Editorial

Challenges in Investigating the Association Between Agent Orange and Cancer: Site-Specific Cancer Risk and Accuracy of Exposure Assessment

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The US military in Vietnam removed vegetative cover near base camps, uncovered enemy forces hiding in thick forests, and destroyed food crops available to enemy forces by spraying herbicides, often by aircraft.[1] One mixture, Agent Orange, contained 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Individuals involved in mixing, spraying, maintaining, and storing Agent Orange and the other herbicide formulations containing 2,4,5-T were exposed to TCDD. Those who may have been exposed include individuals who contacted herbicide-sprayed vegetation or ingested herbicide-contaminated food or water. This included annually more than 850,000 personnel supporting the Republic of Vietnam, including 36,000 Republic of Korea troops.[2] The true number of personnel from either side of the conflict and noncombatant Vietnamese actually exposed to TCDD, and the amount of their exposures, remains unknown.

In this issue of *Cancer,* Yi and Ohrr analyzed cancer incidence among Korean veterans of the Vietnam War (Korean veterans).[3] They compared cancer risk from 1992 through 2003 across Agent Orange exposure categories determined by a model using time and proximity of military units to geographic spray patterns.[4] The findings add to our overall understanding of the health risks from exposures to Agent Orange. Large numbers of individuals were potentially exposed to Agent Orange in Vietnam and this report reminds us of the critical importance of accurate exposure assessment and the desire for epidemiologic studies to provide scientific clarity, even in the most difficult of circumstances.

This is the third report of the cancer experience of Korean veterans.[3] In 2011, Yi and Ohrr reported cause-specific mortality for a cohort of 186,760 veterans (19,124 deaths) during the years 1992 through 2005 and compared it with the age-adjusted national mortality rates for Korean males using standardized mortality ratios (SMRs).[5] In 2013, using the Korean National Cancer Incidence Database to identify cases and calculate national male age-adjusted cancer-specific incidence rates and standardized incidence ratios (SIRs), Yi released an analysis of cancer incidence from 1992 through 2003 among 185,265 veterans (9058 cancer cases).[6] The current report used a subset of the previously identified incident cancers (8592 cancer cases) and calculated age-adjusted hazards ratios (HRs) for 180,251 veterans based on 2 qualitative TCDD exposure classifications (high vs low and no, low, moderate, and high exposure).

The evidence of an association between TCDD exposure and site-specific cancers is inconsistent across the reports concerning Korean veterans. The new analysis demonstrated significantly elevated HRs among the high-exposure group for mouth, salivary, stomach, small intestine, and all cancers combined, with borderline elevations noted for liver and lung and bronchus cancers. The authors reported that statistically significant increases in cancer risk occurred across the 4 qualitative exposure categories for all cancers and cancers of the salivary gland, small intestine, and liver, but acknowledged that the increases in site-specific cancer risk are neither monotonic nor greatest in the highest exposure classification.[3] By contrast, the observed incident and fatal cancers for the mouth, salivary gland, and stomach were below the number expected

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using age-adjusted rates for all Korean men.[5,6] Yi and Ohrr have suggested that the healthy worker effect may account for these inconsistencies.[3]

Comparing the findings for Korean veterans with the review by the Institute of Medicine's (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides is illustrative.[1] The IOM conducts a biannual review of the epidemiologic evidence classifying it as 1) sufficient, 2) limited or suggestive, or 3) inadequate or insufficient.

- Cancers for which there is sufficient evidence of an epidemiologic association with TCDD-contaminated herbicides include soft tissue sarcomas, chronic lymphocytic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma. Korean veterans were found to have fewer connective and soft tissue cancers or lymphoid leukemias than expected. They demonstrated slight, but not statistically significant, increases in the incidence of non-Hodgkin lymphoma (SIR, 1.05 [95% confidence interval (95% CI), 0.90-1.21] and HR, 1.09 [95% CI, 0.81-1.47]) and Hodgkin lymphoma (SIR, 0.96 [95% CI, 0.55-1.69] and HR, 1.27 [95% CI, 0.41-3.93]).[3,5]
- Cancers for which there is limited or suggestive evidence include cancers of the prostate, lung, and larynx, and multiple myeloma. The mortality from, and incidence of, prostate cancer among Korean veterans was found to be slightly elevated compared with national mortality and incidence rates (SMR, 1.05 [95% CI, 1.76-1.45] and SIR, 1.22 [95% CI, 1.02-1.46]).[5,6] However, when using the TCDD exposure index, Korean veterans with high exposure had a decreased risk of prostate cancer compared with those with low exposure (HR, 0.70 [95% CI, 0.49-1.00]).[3] Mortality from lung cancer and laryngeal cancer was less than expected for this cohort. However, lung cancer (HR, 1.12 [95% CI, 1.00-1.27]) and laryngeal cancer (HR, 1.21 [95% CI, 0.87-1.69]) incidence was found to be slightly elevated in the most recent analysis by Yi and Ohrr.[3] Korean veterans experienced elevated, but not statistically significant, mortality and cancer incidence rates for multiple myeloma (SMR, 1.05 [95% CI, 0.77-1.44]; SIR, 1.14 [95% CI, 0.86-1.51]; and HR, 1.14 [95% CI, 0.65-2.01]).
- Cancers for which there is insufficient or inadequate evidence include cancers of the oral cavity, pharynx, nasal cavity, pleura, mediastinum, and other unspecified sites in the respiratory and intrathoracic organs. Korean veterans classified in the high-exposure category were at a significantly greater risk compared with those classified in the low-exposure category for cancers of the mouth and salivary glands. The highest HRs for these cancers were noted in the group with moderate exposure, but the HR for the high-exposure group was also elevated.

