# Evaluation of Postdeployment Cancers Among Active Duty Military Personnel

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Surpassed only by heart disease, cancer is the second highest cause of all deaths, accounting for 1 in every 4 deaths in the United States. According to the American Cancer Society, there will be more than 1.66 million new cancer diagnoses and an estimated 590,000 Americans will die of cancer in 2015.[1] These figures are similar to those reported by the Surveillance, Epidemiology, and End Results Program for 2014.[2] In its most recent Cancer Trends Progress Report – 2011/2012 Update, the National Cancer Institute reports that death rates for the 4 leading types of cancer as well as all cancers combined have been declining, yet incidence rates of some cancers are on the rise.[3] Worldwide, cancer is a leading cause of both morbidity and mortality, with approximately 14 million newly diagnosed cases and more than 8 million deaths attributed to cancer in 2012.[4]

The evidence indicating a connection between occupational and environmental exposures and cancer has been growing in recent years.[5] This is of particular concern because such cancers are theoretically avoidable, as measures can be taken to avoid these nongenetic risk factors. The World Health Organization estimates that 19% of all cancers are attributed to environmental factors, accounting for 1.3 million deaths per year.[6]

The military population presents a unique opportunity to study links between environmental exposures and cancer. Advantageous aspects of studying cancer among military personnel include well characterized person-time, occupation, and, though not always the case, environmental hazards. Access to routine healthcare including recommended cancer screenings at no cost to the service member and robust electronic medical record systems also facilitate assessments of cancer outcomes in the military population. Furthermore, exposures associated with military deployments may influence cancer risk among military personnel.[7] Possible deployment-related exposures have been documented by the Department of Defense,[8,9] to include potential carcinogens (eg, industrial solvents, jet fuel, air pollution, radiation). Behavioral changes during deployment, such as increased tobacco use, have also been documented.[10] It is thus plausible that military deployment and associated exposures may be risk factors for subsequent cancer among warfighters.

## Cancer in the Military

### Vietnam War

Historically, there has been concern regarding military service-related hazards and potential long-term health implications following military deployment. Postdeployment cancer risk is often at the forefront of the issue, as was the case after the Vietnam War.[11-12] As Richards describes in an article reviewing responses to military-associated environmental and occupational exposures:

> During the latter half of the 20th Century, medical knowledge of and concern about carcinogens grew, and human experimentation guidelines became more stringent. During the Vietnam era, concern for troop exposure to environmental contaminants evolved beyond acute exposures and experimentation to encompass long-term occupational and environmental hazards encountered on the battlefield.[13]

By far, the most prominent exposure in terms of health concern generated during this conflict is the herbicide commonly referred to as Agent Orange. Many veterans of the Vietnam conflict between 1965 and 1972 attribute poor postdeployment health outcomes, including rare cancers, to 2,3,7,8-Tetrachlorodibenzodioxin, an extremely toxic dioxin compound that contaminated one of the compounds used to make the herbicide Agent Orange.[14] The scientific evidence linking postdeployment cancer to Agent Orange exposure during the Vietnam War varies. Some studies have not found higher rates of mortality for outcomes such as soft tissue sarcomas,[15] Hodgkin's disease,[16] non-Hodgkin lymphoma, or testicular cancer in Vietnam veterans.[17,18] Another study of participants of the Agent Orange Registry had similar results, showing no difference in prevalence for any type of cancer when comparing Vietnam veterans to non-Vietnam veterans.[17] However, the CDC Selected Cancer Study reported a higher risk of non-Hodgkin's lymphoma among Vietnam veterans when compared to other men.[19] Frumkin summarized the existing literature on Agent Orange and cancer, reporting consistent

to fairly consistent negative results for increases of soft tissue sarcomas, Hodgkin's disease, and gastrointestinal and brain cancers, but inconsistent results of increases in respiratory and prostate cancers among Vietnam veterans.[20] Still yet, in the current Institute of Medicine Report of the health effects of herbicides used in Vietnam, *Veterans and Agent Orange: Update 2012*,[21] the committee found sufficient evidence of an association between soft tissue sarcomas, non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Hodgkin lymphoma, and limited/suggestive evidence of an association with laryngeal, lung, bronchus, trachea, and prostate cancers as well as multiple myeloma.

