

CANCER IN US AIR FORCE VETERANS OF THE VIETNAM WAR

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Introduction

The herbicide Agent Orange was a 1:1 mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and was contaminated, from less than 0.05 to almost 50 parts per million, with 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin)¹. A recent review by the National Academy of Sciences² concluded that there is sufficient evidence of an association between exposure to herbicides and/or dioxin and soft tissue sarcoma, non-Hodgkin's lymphoma and Hodgkin's disease, and limited/suggestive evidence of an association between dioxin or herbicide exposure and cancer of larynx, bronchus, prostate and multiple myeloma.

This report summarizes a study of cancer in veterans of Operation Ranch Hand (RH), the unit responsible for the aerial spraying of herbicides, including Agent Orange, in Vietnam from 1962 to 1971, and in a Comparison (C) cohort of other Air Force veterans who served in the Southeast Asia (SEA) region during the same period that the Ranch Hand unit was active but who were not involved with spraying herbicides. These results were accumulated during the post-service period from each veteran's departure from SEA to December 31, 1999 in men participating in the ongoing Air Force Health Study, a 20-year prospective study of the health, mortality and reproductive outcomes of Ranch Hand veterans. This report updates our previous cancer study by addressing veteran concerns that both cohorts may have experienced an increased risk of cancer, and by addressing the possibility that service in Vietnam, as opposed to service in SEA, may have increased cancer risk.

Methods and Materials

The details of study design and subject selection are published elsewhere³. The study seeks to determine whether veterans of Operation Ranch Hand have experienced adverse health and whether those health effects, if they exist, can be attributed to exposure to herbicides or their dioxin contaminant. The study includes periodic physical examinations and in-person interviews, conducted in 1982, 1985, 1987, 1992, 1997, and 2002. Participation was voluntary and informed consent was given at the examination sites. Information on cancer was derived from physical examinations and medical records. Malignancies were coded from medical records following the rules and conventions of the International Statistical Classification of Diseases and Related Problems, Tenth Revision (ICD 10). Malignancies discovered at death were coded from the underlying causes of death on death certificates. We classified underlying causes of death in accordance with the rules and conventions of the 9th revision of the International Classification of Diseases (ICD 9). Two medical coders independently reviewed medical records and death certificates and a third coder compared the combined results, checking the accuracy and appropriateness of each code, and adjudicating any differences.

We obtained age and calendar-year specific national incidence and mortality rates⁴ for any cancer and cancer, by site and race. We defined Melanoma by ICD 10 codes C440-C449 and morphology codes 872-879. This is parallel to defining melanoma by the ICD 9 code 172. We excluded cases with morphology codes 9590-9989 from the definition of cancer of Buccal cavity (ICD: C000-C009, C019-C029, C030-C069, C079-C119, C129-C148), Digestive System (ICD: C150-C189, C199, C209-C212, C218, C220-C221, C239-C260, C268-C269, C480, C488), Respiratory System (ICD: C300-C301, C310-C329, C339-C349, C381-C384, C388, C390, C398, C399), Lung and Bronchus (ICD: C340-349), Bones and Joints (ICD: C400-C419), Soft Tissue including heart (ICD: C380, C470-C479, C490-C499), Other non-epithelial skin (ICD: C440-C449, excluding morphology codes: 8000-8004, 8010-8012, 8070-8076, 8090-8096, 8720-8790), Genitalia (ICD: C619-C639, C600-C609), Prostate (ICD: C619), Urinary system (ICD: C649, C659, C669-C689), Eye and Orbit (ICD: C690-C699), Brain and other nervous system (ICD: C700-C719, C720-C729), and Endocrine system (ICD: C379, C740-C759, C739). Lymphomas (morphology codes: 9650-9667, 9590-9595, 9670-9717), Multiple Myeloma (morphology codes: 9731-9732) and Leukemia (morphology codes: 9820-9827, 9860-9868, 9871-9874, 9890-9894, 9800-9804, 9830, 9850, 9870, 9880, 9900, 9910, 9930-9941) were combined together for analysis because of small numbers. We classified tumors with morphology codes 9720-9723, 9740, 9741, 9760-9764, 9950-9989, and ICD codes C760-C768, C420-C424 and C770-C779 with morphology codes 8000-9589 as Ill-defined. We defined cancer at any site as cancer included in any of the previous definitions. We classified tumors of the skin not included in the previous definitions, for which national rates are not available, into a category named "Other skin malignancies".

