

Cancer in US Air Force Veterans of the Vietnam War

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Learning objectives

- Cite differences in cancer risk between both Vietnam Air Force veterans who had sprayed dioxin-contaminated herbicides and a comparison non-spraying group on the one hand, and U.S. national cancer rates on the other.
- State in what respects cancer risks differed between the dioxin- exposed and non-exposed veterans.
- Note whether and how these findings are influenced by race and the intensity of herbicide spraying

Abstract

Cancer incidence and mortality were summarized in Air Force veterans of the Vietnam War. The index subjects were Operation Ranch Hand veterans who sprayed 2,3,7,8 tetrachlorodibenzo-p-dioxin (dioxin)-contaminated herbicides in Vietnam. Comparisons served in Southeast Asia during the same period but did not spray herbicides. We assessed cancer incidence and mortality using national rates and contrasted cancer risk in each of three Ranch Hand dioxin exposure categories relative to comparisons. The incidence of melanoma and prostate cancer was increased among white Ranch Hand veterans relative to national rates. Among veterans who spent at most 2 years in Southeast Asia, the risk of cancer at any site, of prostate cancer and of melanoma was increased in the highest dioxin exposure category. These results appear consistent with an association between cancer and dioxin exposure. (J Occup Environ Med. 2004; 46:123–136)

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The herbicide Agent Orange is a 1:1 mixture of 2,4-dichloro-phenoxyacetic acid (2,4-D) and 2,4,5-trichloro-phenoxyacetic acid (2,4,5-T) and is 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.

Herbicides were used in Vietnam by the US Air Force Operation Ranch Hand to defoliate by aerial spraying from C-123 aircraft.² Army personnel also sprayed herbicides on the ground and from helicopters to defoliate the perimeters of base camps and fire bases. From 1962 through 1965, small quantities of Agent Purple (2,4-D; 2,4,5-T), Blue (Cacodylic acid), Pink (2,4,5-T), and Green (2,4,5-T) were sprayed. From 1965 through 1970, more than 11 million gallons of Agent Orange (2,4-D, 2,4,5-T), and smaller quantities of White (2,4-D, picloram) and Blue were sprayed; from 1970 through 1971, only Agents White and Blue were used for defoliation purposes.²

Numerous long-term exposure studies have established the carcinogenicity of dioxin in rats,^{3,4} mice,^{5–7} and hamsters.⁸ The consensus of

most research is that dioxin is only weakly mutagenic and does not covalently bind to DNA or cause it to initiate repair synthesis but that it does behave as a tumor promoter at the cellular level.⁹ The oncogenic response to dioxin in animals has been shown to depend on the age, sex, and strain of species, as well as the dose and route of administration.^{10–12} In varying doses and routes of administration, dioxin has produced malignant neoplasms at multiple anatomical sites in rats (lung, oropharyngeal, thyroid, adrenal glands, and liver),^{4,5} mice (thyroid, thymus, connective tissue, and liver),⁵ and hamsters (cutaneous).⁸ Many toxicological studies of the carcinogenicity of dioxin have focused on the aryl hydrocarbon (Ah) receptor and the induction of cytochrome P-450 enzyme system.^{13–23} The Ah receptor has recently been isolated from human liver,²⁴ skin,²⁵ lymphoblastoid cells,²⁶ tonsils,²⁷ and colon²⁸ in studies of dioxin toxicity in human tissues. Where both human and animal data exist, the sensitivity of humans to dioxin appears similar to that of experimental animals with regard to enzyme induction, chloracne, immunotoxicity, developmental toxicity, and cancer.²⁹ Generalized increases in cancer risk associated with dioxin exposure are considered plausible because this pattern is consistent with animal experiments in which dioxin has been demonstrated to cause cancer at multiple anatomical sites.^{1,29}

This report summarizes a study of cancer in veterans of Operation Ranch Hand, 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.^{30,31} These results were accumulated during the postservice 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,^{32–37} mortality,^{31,38} and reproductive outcomes^{39–42} of Ranch Hand veterans. This report updates our previous cancer study³² by addressing veteran concerns that both cohorts may have experienced an increased risk of cancer and by addressing the possibility that veterans with service in Vietnam or SEA may have increased cancer risk. Our methods include external contrasts of cancer incidence and mortality, with the expected experience derived from national cancer rates, and internal cohort contrasts, which were adjusted for time spent in SEA and for the percentage of time spent in Vietnam.

Materials and Methods

Comparison veterans were matched to Ranch Hand veterans on date of birth, race (Black, non-black), and military occupation (officer pilot, officer navigator, nonflying officer, enlisted flyer, enlisted ground personnel). The study includes periodic physical examinations and in-person interviews conducted in 1982, 1985, 1987, 1992, 1997, and 2002. Data from the 2002 physical examination was not available at this writing. 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, 10th Revision (ICD 10).⁴³ 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).⁴⁴ 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 national cancer incidence rate files, by anatomical site, sex, race, and 5-year intervals of age and calendar year, covering the period 1950 to 2000 from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.⁴⁵ Mortality rate files by anatomical site, sex, race, and 5-year intervals of age and calendar year covering the period from 1950 to 2000 were obtained from the Department of Biostatistics at the University of Pittsburgh. These rates were derived from detailed mortality data from the National Center for Health Statistics and coded to the ICD 9 (personal communication, Ada Youk, PhD, University of Pittsburgh Department of Biostatistics). We used rates for white and black males in age intervals ranging from 15 to 19 through 90 to 95 and calendar-year intervals ranging from 1955 to 1959 to 1995 to 1999; incidence (mortality) rates were expressed in cases per 100,000 (1000) person-years. Lymphomas, multiple myeloma, and leukemia were combined together and referred to as cancers of the lymphopoietic system because of small numbers. We defined cancer at any site as cancer included in any of the SEER anatomical category definitions.