### 1991 Gulf War

Similar to those of the Vietnam conflict, many veterans of the 1991 Gulf War are also concerned about the specter of cancer and possible links to hazards associated with their deployment. Notable hazards of concern to service members during the Gulf War include depleted uranium, petroleum products, pesticides, and chemical and biological warfare agents.[22] However, scientific literature shows mixed findings regarding potential associations between Gulf War exposure and postdeployment cancer risk. A particular exposure event of interest during the Gulf War was the destruction of chemical munitions at Khamisiyah, Iraq. While Bullman et al indicated an increased risk of brain cancer mortality among US Army Gulf War veterans who were potentially exposed to low-level chemical warfare agents at Khamisiyah when compared to Gulf War veterans who were not exposed,[23] a later study by Young et al found no excess in brain cancer.[24] In his report on a study on testicular cancer following Gulf War deployment, Levine stated:

> …testicular cancer was found to be the only significantly increased malignancy among deployed Persian Gulf War veterans. The increase became apparent 2 to 3 years after the Persian Gulf War and peaked 4 to 5 years afterward.[11]

Yet, Knoke et al found that although there was an initial increase in testicular cancer immediately following deployment among Gulf War veterans compared to nondeployed Gulf War era veterans, the difference was no longer observed by 4 years postdeployment.[25] Kang et al described "very small rate differences (less than 1.0%) between Gulf veterans and non-Gulf veterans" for both skin cancer and other cancers, with higher rates among the Gulf War veterans.[26] Kang and Bullman reported

> ...no significant excess of overall cancer deaths or deaths from cancer at any specific site among Gulf veterans compared with non-Gulf veteran controls.[27]

In a 2005 report, *Gulf War and Health*, an Institute of Medicine committee found sufficient evidence of an association between combustion products and lung cancer and limited/suggestive evidence of an association between combustion products and nasal, oral, laryngeal, and bladder cancers and between hydrazines and lung cancer. There was inadequate/insufficient evidence to support conclusions regarding potential associations between fuels, combustion products, hydrazines, and nitric acid for numerous types of cancers.[28]

### Operations Enduring and Iraqi Freedom

Deployment-related exposures are now causing the same concerns regarding cancer among service members following support of Operations Enduring Freedom (OEF) and Iraqi Freedom (OIF). Since 2001, in excess of 2 million US military personnel have deployed to Southwest Asia,[29,30] with environmental hazards including but not limited to pollutants from local industry; military-produced exhaust from vehicles, machinery, and generators; open air burn pit emissions and fumes from fires; high levels of indigenous ambient particulate matter; munitions and weapons; depleted uranium; and radiation.[7,31-39] Potential relationships between exposures in theater and cancer diagnoses subsequent to deployment are again a priority for researchers and public health professionals in the military community.

## Baseline Cancer Rates

In the population of OIF and OEF veterans, one expects a certain amount of cancer to occur, irrespective of deployment history and associated deployment-related environmental exposures. Understanding baseline rates of cancer in the military population is useful when evaluating whether cancer among service members with a history of deployment in support of OIF and/or OEF occurs at excessive rates. Cancer investigations in military populations typically focus on specific types of cancer or are specific to a single service branch. This was the case when Yamane reported on cancer incidence from 1989-2002 among Airmen. In comparison to the general US population, he found standardized incidence ratios for all cancers to be lower than expected among male Air Force service members and as expected among female Air Force service members.[40] Zhu et al later compared incidence rates of a select group of cancers (lung, colorectal, prostate, breast, testicular, and cervical cancers) across the military to US civilians. The authors reported lower incidence rates of colorectal, lung, and cervical cancers, and higher rates of prostate and breast cancers.[7] Although these comparisons provide valuable information, knowledge of rates across all service branches for all types of cancers is important.

