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CONFLICT OF INTEREST

The authors declare no relevant conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Incidence of cancer among U.S. combat casualties: a DoD Trauma Registry study

To the Editor:

Over the past two decades, more than 53 000 military members have been wounded in action during operations in Iraq and Afghanistan. While combat injuries heighten the risk of several chronic medical conditions,[1] the association of combat trauma with cancer is unknown. We sought to determine the cancer incidence in combat casualties compared to a cohort of uninjured service members.

The Department of Defense (DOD) Trauma Registry (DODTR) was utilized to collect data on 10 000 randomly selected U.S. military personnel who were wounded in combat operations in Iraq or Afghanistan from 2002–2016, and whose traumatic injuries were severe enough to warrant hospital admission. A comparator cohort of uninjured Iraq and Afghanistan veterans was created by 1:1 exact matching by year of birth ±1-year, military service branch, and gender, with a 97% match rate achieved. Members were excluded if they died within 90 days of traumatic injury, had pre-existing cancer, multiple battle injuries, missing encounters, or missing variables of interest. Cancer diagnoses were defined using International Classification of Diseases (ICD), Ninth Revision and Tenth Revision clinical modification codes and were obtained from inpatient and outpatient medical records from the DOD and Veterans Affairs Health Systems. The National Cancer Institute's ICD Conversion Program was utilized to categorize hematologic neoplasms and solid tumors.[2] Hematologic neoplasms included leukemias, lymphomas, and plasma cell disorders, whereas solid tumors included cancer of the lung, breast, gastrointestinal tract, genitourinary tract, head and neck, central nervous system, neuroendocrine tumors, melanoma, and non-melanoma skin cancers. The primary endpoint was the incident number of hematologic

neoplasms and solid tumors. Cancer events required an ICD diagnosis to be documented at least once in the member's charts, and duplicate codes were counted as single events. Statistical analyses were performed with the chi-square, Kruskal-Wallis, Fisher's exact tests (as appropriate), and discreet time multivariable logistic regression. Two-sided alpha level was set to 0.05. The Bonferroni method was used to correct for multiple comparisons. Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC). This study was approved by the Institutional Review Board.

Of 10 000 wounded subjects randomly selected from DODTR, 9654 were matched to patients that were deployed, but not wounded. Of these pairs, 820 were excluded (138 for death within 90 days, 642 for missing encounters, 11 for pre-existing cancer, and 29 for missing variables of interest), leaving 8834 members in each group for analysis. Characteristics of the injured and uninjured cohorts are described in Supplementary table 1. Most members were non-Hispanic white males in their twenties who were junior enlisted in the U.S. Army and who endured penetrating or blunt trauma from explosive injuries. There were slightly more African-Americans in the uninjured cohort, and slightly more overweight/obese members in the injured cohort. Of note, data on occupational specialty and deployment exposures to chemical and environmental hazards were not available.

Study results are demonstrated in Table 1. Difference of composite cancers between the two cohorts did not reach significance (96 vs. 71, Odds Ratio [OR] 1.3, 95% CI 0.99–1.82, $p = 0.061$). Similarly, there were no differences in solid tumors between the injured and uninjured cohorts (74 vs. 66, OR 1.1, 95% CI 0.80–1.57, $p = 0.498$). However, there were more hematologic neoplasms in injured than uninjured military members (22 vs. 7, OR 3.1, 95% CI 1.34–7.37, $p = 0.008$). Excess hematologic malignancies were primarily lymphomas (14 vs. 3, OR 4.7, 95% CI 1.34–16.26, $p = 0.008$, Bonferroni corrected $p = 0.023$) which were mostly non-Hodgkin B-cell lymphomas. As non-Hispanic white ethnicity/race, obesity, and smoking are known risk factors for non-Hodgkin B-cell lymphomas,[3] a post-hoc discrete time multivariable logistic regression analysis accounting for race/ethnicity (non-Hispanic white vs. other), overweight/obesity (yes or no), tobacco use (yes or unknown vs. no) and median follow-up time was performed, revealing a nearly twelve-fold increased odds of developing hematologic neoplasms in the injured cohort after adjustment (OR 11.64, 95% CI 1.01–134.39, $p = 0.049$).

