

CANCER IN VETERANS OF OPERATION RANCH HAND AFTER ADJUSTMENT FOR CALENDAR PERIOD, DAYS OF SPRAYING, AND TIME SPENT IN SOUTHEAST ASIA

Michalek, Joel E PhD¹ and Pavuk, Marian MD, PhD²

1. Department of Epidemiology and Biostatistics, University of Texas Health Science Center at San Antonio
San Antonio, Texas 78229

2. Division of Health Studies, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia 30345

Introduction

This report summarizes a study of cancer in veterans of Operation Ranch Hand¹, the unit responsible for the aerial spraying of herbicides, including Agent Orange, in Vietnam from 1962 to 1971, and in a Comparison 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 did not spray herbicides. These results were accumulated during the post-service period from each veteran's departure from SEA to September 30, 2004 in men participating in the Air Force Health Study (AFHS) a 20-year prospective study of the health, mortality and reproductive outcomes of Ranch Hand veterans. This report updates our previous cancer studies, but differs by a) addressing the number of days of actual herbicide spraying, calendar period of service, and time spent in SEA, b) stratifying to focus our investigation on subgroups that we expected to be at increased risk (regardless of the significance of interaction terms in a statistical model), and c) choosing cut points for stratification based on external information rather than statistical significance.

Materials and Methods

The AFHS (study) sought to determine whether veterans of Operation Ranch Hand experienced adverse health and whether those health effects, if they exist, could be attributed to exposure to herbicides or their TCDD contaminant. The details of the study design and subject selection are published elsewhere. The study compared the health and cumulative mortality experience of Ranch Hand veterans with a comparison group of other Air Force veterans who served in SEA during the same period (1962 to 1971) that the Ranch Hand unit was active and who were not involved with spraying herbicides. Comparisons were matched to Ranch Hands on age, race and military occupation. The study included periodic analyses of non-combat mortality, in-person interviews, physical examinations, and reproductive outcomes. Physical examinations were conducted in 1982, 1985, 1987, 1992, 1997 and 2002. Veterans who participated in at least one of the first 5 examinations were included. The study protocol was reviewed and approved by the Institutional Review Boards of the participating organizations. Participation was voluntary and consent forms were signed at the examination site prior to study.

In 1987, blood from willing participants was collected and assayed for TCDD in parts per trillion (ppt) on a lipid weight basis. Veterans with no quantifiable TCDD result in 1987, those who refused in 1987 and subjects new to the study were also asked to give blood for the assay at the 1992, 1997, and 2002 examinations. Consistent with the 2002 AFHS report, for those veterans whose TCDD 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) TCDD levels were replaced by the value of the limit of detection (limit of quantitation) divided by $\sqrt{2}$.

We assigned each veteran to one of four exposure categories, named "Comparison", "Background", "Low" and "High", according to his group, 1987 TCDD level and initial TCDD level. The initial TCDD level at the end of the tour of duty in Vietnam was estimated in Ranch Hands having 1987 TCDD levels above background using a constant half-life of 7.6 years. The Background category was comprised of Ranch

Hands with 1987 TCDD \leq 10 ppt. The cut point separating the Low and High categories (91 ppt) was the median initial TCDD level among all Ranch Hands having TCDD levels measured in 1987 greater than 10 ppt. The category labels “Low” and “High” and the category definitions coincide with those used in previously published analyses; veterans assigned to the “Low” and “High” TCDD exposure categories had elevated TCDD levels relative to Comparisons.

For each veteran, tour dates, the number of days spent in Vietnam and the number of days spent in SEA, and for each Ranch Hand veteran the date of the last day of service in the Ranch Hand unit and for each Comparison veteran the date of the last day of service in SEA were extracted from military records. Days of spraying were computed based on tour dates and ‘Herbs Tape’ data.

Cancer incidence data were obtained from medical records. Malignancies were coded following the rules and conventions of the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM). Malignancies discovered at death were coded from the underlying causes of death on death certificates. We defined “all-site SEER cancer” as a malignancy included in any of the National Cancer Institute Surveillance Epidemiology and End Results (SEER) anatomical category definitions. All-site SEER cancer included the first diagnosed cancer for each individual with any cancer diagnosis.