Dioxin levels were measured on a lipid weight basis in serum^{46,47} 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.⁴⁸ Nondetectable (nonquantifiable) dioxin levels were replaced by the value of the limit of detection (limit of quantitation) divided by $\sqrt{2}$.⁴⁹

To account for variation across time in the types and quantities of herbicides sprayed by Operation

TABLE 1
Sample Size Reduction in US Air Force Veterans

	Ranch Hand	Comparison	Total
Partially or fully compliant to at least one physical examination	1196	1785	2981
Cancer before service in Southeast Asia	7	6	13
Cancer during service in Southeast Asia	0	3	3
Net for external analyses	1189	1776	2965
Missing dioxin ^a			
Serum not collected			
Died before the first dioxin blood draw (1987/1988)	34	39	73
Noncompliant after 1985	120	268	388
Not locatable after 1985	0	2	2
Medically deferred	10	15	25
Refused	8	13	21
Unable to draw blood	1	0	1
Unknown reason	2	0	2
Serum collected			
No result ^b	4	10	14
Missing lipids	1	0	1
Total	180	347	527
Net for internal analyses	1009	1429	2438

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

^b Failure of one or more quality control checks and insufficient serum to repeat the analysis.

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 in two ways: by 1) restricting time spent in SEA to at most 2 years, and 2) 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 as-

signed 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 as weight (kg) divided by the square of height (m), and defined a pack-year as smoking one pack of cigarettes 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: 1) external contrasts of cancer incidence and mortality in each cohort relative to the expected experience derived from US national rates and 2) internal contrasts of the study cohorts with regard to cancer incidence. In both series, we categorized malignancies by site and all sites combined. We used multiplicative Poisson regression models⁵⁰ to compare cancer incidence and cancer mortality with national rates and proportional hazards models⁵¹ to contrast cohorts with regard to cancer incidence. We were unable to consider basal and squamous cell carcinomas in the external contrasts because there were no national rates for

those cancers. Veterans with cancer during or prior to their service in SEA were excluded from all analyses.

Sample size reductions are summarized in Table 1. The external analyses were based on participants partially or fully compliant to at least one of the first five physical examinations, in 1982, 1985, 1987, 1992, and 1997, less those with cancer before or during their service in Southeast Asia ($n = 2965$). The internal analyses were based on the subcohort with nonmissing dioxin measurements ($n = 2438$). These counts are larger than those of our last article on cancer and serum dioxin levels,³² which was based on participants fully compliant to at least one of the first four physical examinations less those with cancer before their SEA service or missing dioxin measurements.

External Contrasts

For cancer incidence, we computed person-years, rates, the expected number of cases by 5-year age and calendar-year intervals, and the age and calendar year adjusted standardized incidence ratio (SIR), defined as the ratio of the observed

TABLE 2

Sample Size (N) and Person Years (PY) by Race, Occupation, and End of Tour Year in US Air Force Veterans

Stratum	Ranch Hand (RH)						Comparison (C)					
	White		Black		Other		White		Black		Other	
	N ^a	PY ^b	N	PY	N	PY	N	PY	N	PY	N	PY
For cancer incidence												
All	1061	29724	71	1995	57	1655	1570	42577	106	2986	100	2913
At most 2	724	20280	48	1364	41	1190	738	19887	50	1409	57	1655
Years in SEA ^c												
RH: 100%VN ^d	633	17855	47	1335	39	1126	382	10241	31	901	34	988
C: 0% VN												
Before 1962 or After 1972 ^e	0	0	0	0	0		20	516	0	0	0	0
1962–1965	108	3468	5	169	5	176	94	2827	9	265	8	283
1966–1970	916	25323	66	1825	51	1451	1213	33297	85	2406	73	2107
1971–1972	37	933	0	0	1	28	243	5937	12	316	19	522
For mortality												
All	1061	32396	71	2128	57	1782	1570	47406	106	3256	100	3043

^a N, sample size.^b PY, person-years.^c SEA, Southeast Asia.^d VN, Vietnam.^e End of tour year.

to the expected number of incident cancer cases. We considered only primary sites and considered multiple site malignancies as independent. We defined time to onset for living veterans with at least one cancer diagnosis as the time in years from the end of service in SEA to the onset of the earliest occurrence of a malignant tumor. For living veterans without cancer, we defined the time to onset as the number of years from the end of service in SEA to 2 years beyond the last physical examination attended, with a cut off date of December 31, 1999. Two years were added to account for additional follow-up after each examination. For deceased veterans without cancer, we defined the survival time as the number of years from the end of service in SEA to the date of death. For each cancer site, we report the observed and expected numbers of cases, the SIR, a 95% confidence interval (CI) for the SIR, the *P* value for a test of the null hypothesis that the SIR is equal to 1.0,⁵⁰ and the *P* value for a test of the hypothesis that the SIR was constant across cohorts.⁵² To test the hypothesis that incidence rates should be decreased in comparison veterans who spent

little or no time in Vietnam and increased in Ranch Hand veterans who spent the majority or all of their SEA service in Vietnam, we stratified by time spent in SEA (≤ 2 years, > 2 years) and the percentage of SEA service spent in Vietnam (comparison: 0%, Ranch Hand: 100%; comparison: $> 0\%$, Ranch Hand: $< 100\%$). Tables are restricted to the first level of each of these two stratification factors, and to all-site cancer, melanoma, and prostate cancer.

