males Only MIL (N=164) | NMIL (N=687) |
|---------------------|------------------------------|---------------|------------------------|---------------|
| Metastatic Lesions  | 33.68                        | 27.11         | 35.98                  | 32.17         |
| Pituitary Adenoma   | 19.47                        | 16.90         | 18.29                  | 14.41         |
| Meningioma          | 16.32                        | 22.64         | 14.02                  | 13.68         |
| GBM                 | 5.79                         | 9.39          | 6.71                   | 12.81         |
| Neurofibromatosis   | 3.68                         | 4.58          | 3.66                   | 4.22          |
| Schwannoma          | 3.68                         | 3.70          | 4.27                   | 2.62          |
| Spinal Cord Lesion  | 3.16                         | 0.66          | 3.05                   | 0.73          |
| Oligodendroglioma   | 2.63                         | 1.77          | 3.05                   | 2.91          |
| Ependymoma          | 2.63                         | 0.99          | 1.83                   | 1.60          |
| Other               | 2.11                         | 2.82          | 1.83                   | 4.08          |
| Cyst                | 2.11                         | 1.71          | 2.44                   | 1.31          |
| Astrocytoma         | 1.58                         | 2.26          | 1.83                   | 2.77          |
| Lymphoma            | 1.58                         | 0.50          | 1.83                   | 0.15          |
| Craniopharyngioma   | 1.05                         | 0.88          | 0.61                   | 1.46          |
| DNET                | 0.53                         | 0.00          | 0.61                   | 0.00          |
| Unknown Brain Lesion| 0.00                         | 2.82          | 0.00                   | 3.79          |
| Hemangioma          | 0.00                         | 1.27          | 0.00                   | 1.31          |

**TABLE 4: Sources of metastatic tumors in the full sample and males only**

MIL: Military Service, NMIL: Non-Military Service, GBM: glioblastoma multiforme, DNET: dysembryoplastic neuroepithelial tumors

**Discussion**

Because of the larger occupational hazards inherent to military service, there may be a difference between primary and secondary CNS (including intra-axial and extra-axial) tumor rates between MIL and NMIL. However, there is little comprehensive research on these tumor types in the United States military population. Although nervous system tumors are the most common form of solid tumors in children, they are less common in adult populations, being the eight most common cancer among those greater than 40 years old [11]. As such, studies are more frequently conducted on cancers more common than primary and secondary CNS cancers. The Veteran Affairs Central Cancer Registry (VACCR) study found that the Veterans Affairs’ and United States’ male cancer population were similar compared to the United States general cancer population [15]. However, another study compared the common cancer incidence rates for the general United States population and found an increase in prostate cancer in military personnel [16]. Although this is not primary or secondary CNS cancer, it is suggestive that cancer patterns vary between military and non-military populations [17].

Previous studies have suggested that there is an elevated risk of meningioma and GBM development in military service populations [7,18]. Our initial analysis showed fewer meningioma diagnoses in the Central Texas MIL population over the three-year time period observed, which was eliminated when cohorts were stratified by gender as women made up a larger proportion of the NMIL cohort (62.1% vs 13.7% in men) and as a gender had double the occurrence of meningiomas (28.20% vs 13.75% in men). This is consistent with the findings of the most recent CBTRUS report showing meningiomas are more than twice as common in women compared to men [11].

Our evaluation does have several limitations. One such limitation is that if a veteran had a non-military payor listed, they were not placed in the MIL cohort. Those with military experience also may have been included in the NMIL cohort if this information was missing. Additionally, meningiomas can also be
incidental findings and given our younger population, incidental meningiomas may not be known if they are relatively healthy with little brain imaging. This is also a limitation stratifying by payor type so that if the military payor types used for classification were not listed as payor in our system, the patient was not placed in the MIL cohort. There is selection bias in that the data is from one geographical source. Also, male gender representation outweighs female representation due to military patient demographics. Future efforts would benefit from data allowing classification by military branch, length of service, and position so that studies could also evaluate for possible risk factors based on exposure and further evaluate based on tour location, position-related exposure in given duties such as radio/microwave electric field frequency, radiation and hazardous/environmental clean-up efforts. Occupational information after completion of military service would also be valuable to further quantify additional exposures.

Lastly, our initial comparison between the MIL and NMIL cohorts showed no difference in percentage of GBM diagnoses. When our male population was analyzed separately, the predominantly female NMIL cohort had a greater increase in proportion of GBMs cases than the MIL cohort, reflective of the fact that GBMs are more than 1.5 times as common in men [11]. The lower occurrence of GBMs in our MIL cohort would appear to contradict findings from previous studies showing increased risk of CNS tumors in military personnel [7]. Given that the NMIL cohort was predominantly composed of Caucasians, in whom GBMs are two times more common than in African Americans [11], the lower occurrence of GBMs in our MIL group could be attributable to the difference in racial composition. The diversity of our MIL cohort is actually in line with the racial demographics of the United States Military Services as a whole, which have been more racially diverse than the civilian workforce since at least the 1970s. Most recent reports show 30.1% of active duty enlisted military as being non-white compared to 24.1% of their age-matched civilian counterparts. Given the differing rates of CNS tumor prevalence amongst different racial and ethnic groups [11], our study serves to highlight the importance of accounting for such factors when studying a military population. It also highlights a factor readers should be cognizant of with international studies of risk associated with military service, such as the case-control studies conducted by Italian authors Fallahi et al. whose study population was 93% Caucasian and included only 10 minority cases [7].

The metastatic source differed between the MIL and NMIL cohorts in our study. There were more breast cancer diagnoses in the NMIL cohort, and more lung cancer diagnoses in the MIL cohort. Breast and lung cancer are the most common cancers in the world, with both being the most common sources of metastases to the brain as well [19]. Because our MIL cohort was largely male and breast cancer affects vastly more women than men, our analysis was rerun on males exclusively with no significant difference between groups. Lung cancer was the most common primary cancer in both groups of males at 79.3% in the MIL group and 69.86% in NMIL group. Although not to the point of significance the differing rate does warrant further investigation for occupational risk factors or whether rates of smoking or other known risk factors differ between groups.

Conclusions

Our study serves as a first look into the frequency of CNS tumors in the Central Texas veteran population. Although it is hindered by many of the limitations present in prior studies, it highlights some of the demographic differences present in the military population and emphasizes how impactful these differences can be. Due to the limitations of retrospective research, we were also unable to ensure which wartime periods, if any, were associated with our MIL cohort data. A next step to this research would be to explore the relationship between military exposures like radiation and possible increase in frequency of brain tumors that were previously reported. Given the fact that more than two million military personnel have been deployed to southwest Asia and exposed to numerous potential carcinogens such as exhaust from military vehicles, fumes from fires, weapons, and depleted uranium since 2001, identifying past and current carcinogenic substances that military personnel are exposed to will be vital to protecting the health of future military members.

Additional Information

Disclosures

**Human subjects:** Consent was obtained or waived by all participants in this study. Baylor Scott & White Research Institute issued approval 019-267. Study approved for research through 08/25/2021. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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