In June 2012, the Armed Forces Health Surveillance Center published a report describing incident diagnoses of cancers and cancer-related deaths in active duty

military personnel from 2000-2011. Results for the 12-year surveillance period showed a crude incident rate of 55.2 per 100,000 person-years, with the lowest annual incidence rate of 50.3 per 100,000 person-years occurring in 2003 and the highest annual incidence rate of 60.1 per 100,000 person-years occurring in 2009. The data indicated no apparent increasing or decreasing trends in overall or site-specific incident cancer diagnoses. Of note, rates of cancer diagnoses among active duty military members have remained stable since 2000.[41]

## Identifying Carcinogens

More than 900 agents have been evaluated by the International Agency for Research on Cancer for determination of potential to cause cancer. A group of four different categories is utilized to classify every agent: carcinogenic to humans (Group 1), probably or possibly carcinogenic to humans (Group 2A and Group 2B, respectively), unclassifiable as to carcinogenicity in humans (Group 3), and probably not carcinogenic to humans (Group 4). In excess of 125 agents have been classified into Group 1.[42] It is suspected or known that some of these environmental carcinogens can be found in the deployment environment.

## Identifying Cancers

The concern for postdeployment cancer due to potential exposure environmental carcinogens in theater has been raised by service members and veterans alike, as demonstrated by advocacy groups such as Burnpits360 and Operation Purple Heart, which allow for self-reported cancer diagnoses on website registries.[43,44] While these concerns are reasonable and recognized by public health professionals in the military community, they have yet to be supported by epidemiologic studies using appropriate populations and suitable comparison groups. However, there are many factors that should be considered when approaching a study intended to establish whether a history of deployment in support of OIF or OEF is associated with subsequent incidence of postdeployment cancer.

### Age

Age is an important factor to consider when designing any epidemiologic investigation pertaining to postdeployment cancers among service members and veterans. Incidence rates of many types of cancers are known to increase with age. As pointed out by the Armed Forces Health Surveillance Center, generally speaking, US military personnel are younger than the general population.[41] When focused on a chronic disease such as cancer that is known to increase with age, in a younger population, priority should be given to cancers that typically occur with highest incidence falling during the young adult years.

### Latency Periods

The empirical latent period for cancers consists of 2 parts: an induction period ranging from the time between the action of a given component cause (ie, an exposure of interest) and the action of the last causal component (ie, biological onset of the cancer) and a subsequent period ranging from the biological onset of the cancer to the clinical detection of the cancer. Minimum empirical latency periods must be taken into account when deciding which cancers to evaluate in service members and veterans postdeployment, as they must be consistent with study hypotheses. Latency periods vary by different type of cancer of interest, with some cancers having a typical latency period of 15 to 20 years or longer, while some cancers typically have latency periods that are considerably shorter. In the former, these types of cancers would be better suited for postdeployment cancer evaluations among veteran populations of wars that occurred at least that far in the past, such as Vietnam or the first Gulf War, yet they would not be appropriate for OIF/OEF veterans as that much time has not yet passed since exposure. On the other hand, it would be prudent to study the latter types of cancers in a population of OIF/OEF deployed service members because time since deployment and typical latency periods align.

### Biologic Plausibility

When selecting cancer outcomes of interest, the focus should be on cancers that are biologically plausible. For example, the following cancers were selected for an upcoming collaborative study between the US Army Public Health Command, the Navy and Marine Corps Public Health Center, and the Department of Veterans Affairs: melanoma, leukemia, lymphoma, and brain, thyroid, testicular, and breast cancers. Those cancers have peak incidence during young adult years, which matches the demographics of our service members with potential exposure(s) of interest.[45] These selections were also made based on suspected or known occupational or environmental risk factors.[46-49] The latent periods of these cancers are also in accordance with investigating the association between in-theater environmental exposures and postdeployment cancer among service members formerly deployed to OIF or OEF.[50,51]

## Karshi-Khanabad: An Example

Recent efforts to understand possible associations between environmental exposures in theater and postdeployment cancer diagnoses include an investigation conducted at the US Army Public Health Command, which explored multiple cancer outcomes among service members formerly deployed to Karshi-Khanabad, an air base located in southeastern Uzbekistan used to support missions in neighboring Afghanistan during OEF.[39] Active

duty members of the US armed forces were located at the Karshi-Khanabad Air Base, also known as K2 or Camp Stronghold Freedom, between 2001 and 2005. General conditions were known to be harsh. Historically, the site was used by the Soviet military to support operations in Afghanistan in the late 1970s. During this time, the Soviet Air Force maintained a fleet of various bomber aircraft at K2, which required an underground fuel distribution system. Furthermore, construction of military equipment (including missiles) in the Soviet era used materials such as asbestos and radioactive material. An occupational and environmental survey performed at K2 in November 2001 by the Center for Health Promotion and Preventive Medicine-Europe.found underground jet-fuel plumes and surface dirt contaminated with asbestos and radioactive uranium.[38] Periodic high levels of dust and other particulate matter (PM) in the air due to seasonal dust storms was also noted.