For cancer mortality, we computed person-years, rates, the expected number of deaths by 5-year age and calendar-year intervals, and the age and calendar year adjusted standardized mortality ratio (SMR), defined as the ratio of the observed to the expected number of cancer deaths. For deceased veterans whose death was caused by cancer, the survival time was defined as the number of years from the end of service in SEA to the date of death. For veterans who died of causes other than cancer, we defined the survival time as the number of years from the end of service in SEA to the date of death. For living veterans, we defined survival time as the number of years from the end of service in SEA to

December 31, 1999. For each cancer site, we report the observed and expected numbers of deaths, the SMR, a 95% CI for the SMR, the *P* value for a test of the null hypothesis that the SMR is equal to 1.0,⁵⁰ and the *P* value for a test of the hypothesis that the SMR was constant across cohorts.⁵² Sample sizes and person-years for cancer incidence and mortality are summarized in Table 2.

Internal Contrasts

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

TABLE 3Demographics in 1982^a by Dioxin Exposure Category in US Air Force Veterans

Stratum	Comparison (n = 1517)	Background (n = 429)	Ranch Hand Low (n = 281)	High (n = 282)
Military Occupation				
Officer (%)	565 (37.3)	260 (60.6)	104 (37.0)	8 (2.8)
Enlisted flyer (%)	232 (15.3)	52 (12.1)	59 (21)	59 (20.9)
Enlisted ground (%)	720 (47.5)	117 (27.3)	118 (42)	215 (76.2)
Race				
Black (%)	85 (5.6)	22 (5.1)	22 (7.8)	14 (5)
Non-black and non-white (%)	87 (5.7)	14 (3.3)	14 (5)	22 (7.8)
White (%)	1345 (88.7)	393 (91.6)	245 (87.2)	246 (87.2)
Serum dioxin ^{b,c} median (range)	4.1 (0.4–54.8)	5.7 (0.6–10)	15.2 (10–29.2)	47.7 (18–617.8)
Initial dioxin ^{b,d} median (range)			66 (32.2–118.5)	245.5 (119.3–4221.9)
Age (years) median (range)	43.3 (31.7–74.5)	45.1 (31.5–68.3)	45.5 (31.8–65.8)	37.2 (32.3–66)
Body mass index at tour (kg/m ²) median (range)	24.7 (17.2–40.7)	24 (17–32.9)	25.2 (17.5–36.3)	25.1 (17.9–35.6)
Pack years median (range)	12.6 (0–115.9)	11.8 (0–103.5)	13.1 (0–115)	10.3 (0–138.9)
Total days in Vietnam median (range)	160 (0–1777)	393 (31–1614)	395 (89–1279)	395 (121–1919)
Total days in SEA ^e median (range)	790 (30–5690)	426 (61–3492)	457 (89–5631)	397 (121–3196)

^a Veterans partially or fully compliant to the 1982 physical exam; Ranch Hand veterans with a nonmissing dioxin measurement.^b Parts per trillion.^c Measured in 1987, 1992, or 1997 in comparison and Ranch Hand categories.^d Serum dioxin extrapolated to end of service in Vietnam in Ranch Hand low and high categories.^e SEA, Southeast Asia.

118.5 ppt, the median initial 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, associated relative risks, 95% CIs, and *P* values, contrasting each of the three Ranch Hand dioxin categories with the comparison category, derived from a proportional hazards model. We report the *P* value for trend, defined as the *P* value for a test of the hypothesis that the coefficient of the log-transformed serum dioxin concentration was equal to 1.0 in the combined cohort. We restricted these internal analyses to all-site cancer, melanoma, and cancer of the prostate because of small or zero cell counts. The analyses of all-site cancer was adjusted for age at tour, military occupation (officer, enlisted flyer, enlisted ground), smoking history (pack-years at the 1982 examination), skin reaction to sun exposure

(burns painfully or freckles with no tan, burns or tans mildly, tans deep brown), and eye color (brown, hazel/green and gray/blue). The analysis of melanoma was adjusted for age at tour, military occupation, skin reaction to sun exposure, and eye color. The analysis of cancer of the prostate was adjusted for age at tour, military occupation, and smoking history.

We restricted these dioxin exposure category analyses by time spent in SEA (at most 2 years) and by the percentage of SEA service spent in Vietnam (Ranch Hand: 100%, comparison 0%) to address concerns that previous analyses may have been biased against finding an association because, for example, comparison veterans who spent time in Vietnam may have experienced increased cancer. When analyzing by category of the percentage of SEA service spent in Vietnam, we additionally adjusted for the logarithm of the number of years of service in SEA. SAS software Version 8.1, (Cary, NC)⁵³ was used throughout.

Results

Table 3 summarizes dioxin levels and demographic characteristics

by dioxin category among those veterans who attended the 1982 physical examination. Ranch Hand veterans in the high category (median age, 37.2 years) were younger than comparison veterans (median age, 43.3 years). Ranch Hand veterans in the high category were predominantly enlisted ground personnel and those in the background category were predominantly officers during the war. In any dioxin category, more than 90% of the veterans were white, approximately 5% were black, and less than 5% were non-white and non-black. The percentages by military occupation and race, and the distributions of dioxin, body mass index, and pack years were similar by stratum of time spent in SEA and the percentage of SEA service spent in Vietnam (data not shown). Most Ranch Hand veterans in all three dioxin categories spent a little over a year in SEA, with most of that stay being in Vietnam, whereas most comparison veterans spent more than 2 years (median, 790 days) in SEA, with less than 6 months in Vietnam (median, 160 days). Among comparison veterans, the

TABLE 4

Standardized Incidence Ratios (SIRs) Comparing Cancer Incidence Rates in US Air Force Veterans Against National Incidence Rates