The analyses were based on cumulative all-site SEER cancer incidence from January 1, 1982 to September 30, 2004. We employed Cox proportional hazards models to contrast the background, low and high categories with the Comparison category with regard to cancer incidence. All analyses were adjusted for year of birth, Body Mass Index (BMI) at the qualifying tour, military occupation, skin reaction to sun exposure (burns painfully or freckles with no tan, burns or tans mildly, tans deep brown), eye color (brown, hazel/green, gray/blue), race (Black, non-black), and smoking history in 1982 (pack-years). We tested for trend by assessing the significance of the coefficient of log(TCDD) in a fully adjusted Cox proportional hazards model of time-to-diagnosis in the combined cohort with log(TCDD) entered into model as a continuously distributed variable (where the argument of the log refers to TCDD measured in 1987 or extrapolated to 1987). All analyses were adjusted for race by restricting to White veterans because approximately 94% of the cohort was White. Rounding sometimes prevents a strict concordance between the confidence interval and the p-value; in these cases the p-value is the determinant of statistical significance.

Calendar period of service was defined as “ \leq 1968” and “ $>$ 1968” and days of spraying was dichotomized as \leq 30 days and $>$ 30 days during or prior to 1967. We hypothesized that herbicides were more heavily contaminated early in the war than late in the war, and that the number of days of spraying was an important determinant of exposure in the Ranch Hand cohort and stratified by calendar period of service and days of spraying. Because all-site SEER cancer risk increased with years of service in SEA among Comparison veterans, we further stratified the analysis of cancer by years of service in SEA (\leq 2 years, $>$ 2 years). The stratum of interest in analyses of cancer was calendar period of service \leq 1968 and $>$ 30 days of spraying during or prior to 1967 and \leq 2 years of service in SEA and we hypothesized that all-site SEER cancer would be associated with the TCDD biomarker in this stratum.

Results

After excluding those with cancer prior to the baseline examination (n=93), non-compliance (n=289), and those without a TCDD measurement (n=84), 2,583 remained for inclusion in statistical analyses of cancer. Table 1 summarizes sample sizes by stratum of calendar period of service (\leq 1968, $>$ 1968) and years served in SEA (\leq 2 years, $>$ 2 years). Three hundred ninety four Comparisons and 394 Ranch Hands had their last year of service during or prior to 1968. Six hundred forty Comparisons and 596 Ranch Hands experienced at most 2 years of service in SEA. Two hundred sixty eight Comparisons had their last year of service during or prior to 1968 and served at most 2 years in SEA and 262 Ranch Hands had their last year of service during or prior to 1968 and served at most 2 years in SEA and experienced at least 30 days of spraying during or prior to 1967.

Demographic information by TCDD category in the stratum defined by last year of service during or prior to 1968 and Ranch Hands with at least 30 days of spraying during or prior to 1967 and its complement showed no appreciable group differences (not shown in any table). Ranch Hand mean TCDD (in log units) was significantly increased among those whose last year of service was during or prior to 1968 relative to the complement stratum (last year \leq 1968: mean=2.7, last year $>$ 1968: mean=2.5, 95% CI 0.07 to 0.3, $p=0.001$). The mean log(TCDD) was significantly increased in enlisted ground ($p=0.005$) and enlisted flyers ($p<0.001$) but not officers ($p=0.79$) among those whose last year of service was during or prior to 1968 (not shown in any table).

Table 1. Analysis sample sizes^a

Calendar Period of Service	Years in Southeast Asia	Comparison	Ranch Hand			
			Bkg ^b	Low	High	Total
\leq 1968 ^c		394	167	88	139	394
$>$ 1968 ^d		994	232	145	103	480
	\leq 2	640	282	142	172	596
	$>$ 2	748	117	91	70	278
\leq 1968	\leq 2	268	120 ^e	49 ^e	93 ^e	262 ^e

- White. Pre-baseline cancer, Ranch Hands with missing TCDD excluded (N=2262).
- Ranch Hand Background
- During or prior to 1968
- Not during or prior to 1968
- At least 30 days of spraying during or prior to 1967

Without stratification, there was no significant increase in the risk of cancer with log(TCDD) in the combined cohort ($p=0.24$) and no significant increase in the risk of all-site SEER cancer in any of the three Ranch Hand TCDD exposure categories (Table 2A). After restriction to those whose last year of service was during or prior to 1968 (Table 2B), the relative risk of cancer increased significantly with log(TCDD) in the combined cohort ($p=0.01$) and in the Low category (RR=1.7, 95% CI 1 to 2.9, $p=0.03$); there was no significant increase in the risk of cancer with log(TCDD) and no significant increased risk in any of the Ranch Hand TCDD exposure categories in the complement stratum. With restriction to veterans who served at most 2 years in SEA (Table 2C), the risk of cancer increased with log(TCDD) in the combined cohort ($p=0.05$) and was elevated in the Low and High categories but not significantly. With restriction to the stratum of interest (Table 2D), the risk of cancer increased significantly with log(TCDD) in the combined cohort ($p=0.005$) and the relative risk was significantly increased in the High category (RR=2.2, 95% CI 1.1 to 4.4, $p=0.03$).