Although efforts for remediation of the environmental health risks present at K2 were made (eg, covering the contaminated areas with clean soil and declaring these areas "off-limits"), exposure to the toxicants mentioned above during deployment to K2 was plausible. In other settings, exposure to jet fuel plumes, asbestos-contaminated soil, radioactive materials, and/or dust and PM have resulted in documented adverse health outcomes, including both acute and chronic disease. As such, this investigation focused on identifying the frequency of postdeployment medical encounters for health outcomes consistent with exposure to the identified toxicants, with an emphasis on cancer due to the various types among personnel previously deployed to K2.[52-61]

At the request of a US Central Command Force Health Protection Officer, an evaluation of health outcomes among active duty military personnel with a history of deployment to K2 was conducted to address concerns for exposure(s) of health consequence among Army, Air Force, and Marine Corps personnel deployed to the air base. The Army Public Health Command subsequently conducted a comparative health assessment using one year of postdeployment medical follow-up. In the context of the above discussion regarding latency periods for cancer outcomes, the US Army Special Operations Command Surgeon later requested that the original analysis be repeated to incorporate up to 10 years of follow-up, using all available postdeployment medical encounter data. In response to this request, a retrospective cohort study was conducted in order to assess postdeployment health status among service members formerly deployed to K2. This was accomplished by linking K2 deployment rosters from 2001-2005 with postdeployment inpatient and outpatient medical records from 2001-2011. Additionally, a reference group of personnel stationed in South Korea during the same period was selected for comparison. The results are presented in the Table.

The results of this analysis are somewhat mixed, with relative risks lower than one for about half of the specific cancer type outcomes and relative risks higher than one for the other half. The only statistically significant findings were for malignant melanoma and neoplasms of lymphatic and hematopoietic tissues (excluding Non-Hodgkin Lymphoma and Leukemia; highlighted in bluein the Table), indicating a risk approximately 3.7 times greater and 5.6 times greater among those deployed to K2 compared to those stationed in Korea. Concern for postdeployment cancer at K2 is warranted, given the relative risks above one, irrespective of statistical significance and the limitations of this particular analysis. Although the environmental hazard risk profile may differ somewhat between K2 and other OIF/OEF locations, these results bolster the rationale for conducting broader studies to evaluate incidence of cancers following military deployment.

## Challenges and Limitations

Long latency periods, low incidence rates of most types of cancer, and appropriate selection of nondeployed controls present challenges for investigators wishing to evaluate postdeployment cancer risk. Only very recently has a sufficient amount of time elapsed in order to assess cancer incidence following OIF and OEF deployments. Given the low incidence rates of most types of cancers, researchers must take care to ensure that study sample sizes are large enough to provide adequate statistical power to detect associations, should they exist. Epidemiologic studies comparing cases to controls with respect to OIF/OEF deployment status presents a challenge due to a high prevalence of deployment for any military personnel serving between 2001 and 2014. As such, a large well-powered study is imperative.

Additional challenges include a lack of data on individual environmental exposures over time as well as a lack of exact locations of each service member during military deployments. As a result, deployment in general is typically used as a proxy for deployment-associated exposures. Also limiting to epidemiologic studies such as these is the lack of information on behavioral habits such as smoking, which can have significant effects on certain types of cancer.

Cancer case definitions are often based on ICD-9-CM coded medical encounter data from military medical record databases. Using administrative records to

Age-Adjusted Relative Risks and Corresponding 95% Confidence Intervals for Cancer Outcomes, Comparing US Military Personnel Deployed to K2 to US Military Personnel Stationed in Korea