Race/Site	Ranch Hand					Comparison					
	OBS ^a	EXP ^b	SIR ^c	P ^d	95% CI ^e	OBS	EXP	SIR	P	95% CI	P ^f
White											
All sites ^g	134	123.34	1.09	0.34	0.91–1.28	163	172.54	0.94	0.47	0.81–1.10	0.23
Buccal cavity	6	6.48	0.93	0.90	0.38–1.93	5	8.90	0.56	0.18	0.21–1.24	0.41
Digestive system	16	26.43	0.61	0.03	0.36–0.96	31	36.38	0.85	0.38	0.59–1.19	0.26
Respiratory System	33	29.19	1.13	0.47	0.79–1.57	48	40.05	1.20	0.22	0.89–1.58	0.8
Melanoma	17	7.30	2.33	<0.001	1.40–3.65	15	10.24	1.46	0.15	0.85–2.36	0.19
Prostate ^g	36	24.71	1.46	0.03	1.04–2.00	54	33.34	1.62	<0.001	1.23–2.10	0.62
Urinary system	14	13.20	1.06	0.79	0.60–1.74	8	18.19	0.44	0.01	0.20–0.84	0.04
Brain and Nervous system	5	2.71	1.84	0.20	0.68–4.08	2	3.78	0.53	0.38	0.09–1.75	0.11
Lymphopoietic	10	11.82	0.85	0.63	0.43–1.51	9	16.46	0.55	0.05	0.27–1.00	0.34
Ill-defined	7	3.19	2.20	0.06	0.96–4.34	11	4.37	2.51	0.01	1.32–4.37	0.78
Black											
Any site	7	8.04	0.87	0.76	0.38–1.72	9	12.32	0.73	0.35	0.36–1.34	0.73
Urinary system	2	0.45	4.40	0.09	0.74–14.52	0	0.70	0.00			
Other than white or black											
Any site	5	3.42	1.46	0.39	0.54–3.24	7	6.77	1.03	0.88	0.45–2.05	0.55
All races											
Any site	146	135.80	1.08	0.38	0.91–1.26	179	193.81	0.92	0.29	0.80–1.07	0.17

^a OBS, Observed number of veterans diagnosed with the cancer.^b EXP, expected number of veterans with cancer.^c SIR, standardized incidence ratios, by 5-year age and 5-year calendar-year brackets.^d P value (Mid-p method) for testing SIR = 1. Bold text implies significant ($P \leq 0.05$).^e 95% confidence interval (Mid-p method) for the SIR.^f P value for the test of homogeneity comparing SIR in the Ranch Hand cohort with the SIR in the comparison cohort.^g This study had a power of 88% to detect SIR = 1.3 for all-site cancer and 98% to detect SIR = 2.0 for prostate cancer in Ranch Hand veterans.

median number of days spent in Vietnam was 225 among those who spent >0% of their SEA service in Vietnam; the median number was 90 days among those who spent at most 2 years in SEA and 230 days among those who spent more than 2 years in SEA (data not shown).

External Contrasts

No significant increase in the incidence of all cancers combined relative to national rates (Table 4) was found in white veterans in either cohort (Ranch Hand SIR = 1.09, 95% CI = 0.91 to 1.28, $P = 0.34$; Comparison SIR = 0.94, 95% CI = 0.81 to 1.10, $P = 0.47$). However, the incidence of melanoma (SIR = 2.33, 95% CI = 1.4–3.65, $P < 0.001$) and cancer of the prostate (SIR = 1.46, 95% CI = 1.04 to 2.00, $P = 0.03$) was significantly increased in White Ranch Hand veterans. The incidence of cancer of the

digestive system was significantly decreased in Ranch Hand veterans (SIR = 0.61). The incidence of cancer of the prostate (SIR = 1.62) and cancer at ill-defined sites (SIR = 2.51) was significantly increased, and the incidence of cancer of the urinary system (SIR = 0.44) and of the lymphopoietic system (SIR = 0.55) was significantly decreased in white comparison veterans. The SIR for urinary system cancer in white Ranch Hand veterans was nonsignificantly increased (SIR = 1.06), producing significant variation in the SIR between groups for this site ($P = 0.04$). No significant increases in all-site cancer incidence were found among black veterans. Without regard to race, no significant increase in the incidence of all-site cancer was found in either cohort. The distributions of melanomas by anatomical location were similar in

white Ranch Hand (ear = 1, face = 2, trunk = 10, upper limbs = 4) and comparison (ear = 3, face = 0, trunk = 10, upper limbs = 2) veterans.

Restriction to veterans whose tour ended between 1966 and 1970 (Table 5), the period of heaviest Agent Orange spraying, revealed that the incidence of melanoma (SIR = 2.57), and cancer of the prostate (SIR = 1.68) was significantly increased in white Ranch Hand veterans. The incidence of cancer of the prostate (SIR = 1.64) and cancer at ill-defined sites (SIR = 2.67), based on nine cases, was significantly increased in white Comparison veterans who served during the same period. The incidence of cancer of the urinary system (SIR = 0.28) was significantly reduced in comparison veterans, based on 4 cases and nonsignificantly increased in Ranch Hand veterans (SIR = 1.28); this

TABLE 5

Standardized Incidence Ratios (SIRs) in US Air Force Veterans With Tours Between 1966 and 1970

Race/Site	Ranch Hand					Comparison					
	OBS ^a	EXP ^b	SIR ^c	P ^d	95% CI ^e	OBS	EXP	SIR	P	95% CI	P ^f
White											
Any site	117	102.22	1.14	0.15	0.95–1.37	125	133.40	0.94	0.47	0.80–1.11	0.12
Buccal Cavity	6	5.41	1.11	0.76	0.45–2.31	4	6.88	0.58	0.27	0.18–1.40	0.31
Digestive System	14	21.84	0.64	0.08	0.36–1.05	24	28.03	0.86	0.46	0.56–1.25	0.39
Respiratory System	26	24.17	1.08	0.69	0.72–1.55	37	30.81	1.20	0.27	0.86–1.64	0.67
Melanoma	16	6.21	2.57	<0.001	1.52–4.09	12	7.98	1.51	0.17	0.82–2.56	0.16
Prostate	34	20.19	1.68	0.005	1.19–2.33	42	25.53	1.64	0.003	1.20–2.20	0.92
Urinary system	14	10.95	1.28	0.36	0.73–2.10	4	14.07	0.28	0.002	0.09–0.69	<0.001
Brain and nervous system	5	2.29	2.18	0.11	0.80–4.84	2	2.93	0.68	0.65	0.11–2.25	0.14
Lymphopoietic	7	9.97	0.70	0.36	0.31–1.39	4	12.77	0.31	0.01	0.10–0.76	0.19
Ill-defined	4	2.64	1.51	0.40	0.48–3.65	9	3.36	2.67	0.01	1.30–4.90	0.34
Black											
Any site	5	7.05	0.71	0.46	0.26–1.57	7	9.63	0.73	0.41	0.32–1.44	0.97
Urinary System	2	0.39	5.08	0.07	0.85–16.79	0	0.55	0			