Dioxin levels were measured on a lipid weight basis in serum collected from veterans who completed the 1987 physical examination. Additional measurements were made in 1992 and 1997. For those veterans whose dioxin level was not measured in 1987, the subsequent measure was extrapolated to 1987 using a first-order kinetics model with a constant half-life of 7.6 years. Non-detectable (non-quantifiable) dioxin levels were replaced by the value of the limit of detection (limit of quantitation) divided by the square root of 2.

To account for variation across time in the types and quantities of herbicides sprayed by Operation Ranch Hand, we assigned each veteran to one of four tour date categories defined by the year his tour ended; these were 'Before 1962 or After 1972' (when no herbicide was sprayed), '1962-1965' (pre-Agent Orange), '1966-1970' (predominantly Agent Orange) and '1971-1972' (Post Agent Orange)¹. We attempted to isolate a 'Vietnam' effect two ways: by a) restricting time spent in SEA to at most 2 years, and b) by restricting Comparison veterans to those who spent 0% and Ranch Hand veterans to those who spent 100% of their SEA service in Vietnam. The 2-year cut point was chosen after an examination of scatter plots of the percentage of SEA service spent in Vietnam versus years spent in SEA in an attempt to identify Ranch Hand veterans who spent the majority of their SEA service in Vietnam and Comparison veterans who spent the majority of their SEA service outside of Vietnam. The 2-year cut point appeared to provide the best single cut to serve this purpose. To this end, we assigned each veteran to one of two categories of time spent in SEA, defined by 'At most 2 years in SEA', and 'More than 2 years in SEA'. We also assigned each veteran to one of two categories of the percentage of SEA service spent in Vietnam, defined by 'Comparison: 0% and Ranch Hand: 100%' and 'Comparison: >0% and Ranch Hand: <100%'. We estimated body mass index (BMI) as weight (kg) divided by the square of height (m), defined a pack-year as smoking one pack of cigarettes per day for one year, and a drink year as drinking 2

ounces of 80 proof whiskey (or 12 ounces of beer or one glass of wine) per day for one year. We assigned each veteran to one of three military occupation categories (officer, enlisted flyer, enlisted ground).

We conducted two series of analyses: a) external contrasts of cancer incidence in each cohort relative to the expected experience derived from U.S. national rates, and b) internal contrasts of the study cohorts with regard to cancer incidence. In both series, we categorized malignancies by site and all sites combined. We employed multiplicative Poisson regression models to compare cancer incidence with national rates, summarized by the Standardized Incidence Ratio (SIR), and proportional hazards models to contrast cohorts with regard to cancer incidence, summarized by the Relative Risk (RR). The external analyses were restricted to veterans who had participated in at least one physical examination or interview. The internal analyses were restricted to veterans who had participated in at least one physical examination and who had a non-missing dioxin measurement. Veterans with cancer during or prior to their service in SEA were excluded from all analyses. Sample size reductions are summarized in Table 1.

Table 1. Sample size reduction in US Air Force veterans.

| | Ranch Hand | Comparison | Total |
|--|------------|------------|-------|
| Attended at least one examination or interview | 1196 | 1785 | 2981 |
| Cancer prior to service in Southeast Asia | 7 | 6 | 13 |
| Cancer during service in Southeast Asia | 0 | 3 | 3 |
| Net | 1189 | 1776 | 2965 |
| Missing Dioxin ^a | 180 | 347 | 527 |

a. These exclusions were taken into account for the internal analysis of malignancy versus dioxin category.