This study is a first step toward understanding the incidence of cancer among U.S. combat casualties who served during operations in Iraq and Afghanistan. Although cancer diagnoses were rare in this young cohort, there was a suggestion of an increased risk of lymphoma, even after accounting for race/ethnicity, body mass index, tobacco use and follow-up time. Of all the lymphoma types and subtypes included in this analysis (ICD-9-CM codes 201.00–202.98, ICD-10-CM codes C81.0-C96.6), most incident lymphomas were non-Hodgkin B-cell lymphomas. The incidence rate of lymphoma in the injured group was 19.4 cases per 100 000 person years, which is higher (p-value $= 0.021$) than the uninjured group (4.5 cases per 100 000 person years) as well as the background age-adjusted incidence rate of Hodgkin and non-Hodgkin lymphomas among non-Hispanic white males ages 20–30 diagnosed during the same time frame from the Surveillance, Epidemiology and End-Result (SEER) database (8.7 cases per 100 000 person years).[4]

The major limitation of this study is the small numbers of incident cases which is expected given the young age of the cohort. Although injured personnel require more medical care, in the absence of increased incidental solid tumors commonly diagnosed in service members,[5] it is unlikely that selection bias from increased healthcare utilization (e.g., computed tomography imaging) accounted for these results. Similarly, although not captured in the DODTR, it is unlikely that occupational specialty or hazardous occupational exposures accounted for these results. Because there are thousands of military occupation codes, occupational specialty could not be compared between the two cohorts. Although combatants such as infantrymen are more likely to experience trauma, they are also more likely to engage in regular, rigorous exercise and less likely to be sedentary than non-combatant personnel, and hence theoretically at lower risk to develop malignancy, not higher. Although certain chemicals (such as benzene), insecticides and herbicides (Agent Orange) have been associated with Hodgkin and non-Hodgkin lymphoma,[3,6] there is currently no strong evidence that modern day wartime exposures heighten the risk of lymphoma. Many explosive injuries endured among military personnel in Iraq and Afghanistan were from improvised explosive devices (IEDs). Although it is unknown whether IEDs contain carcinogenic chemicals, if they do then this is one possible explanation for our study results.

Although the difference in incident lymphomas between deployed/injured and deployed/uninjured military personnel was nearly 12-fold after adjustment, the absolute difference was small. In this context, the results of this study are hypothesis generating, and serve as a signal that veterans who endured battle injuries in theater may be at an increased risk for lymphoma as they age. Long-term surveillance of combat casualties is required to further define cancer risk and understand possible mechanisms by which lymphoma develops in this population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

C.B.D. analyzed the data and wrote the manuscript; K.S. analyzed the data and edited the manuscript; A.V.D. gathered data from the Veterans Health Administration, analyzed the data, and edited the manuscript; K.K.C. started the study, analyzed the data, and edited the manuscript; E.P. gathered data from the D.O.D.T.R., analyzed the data and edited the manuscript; I.J.S. started the study, gathered the data, analyzed the data, and edited the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article are available within the article and from the DoD Trauma Registry at https://jts.amedd.army.mil/index.cfm/data/registries.