^a OBS, observed number of veterans diagnosed with the cancer.^b EXP, expected number of veterans with cancer.^c SIRs, Standardized incidence ratios by 5-year age and 5-year calendar-year brackets.^d P value (Mid-p method) for testing SIR = 1. Bold text implies significant ($P \leq 0.05$).^e 95% confidence interval (Mid-p method) for the SIR.^f P value for the test of homogeneity comparing SIR in the Ranch Hand cohort with the SIR in the comparison cohort.

TABLE 6

Standardized Incidence Ratios (SIRs) for cancers in White US Air Force Veterans

Site	Ranch Hand					Comparison					
	OBS ^a	EXP ^b	SIR ^c	P ^d	95% CI ^e	OBS	EXP	SIR	P	95% CI	P ^f
Restricted to those who spent at most 2 years in South East Asia.											
Any site	78	71.53	1.09	0.44	0.87–1.35	38	60.32	0.63	<0.001	0.45–0.86	<0.001
Melanoma	11	4.66	2.36	0.01	1.24–4.10	3	4.15	0.72	0.62	0.18–1.96	0.05
Prostate	21	13.62	1.54	0.06	0.98–2.32	7	10.28	0.68	0.31	0.30–1.35	0.05
Restricted to Ranch Hand veterans who spent 100% of their Southeast Asia service in Vietnam and to comparison veterans who spent 0% of their Southeast Asia service in Vietnam.											
Any site	62	56.75	1.09	0.48	0.84–1.39	23	30.57	0.75	0.16	0.49–1.11	0.12
Melanoma	12	3.94	3.05	<0.001	1.65–5.18	2	2.04	0.98	0.94	0.16–3.24	0.12
Prostate	17	10.26	1.66	0.05	1.00–2.60	3	5.08	0.59	0.37	0.15–1.61	0.08

^a OBS, observed number of veterans diagnosed with the cancer.^b EXP, Expected number of veterans with cancer.^c SIR, standardized Incidence ratios, by 5-year age and 5-year calendar-year brackets.^d P value (Mid-p method) for testing SIR = 1. Bold text implies significant ($P \leq 0.05$).^e 95% Confidence interval (Mid-p method) for the SIR.^f P value for the test of homogeneity comparing SIR in the Ranch Hand cohort with the SIR in the comparison cohort.

variation in the SIR between groups was significant ($P < 0.001$). In comparison veterans, the incidence of cancer of the lymphopoietic system (SIR = 0.31) was significantly reduced ($P = 0.01$) based on four cases

Restriction to white veterans with at most 2 years in SEA (Table 6) revealed a significant increase in melanoma incidence in Ranch Hand veterans (SIR = 2.36, 95% CI = 1.24 to 4.10, $P = 0.01$) but not in comparison

veterans (SIR = 0.72), and significant variation in the SIR ($P = 0.05$). The risk of prostate cancer was borderline significantly increased in Ranch Hand veterans (SIR = 1.54, 95% CI = 0.98 to 2.32, $P = 0.06$) but not in Comparison veterans (SIR = 0.68), and this variation in the SIR was significant ($P = 0.05$).

Restriction to white Ranch Hand veterans who spent 100% of their SEA service in Vietnam and comparison

veterans who spent 0% of the SEA service in Vietnam (Table 6) revealed a significant increase in the incidence of melanoma (SIR = 3.05, 95% CI = 1.65 to 5.18, $P < 0.001$) and cancer of the prostate (SIR = 1.66, 95% CI = 1.00 to 2.60, $P = 0.05$).

The risk of death from cancer (Table 7) was significantly decreased in both white and non-white veterans in both cohorts (white Ranch Hand SMR = 0.73, 95% CI = 0.54 to

TABLE 7

Standardized Mortality Ratios (SMRs) Comparing Cancer Mortality in US Air Force Veterans Against National Rates

Site	Ranch Hand					Comparison					
	OBS ^a	EXP ^b	SMR ^c	P ^d	95% CI ^e	OBS	EXP	SMR	P	95% CI	P ^f
White											
Any site ^g	45	61.67	0.73	0.03	0.54–0.97	67	86.25	0.78	0.03	0.61–0.98	0.75
Buccal cavity	0	1.56	0.00			1	2.18	0.46			
Digestive	6	14.36	0.42	0.02	0.17–0.87	14	20.08	0.70	0.17	0.40–1.14	0.29
Respiratory	21	24.15	0.87	0.54	0.55–1.31	38	33.58	1.13	0.44	0.81–1.54	0.33
Prostate ^g	2	2.84	0.70	0.69	0.12–2.33	3	3.91	0.77	0.70	0.20–2.09	0.93
Urinary system	1	1.13	0.89			1	1.57	0.64			
Central nervous system	3	2.25	1.33	0.58	0.34–3.62	1	3.21	0.31			
Lymph or hematological system	6	6.31	0.95	0.96	0.39–1.98	5	8.91	0.56	0.18	0.21–1.24	0.38
Other sites	4	5.03	0.79	0.70	0.25–1.92	2	7.06	0.28	0.04	0.05–0.94	0.21
Non-white											
Any site	2	7.36	0.27	0.03	0.05–0.90	5	12.65	0.40	0.02	0.14–0.88	0.65