We assigned each veteran to one of four dioxin categories based on his cohort (Ranch Hand, Comparison), dioxin concentration, and half-life extrapolated initial dioxin concentration. Comparison veterans with a dioxin measurement were assigned to the 'Comparison' category. Ranch Hand veterans with a dioxin measurement not exceeding 10 parts per trillion (ppt) were assigned to the 'Background' category. Ranch Hand veterans with dioxin exceeding 10 ppt had their initial dioxin at the end of service in Vietnam estimated using a first-order kinetics model with a constant half-life of 7.6 years. Ranch Hand veterans with a dioxin body burden exceeding 10 ppt and an initial dioxin less than or equal to 118.5 ppt, the median dioxin among those with dioxin exceeding 10 ppt, were assigned to the 'Low' category and those with an initial dioxin greater than 118.5 ppt were assigned to the 'High' category. We analyzed by category of time spent in SEA and category of the percentage of time spent in Vietnam. We report for each site the number of first incident cases in each dioxin category and associated relative risks.

Results and Discussion

No significant increase in the incidence of cancer at any site relative to national rates (Table 2) was found in White veterans in either cohort (RH: SIR=1.09, p=0.34, C: SIR=0.94, p=0.47). The incidence of melanoma was significantly increased in Ranch Hand veterans (SIR= 2.33, p<0.001), and the incidence of cancer of the genitalia (RH: SIR=1.42, p=0.04, C: SIR=1.51, p<0.001) and prostate (RH: SIR=1.58, p=0.01, C: SIR=1.68, p<0.001) were significantly increased in both cohorts, however. Adjustment for four date revealed significant increases in risk among those

who served in Vietnam between 1966 and 1970, the period of heaviest Agent Orange spraying.

Table 2. Standardized incidence ratios comparing cancer incidence rates in White US Air Force veterans with national incidence rates.

| Site | Ranch Hand | | | | Comparison | | | |
|----------------|------------|--------|------|---------|------------|--------|------|---------|
| | OBS | EXP | SIR | p-value | OBS | EXP | SIR | p-value |
| Any site | 134 | 123.34 | 1.09 | 0.34 | 163 | 172.54 | 0.94 | 0.47 |
| Buccal Cavity | 6 | 6.48 | 0.93 | 0.90 | 5 | 8.90 | 0.56 | 0.18 |
| Digestive | 16 | 26.43 | 0.61 | 0.03 | 31 | 36.38 | 0.85 | 0.38 |
| Respiratory | 33 | 29.19 | 1.13 | 0.47 | 48 | 40.05 | 1.20 | 0.22 |
| Lung, Bronchus | 30 | 23.54 | 1.27 | 0.19 | 45 | 32.70 | 1.38 | 0.04 |
| Melanoma | 17 | 7.30 | 2.33 | <0.001 | 15 | 10.24 | 1.46 | 0.15 |
| Genitalia | 38 | 26.85 | 1.42 | 0.04 | 55 | 36.46 | 1.51 | <0.001 |
| Prostate | 36 | 22.82 | 1.58 | 0.01 | 54 | 32.08 | 1.68 | <0.001 |

Among veterans who spent less than two years in Southeast Asia, the risk of cancer at any site was significantly increased in the Low (RR=2.23, p=0.01) and High (RR=2.02, p=0.04) dioxin exposure categories (Table 3). In the combined cohort, the risk of cancer at any site increased significantly with serum dioxin level (RR=1.24, p=0.04). Corresponding results in Ranch Hands who spent 100% of their Southeast Asia tour of duty in Vietnam were similar.

Table 3. Relative risks of cancer at any site by dioxin category in White US Air Force veterans who spent less than 2 years in Southeast Asia.

| | Trend (N=1,192) | Comparison (N=580) | Ranch Hand | | |
|---------------|--------------------|-----------------------|-----------------------|----------------|-----------------|
| | | | Background (N=287) | Low (N=151) | High (N=174) |
| Count (%) | | 34 (5.86) | 28 (9.76) | 22 (14.57) | 15 (8.62) |
| Relative Risk | 1.24 | | 1.44 | 2.23 | 2.02 |
| P-Value | 0.04 | | 0.21 | 0.01 | 0.04 |

a. Based on a test of significance of the coefficient of log(dioxin) in a proportional hazards model on the combined cohort.

These data suggest that exposure to dioxin or dioxin-contaminated herbicides may be associated with cancer in Ranch Hand veterans

References

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