Cancer in US Air Force veterans not involved with spraying herbicides during the Vietnam War

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Introduction

The Air Force Health Study is a 20-year prospective study examining the health, mortality and reproductive outcomes in US Air Force veterans of Operation Ranch Hand who sprayed herbicides in Vietnam from 1962 to 1971. Comparison veterans flew or serviced C-130 transport aircraft in Southeast Asia (SEA) during the same time period but did not spray herbicides. They were stationed mostly in Taiwan, the Philippines, Guam, Japan, and Thailand and spent on average less than 30% of their SEA service in Vietnam. Comparison veterans also spent approximately 30% more time in SEA than Ranch Hand veterans.

No increases in Ranch Hand cancer mortality and morbidity were found in earlier investigations[1-2], but a recent study contrasting cancer rates in Air Force veterans and in the general US (white male) population reported increases in cancer at all SEER sites, prostate cancer and melanoma in Ranch Hand veterans and cancer at all SEER sites and prostate cancer in Comparison veterans[3]. Associations between dioxin exposure category and cancer were found after restriction to Ranch Hand veterans who served in SEA no more than 2 years and to those who spent all of their SEA service in Vietnam[3]. Overall cancer incidence in the general population in countries of SEA is about half of that in the United States[4], but cancers of the oral cavity/nasopharynx and liver are more prevalent in this region[5]. Here we examine in more detail whether years served in SEA had any effect on the risk of cancer among Comparison veterans.

Methods

Comparisons who attended at least one of the periodic physical examinations conducted in 1982, 1985, 1987, 1992, and 1997 were included in this study. They were matched to Ranch Hand veterans on date of birth, race and military occupation. Participation was voluntary and informed consent was given at the examination facility. Cancer incidence data was obtained from medical records following the rules and conventions of the International Classification of Diseases, 9th Edition, Clinical Modification. "All-site SEER" cancer was defined as cancer included in any of the National Cancer Institute Surveillance Epidemiology and End Results (SEER) anatomical

category definitions. In addition to all SEER cancer sites, "all-site" cancer included basal and squamous cell carcinoma. We calculated body mass index (BMI) 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. Each veteran was assigned to one of three military occupation categories (officer, enlisted flyer, enlisted ground personnel).

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[6]. The statistical analyses were performed using cumulative cancer incidence data to 31 December 1999. Each veteran was assigned to one of the four quartiles of years served in the SEA. We employed proportional hazards models to contrast cancer incidence in the second, third and fourth SEA quartiles with the first quartile. The date of entry into follow-up was the date of the end of the last tour of duty in the SEA region. The end of follow-up was defined as the earliest of the first cancer diagnosis, death, or December 31, 1999. The Comparison tours of duty in the SEA region ranged from 1942 to 1982, but the majority served in SEA between 1962 and 1971 when the herbicide spraying occurred. We assumed a 15-year latency period in our primary analysis. Secondary analyses assumed latencies of 10 and 20 years. All analyses were adjusted for year of birth, BMI during the SEA tour of duty that qualified each veteran for inclusion in the study, military occupation and race. Analyses of melanoma and non-melanoma skin cancers were restricted to non-black veterans and additionally adjusted for skin reaction to sun exposure, and eye color. We adjusted for smoking (pack-years) at baseline in analyses of all-site cancer, all-site SEER cancer, cancer of the respiratory system, and prostate cancer.

Results

Demographic characteristics of 1,784 Comparison veterans by quartile of years served in SEA are presented in Table 1. The median days in SEA increased from 323 in the first quartile to 1525 in the fourth quartile. The mean year of birth decreased from 1945 in the first quartile to 1934 in the fourth SEA quartile and the median of pack-years of smoking increased from 8.4 in the first quartile to 19.2 in the fourth quartile, most likely related to the variation in birth year. Other variables did not show substantial variation by time spent in SEA. Consistent with the lack of the occupational exposure to dioxin-contaminated herbicides, the median dioxin levels ranged between 3.8 and 4.3 ppt.

Two hundred fifty-five veterans were diagnosed with at least one all-site cancer and 151 veterans had at least one SEER defined cancer 15 years or more after the end of service in SEA (Table 2). A statistically significant increased risk of all-site SEER cancer was observed in the fourth SEA quartile relative to the first quartile (RR=3.0, 95% CI 1.6 to 5.5, $p<0.001$). We found a similar increase for prostate cancer (RR=8.7, 95% CI 2 to 37.1, $p=0.003$). The p-values for trend were increased significantly for these associations ($p<0.001$ for both) and for cancer of the digestive system ($p=0.03$). The sample sizes in Table 2 are reduced due to the 15-year latency. For example, in the analysis of all-site cancers, 226 veterans were excluded because they were not alive and cancer-free 15 years after their last SEA tour, giving a total sample size of 1,559. Of the 226 exclusions, 28 were diagnosed with a SEER site cancer and 72 with basal cell or squamous cell carcinoma within 15 years of service in SEA. We observed no increases in the risk of respiratory cancers (n=44) or cancer of the basal or squamous cells (n=146) with years served in SEA (data not shown). The numbers of incident cases of soft tissue sarcoma, cancer of the brain and nervous

system, endocrine and lymphopoetic system and melanoma were too small to analyze. Similar results were produced when we changed the latency period to 10 or 20 years (data not shown).