^a OBS, observed number of veterans diagnosed with the cancer.^b EXP, expected number of veterans with cancer.^c SMRs, standardized mortality ratios by 5-year age and 5-year calendar-year brackets.^d P value (Mid-p method) for testing SMR = 1. Bold text implies significant ($P \leq 0.05$).^e 95% confidence interval (Mid-p method) for the SMR.^f P value for the test of homogeneity comparing SMR in the Ranch Hand cohort with the SMR in the comparison cohort.^g This study had a power of 95% to detect SMR = 1.5 for deaths caused by cancer at all sites, 24% to detect SMR = 2, and 99% to detect SMR = 5 for deaths caused by prostate cancer in Ranch Hand veterans.

0.97, $P = 0.03$; white comparison SMR = 0.78, 95% CI = 0.61 to 0.98, $P = 0.03$, non-white Ranch Hand SMR = 0.27, 95% CI = 0.05 to 0.90, $P = 0.03$; non-white comparison SMR = 0.40, 95% CI = 0.14 to 0.88, $P = 0.02$). Stratification by the number of years served in SEA (at most 2 years or more than 2 years) and by the percentage of SEA service spent in Vietnam (Ranch Hand: 100%, comparison: 0% or Ranch Hand: <100%, comparison: >0%), and restriction to veterans whose tour ended between 1966 and 1970, revealed no significant increase in the SMR for any cause of death in either cohort (data not shown).

Internal Contrasts

Restriction to white veterans who spent at most 2 years in SEA (Table 8) revealed a significantly increased risk of cancer at any site in the high (relative risk [RR] = 2.02, $P = 0.04$) and low (RR = 2.23, $P = 0.01$) dioxin categories, comprising a significant trend ($P = 0.04$). The risk of melanoma was significantly increased in the high (RR = 7.51, $P =$

0.04) and low (RR = 7.42, $P = 0.02$) dioxin categories, comprising a significant trend ($P = 0.004$), and the risk of cancer of the prostate (RR = 6.04, $P = 0.01$) was significantly increased in the high category among white veterans. There were no significant increases in the risk of cancer in any of the three Ranch Hand dioxin categories among white veterans whose tour in SEA was more than 2 years in length (data not shown).

Restriction to white Ranch Hand veterans who spent 100% of their SEA service in Vietnam and comparison veterans who spent 0% of the SEA service in Vietnam (Table 9) revealed a significant increase in the risk of cancer at any site in the high (RR = 3.34, $P = 0.02$) and low (RR = 3.79, $P = 0.005$) dioxin categories and a borderline significant increase in the background category (RR = 2.57, $P = 0.06$). The risk of melanoma was borderline significantly increased in the low dioxin category (RR = 7.18, $P = 0.07$) and increased in the high category (RR = 5.52), comprising a significant trend ($P = 0.04$). There were no signifi-

cant increases in the risk of cancer in any of the three Ranch Hand dioxin categories among white Ranch Hand veterans who spent <100% of their SEA service in Vietnam relative to comparison veterans who spent >0% of their SEA service in Vietnam (data not shown).

Discussion

To our knowledge, this is the only cancer incidence study of US Vietnam veterans. It was based on 35 to 40 years of postwar follow-up, with all outcomes verified by record review. Full ascertainment was attained. The Ranch Hand exposures, although perhaps higher than many other Vietnam veterans, were not as great as those among industrial cohorts; the highest initial dose among Ranch Hand veterans was approximately 4000 ppt, about one tenth of the maximum predicted dose among workers in the National Institute for Occupational Safety and Health study,⁵⁴ for example. Among Vietnam veterans, the Ranch Hand unit is one of the few well-defined cohorts with demonstrably increased serum dioxin levels.

TABLE 8

Relative Risks^a of Cancer by Dioxin Category in White US Air Force Veterans: Restricted to Those Who Spent at Most 2 years in Southeast Asia

Site	Dioxin ^b (n = 1192)	Comparison (n = 580)	Background (n = 287)	Ranch Hand	
				Low (n = 151)	High (n = 174)
Any site ^d					
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 ^c	0.04		0.21	0.01	0.04
95% CI	1.01–1.53		0.82–2.53	1.24–4.00	1.03–3.95
Melanoma					
Count (%)		3 (0.52)	4 (1.39)	4 (2.65)	3 (1.72)
Relative risk	2.24		2.99	7.42	7.51
P value ^c	0.004		0.21	0.02	0.04
95% CI	1.29–3.89		0.53–16.8	1.34–41.04	1.12–50.21
Prostate ^d					
Count (%)		7 (1.21)	10 (3.48)	6 (3.97)	5 (2.87)
Relative risk	1.48		1.50	2.17	6.04
P Value ^c	0.10		0.46	0.19	0.01
95% CI	0.93–2.35		0.51–4.40	0.68–6.87	1.48–24.61

^a Cancer at any site was adjusted for age at tour, military occupation, pack-years, reaction to sun exposure and eye color. Melanoma was adjusted for age at tour, military occupation, skin reaction to sun exposure, and eye color. Cancer of the prostate was adjusted for age at tour, military occupation, and pack-years

^b Log transformed.

^c Bold text implies $P \leq 0.05$.

^d This study had a power of 93% to detect relative risk = 2.5 for all-site cancer and 89% to detect relative risk = 5 for prostate cancer in the contrast of the high and comparison dioxin exposure categories.

95% CI, 95% confidence interval.