TABLE 1 Results by cancer type

Cancer type	Malignancy	Deployed & injured (n = 8834)	Deployed & uninjured (n = 8834)	*p* value	Bonferroni-corrected *p* value
All	All cancers, n (%)			0.061	n/a
	Yes	95 (1.08)	71 (0.80)		
	No	8739 (98.92)	8763 (99.20)		
	All hematologic cancers, n (%)			0.008	n/a
	Yes	22 (0.24)	7 (0.08)		
	No	8812 (99.76)	8827 (99.92)		
	All solid tumors, n (%)			0.497	n/a
	Yes	74 (0.84)	66 (0.75)		
	No	8760 (99.16)	8768 (99.25)		
Hematologic neoplasms	Leukemia, n (%)			0.317	0.951
	Yes	6 (0.07)	3 (0.03)		
	No	8826 (99.93)	8829 (99.97)		
	Lymphoma, n (%)			0.008	0.023
	Yes	14 (0.16)	3 (0.03)		
	No	8818 (99.84)	8829 (99.97)		
	Plasma cell disorders, n (%)			0.564	1
	Yes	2 (0.02)	1 (0.01)		
	No	8830 (99.98)	8831 (99.99)		
Solid tumors	Lung, n (%)			0.705	1
	Yes	4 (0.05)	3 (0.03)		
	No	8828 (99.95)	8829 (99.97)		
	Breast, n (%)			0.18	1
	Yes	1 (0.01)	4 (0.05)		
	No	8830 (99.98)	8824 (99.91)		
	Gastrointestinal, n (%)			0.818	1
	Yes	9 (0.10)	10 (0.11)		
	No	8823 (99.90)	8822 (99.89)		
	Genitourinary, n (%)			0.777	1
	Yes	24 (0.27)	26 (0.29)		
	No	8808 (99.73)	8806 (99.71)		
	Melanoma, n (%)			0.058	0.462
	Yes	2 (0.02)	8 (0.09)		
	No	8830 (99.98)	8824 (99.91)		
	Head and neck, n (%)			0.739	1
	Yes	5 (0.06)	4 (0.05)		
	No	8827 (99.94)	8828 (99.95)		
	Central nervous system, n (%)			0.527	1
	Yes	6 (0.07)	4 (0.05)		
	No	8826 (99.93)	8828 (99.95)		
	Neuroendocrine, n (%)			0.317	1
	Yes	3 (0.03)	1 (0.01)		
	No	8829 (99.97)	8831 (99.99)		
	Non-melanoma skin cancer, n (%)			0.841	1
	Yes	13 (0.15)	12 (0.14)		
	No	8819 (99.85)	8820 (99.86)		

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Clinical features and survival outcomes in patients with chronic myelomonocytic leukemia arising in the context of germline predisposition syndromes

To the Editor:

Chronic myelomonocytic leukemia (CMML) is an aggressive hematologic malignancy characterized by sustained peripheral blood monocytosis with overlapping features of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN).[1] Chronic myelomonocytic leukemia is an aging disease, characterized by the sequential accumulation of leukemia-associated driver mutations occurring on a background of clonal hematopoiesis (CH).[2] The median age at CMML diagnosis is 73 years, with a male preponderance.[3] Clonal hematopoiesis involving *TET2* or *TET2/SRSF2* mutations skews hematopoiesis with a monocyte bias,[4] and the subsequent accumulation of epigenetic (*ASXL1*) and signaling mutations (*NRAS*, *CBL*, *PTPN11*, *KRAS* and *JAK2*) contributes to CMML development and phenotypic heterogeneity.[5] Germline predisposition syndromes are cancer risk disorders that occur due to constituent aberrations in important homeostatic and tumor suppressor genes. These syndromes can broadly be classified into a) general cancer predisposition syndromes (e.g., *TP53*, *ATM*, *CHEK2*, and *CDK2NA*) and b) cancer risk syndromes specifically increasing risk for hematologic malignancies (e.g., *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, *CEBPA*, *DDX41*, *SAMD9*, and *SAMD9L*).[6] With better sequencing techniques and deeper understanding of cancer predisposition states, greater efforts are being placed to identify germline variants in individuals presenting with hematologic malignancies. This is especially applicable when patients present with antecedent thrombocytopenia (e.g., *RUNX1*, *ANKRD26*, and *ETV6*), syndromic features (e.g., *GATA2*, *SAMD9*, and *SAMD9L*), multiple cancers (e.g., *TP53*, *CDK2NA*, and *CHEK2*), or > 1 first-degree relative with hematologic malignancies.[6] Although germline mutations involving *PTPN11*, *CBL* and *NF1* have been documented in juvenile myelomonocytic leukemia, systematic assessment for germline risk