Perhaps the greatest challenge in determining with accuracy the relationship between TCDD exposure and human illness has been inadequate exposure assessment, particularly for those present in Vietnam during the spraying of Agent Orange. Exposure information was not collected at the time of spraying, thereby forcing researchers to attempt to reconstruct past exposures. Researchers have used for this purpose survey data based on individual recall, military records of spray patterns and personnel deployment in Vietnam, and lipid-adjusted TCDD serum (blood) concentrations collected $\geq$10 years after exposure. The most reliable and efficient exposure assessments have been those in which blood sample results correlate well with qualitative exposure models. In those circumstances, although a relatively small number of individuals had blood samples taken, the predictive modeling has been applied to an entire cohort with a reasonable expectation of reliability. For example, 15 to 37 years after worker exposures took place, TCDD blood levels among 253 of 5172 herbicide manufacturing workers remained strongly correlated with their duration of employment in the production of contaminated 2,4,5-T.[7]

Blood sampling of Vietnam veteran cohorts has been reported. US Vietnam veterans directly involved in herbicide spraying operations were found to have elevated blood TCDD levels >10 years after exposure. In 1987, US Air Force veterans involved in the Vietnam herbicide spraying operations who served as ground crew or enlisted men were reported to have higher TCDD blood levels than flight crew and officers.[8] In addition, their levels were higher than those of 646 US Vietnam War ground troops sampled in 1986 and 1987.[9] TCDD blood levels measured in 1986 and 1987 among US Vietnam veteran ground troops did not differ from those of 97 US veterans who served during the same time period outside of Vietnam. In 1987, an exposure reconstruction effort based on modeling proximity to herbicide spray patterns and military deployment records did not correlate or predict blood TCDD levels in US Vietnam ground troops. Not surprisingly, Yi et al reported even lower blood TCDD levels and a similar lack of correlation in 102 Korean veterans who were sampled in 2001.[10] When TCDD blood sample results do not correlate with reconstructed exposure models, it could be because the models could be incorrect,

the blood sample results may not reflect past exposures, or both.

Efforts to improve TCDD exposure modeling have continued.[4] The IOM Committee on Making Best Use of the Agent Orange Exposure Reconstruction Model recognized some value in the application of the model,[11] which was ultimately used by Yi and Ohrr.[3] The committee reported that there are valid reasons to apply the model and to remain cautious when interpreting its results. The committee stated that using this model and finding a positive association with a previously established health outcome would "...provide evidence in support of the veterans having experienced health problems as a result of herbicide exposure...(and)...credibility to the ability of the model to classify exposure."[11] The committee cited several possible interpretations for a negative association with a previously established health outcome including: 1) the inability to accurately classify exposure; 2) an accurate exposure classification but exposure levels that were insufficient to increase cancer risk; or 3) the association between TCDD and the established health outcome was spurious. Despite the large size of the Korean veteran cohort, none of the site-specific cancer outcomes classified by the IOM as having either sufficient or limited evidence of an association were found to be statistically significantly elevated. Nevertheless, the positive association reported for mouth and salivary cancers may encourage the IOM to reclassify these cancers as having limited or sufficient evidence. It will be interesting to observe how the IOM interprets the credibility of these results given the use of the exposure model and the negative results for the other cancer outcomes.

Epidemiologic studies of associations between low-level chemical exposures and site-specific cancer outcomes are difficult, requiring the identification and tracking of large populations over many years, an ability to diagnose and report site-specific cancer outcomes, and an accurate assessment of exposure. Each year during the Vietnam War, >850,000 troops supporting the Republic of Vietnam could have been exposed to TCDD. Exposures may also have occurred to the Viet Cong, to regular troops supporting the Democratic Republic of Vietnam, and to the resident Vietnamese population living or occupying areas near the spray zones and US air bases. Yi and Ohrr have demonstrated that it is possible to identify and follow a large cohort of these individuals and to diagnose and report their cancer outcomes.[3] Ideally, follow-up would have begun immediately after the exposure period. Follow-up for this cohort did not begin until 1992, approximately 20 years later than possible exposures to Agent Orange. Elevated site-specific cancer risks occurring within the first 20 years after exposure may have been missed. Additional follow-up of their cohort could be extended beyond 2003. Perhaps other large-scale epidemiologic studies of potentially exposed cohorts will follow. However, a critical difficulty, one that may never be overcome, is accurate exposure assessment. Without reliable exposure assessments we will not know who was exposed and to what degree, or whether modest increases in cancer risk have been overwhelmed by exposure misclassification.

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