Epidemiological studies of cancer and dioxin exposure have been based on cohorts of civilians exposed by occupation,^{54–71} veterans who served in the Vietnam era,^{72–80} and as a consequence of industrial accidents.^{81–86} A combined cohort study⁵⁵ found an increase in the risk of mortality due to cancers of all types in exposed workers. Generalized increases in cancer risk associated with dioxin exposure are considered plausible because this pattern is consistent with animal experiments in which dioxin has been demonstrated to cause cancer at multiple anatomical sites.^{2,29} We expected to find evidence of increased cancer risk among Ranch Hand veterans who served during the period of heaviest spraying, at most 2 years in the SEA region, and among those who spent 100% of their SEA service in Vietnam.

Overall, the incidence of cancer at any site was not significantly increased relative to national cancer

incidence rates (Ranch Hand SIR = 1.09, comparison SIR = 0.94). Analyses by anatomical site revealed differences, however. Restricting to white veterans, we found a significantly increased incidence of melanoma among Ranch Hand veterans (SIR = 2.33) and a significantly increased incidence of prostate cancer in both groups (Ranch Hand SIR = 1.46, comparison SIR = 1.62). An increased incidence of melanoma and prostate cancer was found among Ranch Hand veterans who served between 1966 and 1970, the period of heaviest Agent Orange spraying, in parallel with the increases already noted in the entire cohort. Prostate cancer has been categorized as exhibiting limited or suggestive evidence of an association with herbicides used in Vietnam, or their dioxin contaminant, by the National Academy of Sciences, based primarily on a study of Australian veterans that found an increase in

risk relative to national rates (212 observed versus 147 expected).²

Cancer mortality was not significantly increased in either cohort relative to national death rates. Stratification by time spent in SEA or the percentage of SEA service spent in Vietnam and by tour date did not reveal any significant increases in cancer mortality.

Internal analyses found an increased risk of cancer at any site in Ranch Hand veterans in the High dioxin category among those who spent at most 2 years in SEA (RR = 2.02); the incidence of melanoma (RR = 7.51) and cancer of the prostate (RR = 6.04) were also increased in the high category. With restriction to Ranch Hand veterans who spent 100% and comparison veterans who spent 0% of their SEA service in Vietnam, the risk of cancer at any site (RR = 3.34) was increased in the high dioxin exposure category. These results differ from our latest published analysis³² that did not use

TABLE 9

Relative Risks^a of Cancer by Dioxin Category in White Air Force Veterans: Restricted to Ranch Hand Veterans Who Spent 100% of Their Southeast Asia Service in Vietnam and to Comparison Veterans Who Spent 0% of Their Southeast Asia Service in Vietnam

Site	Dioxin ^b (n = 840)	Comparison (n = 291)	Background (n = 252)	Ranch Hand	
				Low (n = 132)	High (n = 165)
Any site ^d					
Number (%)		17 (5.84)	25 (9.92)	19 (14.39)	12 (7.27)
Relative risk	1.23		2.57	3.79	3.34
P value ^c	0.10		0.06	0.005	0.02
95% CI	0.96–1.57		0.97–6.84	1.49–9.66	1.25–8.93
Melanoma					
Number (%)		2 (0.69)	5 (1.98)	4 (3.03)	3 (1.82)
Relative risk	1.68		3.93	7.18	5.52
P value ^c	0.04		0.22	0.07	0.11
95% CI	1.02–2.79		0.44–35.29	0.88–58.8	0.66–46.09
Prostate ^d					
Number (%)		3 (1.03)	9 (3.57)	4 (3.03)	4 (2.42)
Relative Risk	1.07		2.48	2.36	4.67
P-Value ^c	0.80		0.34	0.38	0.10
95% CI	0.64–1.78		0.38–16.07	0.35–16.01	0.75–29.07

^a Cancer at any site was adjusted for age at tour, military occupation, pack-years, skin reaction to sun exposure, eye color, and the logarithm of years served in SEA. Melanoma was adjusted for age at tour, military occupation, skin reaction to sun exposure, eye color, and the logarithm of years served in SEA. Cancer of the prostate was adjusted for age at tour, military occupation, pack-years, and the logarithm of years served in SEA.

^b Log transformed.

^c Bold text implies significant ($P \leq 0.05$).

^d This study had a power of 86% to detect relative risk = 2.5 for all-site cancer and 74% to detect relative risk = 5 for prostate cancer in the contrast of the high and comparison dioxin exposure categories.

95% CI, 95% confidence interval.

the SEER definition of all-site cancer but instead combined all sites, including all types of skin cancer and all systemic cancers, and did not adjust for time spent in the SEA region or the percentage of SEA service spent in Vietnam. In that analysis, we found a decreased risk in the high dioxin exposure category and no dose response (background: odds ratio [OR] = 0.8, low OR = 1.3, high OR = 0.7). The results presented here differ in part because time spent in the SEA region was adversely associated with cancer risk in comparison veterans; those who spent at most 2 years in SEA had a significantly lower risk of cancer than those who spent more than 2 years in SEA. By stratifying by time spent in the region, we partially removed the influence of this confounder to reveal a significant dose-response in the Ranch Hand cohort in our dioxin category analysis. Corresponding patterns with numerically

greater relative risks, based on smaller cell counts, were observed after restricting to comparisons who spent 0% of their SEA service in Vietnam, because the percentage of SEA service spent in Vietnam was also a confounding variable considered here but not in any of our previous reports or articles.