| Outcome | K2 | | | | Korea | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age | | | | Age | | | | | |
| | Young | | Old | | Young | | Old | | Age-Adjusted* | |
| | n | % | n | % | n | % | n | % | RR | 95% CI |
| All cancer | 11 | 0.39 | 50 | 1.21 | 41 | 0.28 | 133 | 1.00 | 1.23 | 0.92-1.65 |
| Brain cancer | 1 | 0.04 | 4 | 0.10 | 0 | 0.00 | 8 | 0.06 | 2.04 | 0.68-6.09 |
| Cervical cancer | 0 | 0.00 | 0 | 0.00 | 1 | 0.01 | 0 | 0.00 | 0 | -- |
| Leukemia | 0 | 0.00 | 1 | 0.02 | 5 | 0.03 | 4 | 0.03 | 0.43 | 0.05-3.63 |
| Malignant melanoma | 1 | 0.04 | 7 | 0.17 | 3 | 0.02 | 5 | 0.04 | 3.68 | 1.35-10.04 |
| Neoplasm of bone/connective tissue/skin/breast | 1 | 0.04 | 3 | 0.07 | 5 | 0.03 | 9 | 0.07 | 1.06 | 0.35-3.22 |
| Neoplasm of colon/rectum | 2 | 0.07 | 3 | 0.07 | 2 | 0.01 | 9 | 0.07 | 1.6 | 0.57-4.51 |
| Neoplasm of digestive organs/peritoneum | 0 | 0.00 | 1 | 0.02 | 1 | 0.01 | 6 | 0.05 | 0.48 | 0.06-3.95 |
| Neoplasm of female breast | 1 | 0.04 | 3 | 0.07 | 1 | 0.01 | 9 | 0.07 | 1.35 | 0.43-4.24 |
| Neoplasm of genitourinary organs | 1 | 0.04 | 4 | 0.10 | 2 | 0.01 | 8 | 0.06 | 1.74 | 0.60-5.08 |
| Neoplasm of lip/oral cavity/pharynx | 1 | 0.04 | 3 | 0.07 | 0 | 0.00 | 6 | 0.05 | 2.18 | 0.64-7.49 |
| Neoplasm of lung/bronchus | 0 | 0.00 | 4 | 0.10 | 0 | 0.00 | 0 | 0.00 | -- | -- |
| Neoplasm of lymphatic and hematopoietic tissue | 2 | 0.07 | 5 | 0.12 | 6 | 0.04 | 0 | 0.00 | 5.64 | 1.70-18.70 |
| Neoplasm of respiratory/intrathoracic organs | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 2 | 0.02 | 0 | -- |
| Neoplasm of testis | 1 | 0.04 | 2 | 0.05 | 8 | 0.05 | 12 | 0.09 | 0.57 | 0.17-1.91 |
| Non-Hodgkin lymphoma | 0 | 0.00 | 3 | 0.07 | 4 | 0.03 | 8 | 0.06 | 0.89 | 0.25-3.26 |
| Prostate cancer | 0 | 0.00 | 4 | 0.10 | 0 | 0.00 | 18 | 0.14 | 0.71 | 0.24-2.10 |
| Neoplasm of other and unspecified sites | 0 | 0.00 | 3 | 0.07 | 3 | 0.02 | 27 | 0.20 | 0.33 | 0.10-1.09 |
| Neoplasm of uncertain behavior (plasma cells) | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | -- | -- |

*RR indicates relative risk. CI indicates confidence intervals.

ascertain cancer cases may result in false positives. For example, not only are some cancers not well defined, but some require several encounters, sometimes with multiple specialists or requiring different medical procedures, in order to make a definitive diagnosis. In such circumstances, an ICD-9-CM code may reflect a true case of cancer or the medical encounter may signify that a patient is in the process of fulfilling diagnostic evaluations necessary to rule out cancer. Using medical encounter data for case ascertainment presents another limitation of this study: whereas medical encounter data capture is complete for service members who remain in service, the same cannot be said for personnel who leave military service. This becomes particularly problematic when studying chronic health outcomes such as cancer, with the latency periods often years after exposure, beyond the average time of military service. Investigators are currently attempting to establish methodology for linking medical encounter records from military service with medical encounter records from the Veterans Administration (VA) in order to minimize loss of follow up due to attrition from military service. However, this methodology will still fail at perfect case capture, as a certain portion of veterans are not VA beneficiaries or simply choose to obtain healthcare services outside the VA health system. It has been suggested that state cancer registries be used as additional sources of data in postdeployment cancer studies, however, the feasibility of this approach has yet to be explored.

Although many challenges are presented to researchers seeking to determine whether or not cancer incidence is elevated among military service members and veterans formerly deployed in support of OIF and OEF relative to personnel without a history of deployment, it is an important topic that is worthy of public health efforts and resources.

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