Table 2. SEER Cancer by TCDD exposure category and stratum

Stratum	Trend ^a	Comp ^b	Bkg ^c	Ranch Hand	
				Low	High
A) Unstratified^d					
N	2262	1388	399	233	242
Number (%)	347 (15.3)	212 (15.3)	64 (16)	46 (19.7)	25 (10.3)
RR ^e (CI)	1.1 (1-1.2)		1 (0.8-1.4)	1.3 (1-1.8)	0.9 (0.6-1.4)
P-value	0.24		0.89	0.1	0.65

Table 2 (Continued)

B) Stratified by calendar period of service^f						
≤1968 ^g	N	788	394	167	88	139
	Number (%)	118 (15)	55 (14)	20 (12)	22 (25)	21 (15.1)
	RR ⁵ (CI)	1.2 (1.0-1.5)		0.7 (0.4-1.3)	1.7 (1-2.9)	1.5 (0.9-2.6)
	P-value	0.01		0.26	0.03	0.14
Comple- ment ^h	N	1474	994	232	145	103
	Number (%)	229 (15.5)	157 (15.8)	44 (19)	24 (16.6)	4 (3.9)
	RR ⁵ (CI)	1 (0.8-1.1)		1.3 (0.9-1.9)	1.1 (0.7-1.7)	0.4 (0.1-1)
	P-value	0.65		0.11	0.7	0.05
C) Stratified by years served in Southeast Asiaⁱ						
≤2 years	N	1236	640	282	142	172
	Number (%)	135 (10.9)	56 (8.8)	36 (12.8)	24 (16.9)	19 (11)
	RR ⁵ (CI)	1.2 (1-1.4)		1.1 (0.7-1.7)	1.6 (1-2.5)	1.6 (0.9-2.8)
	P-value	0.05		0.71	0.08	0.11
D) Stratified by calendar period of service, days of spraying, years in Southeast Asia^j						
≤1968 and ≥30 days pre-1967 and ≤2 yr	N	530	268	120	49	93
	Number (%)	67 (12.6)	30 (11.2)	10 (8.3)	12 (24.5)	15 (16.1)
	RR ⁵ (CI)	1.4 (1.1-1.7)		0.5 (0.2-1.1)	1.7 (0.8-3.5)	2.2 (1.1-4.4)
	P-value	0.005		0.09	0.14	0.03

- Based on a proportional hazards model of time-to-diagnosis in the combined cohort with log(TCDD) entered into model as a continuously distributed variable, adjusted for year of birth, military occupation, Body Mass Index (BMI) at the qualifying tour, smoking history (pack-years), skin reaction to sun (burns painfully or freckles with no tan, burns or tans mildly, tans deep brown), eye color (brown, hazel/green and gray/blue), years served in Southeast Asia
- Comparisons
- Ranch Hand Background
- Analysis sample sizes (Table 1 first two rows combined)
- Relative risk (RR) and 95% confidence interval (CI) based on a proportional hazards model of time-to-diagnosis, adjusted for year of birth, military occupation, BMI at the qualifying tour, smoking history (pack-years) skin reaction to sun (burns painfully or freckles with no tan, burns or tans mildly, tans deep brown), eye color (brown, hazel/green and gray/blue), years served in Southeast Asia
- Analysis sample sizes (Table 1, first two rows)
- During or prior to 1968
- Not during or prior to 1968
- Analysis sample sizes (Table 1, 3rd and 4th rows)
- Analysis sample sizes (Table 1, 5th row)

Conclusion

Stratification by calendar period of service, days of spraying, and time spent in Southeast Asia revealed a significant trend of increased all-site SEER cancer risk and a significantly increased risk in the highest Ranch Hand TCDD exposure category. These data suggest that calendar period of service, days of spraying, and time spent in Southeast Asia are important confounders in the Air Force Health Study.

Reference

Michalek JE and Pavuk M. *Journal of Occupational and Environmental Medicine* 2008;50;330-340.