Melanoma risk was significantly increased in the Ranch Hand cohort relative to national rates; the risk was nonsignificantly increased in the comparison cohort, and the variation in relative risk was not significant. However, when we restricted to veterans with at most 2 years in SEA, the Ranch Hand SIR remained significantly increased, the comparison SIR decreased, and the variation in SIR reached statistical significance, suggesting a relation between melanoma risk and herbicide exposure in Ranch Hand veterans. This interpretation is supported by our internal analysis of melanoma based on se-

rum dioxin exposure categories, which revealed a significant trend of increased relative risk (background RR = 2.99, low RR = 7.42, high RR = 7.51) based on fewer than five cases in each exposure category among those who spent at most 2 years in SEA. The National Academy of Sciences has concluded that there is inadequate or insufficient evidence to determine whether an association exists between exposures to herbicides and melanoma.² The possibility that sunlight exposure may account for the increased SIR is diminished by the variation in risk with cohort and dioxin category.

There was no evidence of a “healthy-worker” effect relative to national incidence rates in either cohort. A healthy worker effort was suggested by the mortality contrasts with national rates, however, because the risk of death from cancer at any site was significantly decreased in both cohorts and most of the

site-specific SMRs were less than 1.0.

We considered the possibility that some of the increases in the SIR could have been caused by the repeated physical examinations these men received during their participation in the study. At every examination, participants received a rectal examination and a dermatological examination and suspicious lesions were subjected to a punch biopsy. At the 1992 and 1997 examinations, prostate-specific antigen was measured. A record review found that 10 of the 32 melanoma cases (Ranch Hand = 6, comparison = 4) and 53 (Ranch Hand = 25, comparison = 28) of the 90 prostate cases were diagnosed as a direct result of the examinations. These data are consistent with the hypothesis that the increased SIR for melanoma and prostate cancer might be at least partially explained by the medical examinations these men received. However, these data do not explain the increases in risk found in the high dioxin exposure category because medical and support staff were blinded to the exposure history, military occupation, tour dates, time spent in Vietnam, and dioxin levels of every participant.

This study is limited by adjustment of the external analyses for only age, race, and calendar period, a consequence of the lack of published cancer incidence rates adjusted for smoking history, for example. Our internal analyses were adjusted for known risk factors, but there is the possibility that there were others that we did not measure. Also of concern was the number of statistical tests we performed. In Table 4, for example, we found seven statistically significant results ($P \leq 0.05$) of the 28 tests, or 25% of the tests we performed. Although some or all of these significant findings could reflect chance differences resulting from the many analyses we conducted, the pattern of increased risk of melanoma and prostate cancer overall and in subgroups and time

periods of a priori interest, and in strata defined by tour date category, time spent in SEA and the percentage of SEA service spent in Vietnam, suggests that at least some of these findings may not be attributable to chance. Statistical power (footnoted in Tables 4, 7, 8, and 9) was limited in some analyses due to stratification.

This study was also limited by uncertainties regarding dioxin exposure. The serum dioxin measurements were accurate⁸⁷ and correlate with reported skin exposure to herbicide in Vietnam,⁸⁸ but were made up to 30 years after exposure. Our initial dose calculation was based on a first-order decay law with an assumed constant half-life. The accuracy of our extrapolated initial dose estimate is unknown but appears reasonable in light of a recent combined analysis of dioxin elimination in Ranch Hand veterans and men exposed in the Seveso accident.⁸⁹ Furthermore, we regard the background category as a mixture of exposed and unexposed veterans whose true status could not be determined with available data. The time since exposure varied between 15 and 26 years, or two or three dioxin half-lives. The elimination of dioxin in the intervening years and lack of alternative evidence of exposure left the exposure status of Ranch Hand veterans with background levels (below 10 ppt) irresolvable.

Interpretations of cohort contrasts in this study have been limited because, by design, both cohorts were comprised of veterans of the Vietnam War. Thus, this study was not designed to directly assess the SEA or Vietnam experience but rather the effect, if any, of occupational exposures to herbicides in Ranch Hand veterans relative to other Vietnam veterans who were not occupationally exposed. The Vietnam experience has been the focus of other studies, primarily of US Army veterans of the War.^{90,91} Thus, a "Vietnam" effect, if equally expressed by both Ranch Hand and Comparison

veterans, would not be detectable in this study. To address that possibility, we used the national population as a reference and stratified by time spent in the SEA region and the percentage of SEA service spent in Vietnam.

Because it was impossible to know exactly the kind and amount of herbicide or other chemical exposures experienced during the War by these veterans, we considered indirect measures of the Vietnam experience and herbicide exposure based on general knowledge of the war derived from published accounts. The partition of the war time period according to the types and amounts of herbicides sprayed, and restriction of length of tour in SEA to at most 2 years, to Ranch Hand veterans with 100% of their SEA service spent in Vietnam and to comparison veterans with 0% of their SEA service spent in Vietnam were attempts to maximize the Agent Orange exposure opportunity among Ranch Hand veterans and minimize it among comparison veterans. Categorizing veterans by time spent in SEA approximated categorization by the percentage of SEA service spent in Vietnam. Stratification by the percentage of SEA service spent in Vietnam gave a clearer dichotomy on the Vietnam experience, but the sample sizes were much reduced. Although both categorizations were less than ideal, consistencies of results between them suggested an association between cancer and Agent Orange or dioxin exposure. Our methods were derived from discussions with the Ranch Hand Advisory Committee, a non-governmental panel of scientists appointed by the Food and Drug Administration to oversee the study.

In conclusion, contrasts with the national population and internal contrasts by dioxin exposure category with regard to cancer incidence revealed increased risks of cancer of the prostate in both Ranch Hand and comparison cohorts. An increase in melanoma risk among Ranch Hand

veterans suggested an adverse association with dioxin exposure. Restriction to veterans with at most 2 years in SEA and to Ranch Hand veterans who spent all of their SEA service in Vietnam revealed increased melanoma risk in Ranch Hand veterans, consistent with an association with dioxin exposure. Internal contrasts by dioxin category provided consistent results, in strata defined by time spent in SEA and the percentage of SEA service spent in Vietnam. No increases in cancer mortality were found in Ranch Hand veterans.

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