Discussion

We observed increased trends in the risk of cancer at all SEER sites, of the digestive system, and of the prostate with years served in the SEA region in US Air Force veterans who served as comparisons in the Air Force Health Study. These increases suggest that time spent in SEA may be a surrogate for a major risk factor or combination of risk factors not recognized previously. Exposure to hosts of infectious disease in subtropical climates, change in diet and possible increases in smoking and alcohol consumption may have all contributed, especially in those who stayed the longest, to the increases seen in this study. Several viruses have been implicated in etiology of human cancers including human T-cell lymphotropic virus type 1, hepatitis B virus (liver hepatocellular carcinoma, endemic in SEA), the Epstein Bar virus, and different strains of human papillomavirus[7]. The number of liver cancers (only one case identified) was too small to evaluate effect of hepatitis B virus infection in this study.

A WHO-coordinated eradication campaign for malaria coincided with the calendar period during which most of these veterans served in the SEA region[8]. Massive use of DDT and other pesticides was the paramount of those activities[9]. Some epidemiologic studies reported increased risk with exposure to DDT and its metabolites for cancers of pancreas[10], liver and multiple myeloma[11], non-Hodgkin lymphoma[12] and prostate[13-14], while others found no increase in risk for these cancer sites[15-18]. In this study, no measure of exposure to DDT or other organochlorines was available.

We also examined years spent only in Vietnam in association with cancer risk, because time served in Vietnam was included in the total time spent in SEA. The adjusted relative risk for all-site SEER cancer was increased but to a lesser degree (RR=2.2, 95% CI 1.2-4.2, trend: p=0.006), most likely because of shorter time spent in Vietnam (data not shown). When only time in SEA outside of Vietnam was considered, risks similar to those seen for total time in SEA were observed. Time spent in Vietnam and time spent in SEA outside of Vietnam were not correlated (r=0.01, p=0.63).

Study strengths include detailed record verification of all reported cancers, strict quality control, and adjustment for skin reaction to sunlight, and smoking history. We were limited by the lack of exposure information to examine possible associations with other organochlorines, incomplete information regarding the location of each tour of duty in different countries of Southeast Asia, and the possible confounding by unknown or unmeasured risk factors.

In conclusion, we observed significant increases in the risk of all-site SEER cancer and prostate cancer in the fourth quartile of years served in the SEA region and a significant trend of increased risk of cancer of the digestive system cancer with years served in the SEA region in US Air Force veterans who did not spray herbicides during the Vietnam War. While Comparison veterans were not occupationally exposed to dioxin-contaminated herbicides, we cannot exclude

the possibility that environmental exposures, or behavioral changes they may have experienced in SEA contributed to the increases seen here.

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Table 1. Demographic characteristics by quartile of years served in Southeast Asia in Comparison US Air Force Vietnam veterans.

	Years in Southeast Asia[1]			
Outcome	0.1 to 1.3 (n=441)	1.3 to 2.1 (n=453)	2.1 to 3.6 (n=443)	3.6 to 15.6 (n=447)
Year of birth	1945	1944	1937	1934
Age at qualifying tour (years)	24.2	25	30.6	33.5
Median Smoking (Pack-years at baseline)	8.4	8.4	13.6	19.2
Median Dioxin (ppt[2])	3.8	3.7	4	4.3
Median year of qualifying tour	1968	1969	1969	1968
Mean BMI at qualifying tour (Std)	24.8 (3)	24.4 (2.8)	25 (3.1)	25.6 (3.1)
Median Days in Southeast Asia	323	488	791	1525
Median Days in Vietnam	75	122	223	256
Asbestos exposure (%)	28.2	29.3	31.1	26.5
Industrial chemical exposure (%)	64.6	64.9	60	58.9
Insecticide exposure (%)	62.9	63.1	63.2	65.5
Ionizing radiation exposure (%)	22.3	25.7	30.8	31.7
Black (%)	4.8	6.8	5	7.2
Officer (%)	31.5	36.9	44.7	37.1
Enlisted flyer (%)	10.4	12.4	15.8	22.1
Enlisted ground (%)	58	50.8	39.5	40.7

1. Years in Southeast Asia could not be computed for one veteran, a non-black officer without a history of cancer, due to missing tour dates.
2. Parts per trillion in serum lipid.

Table 2. Cancer incidence 15 years or more after the end of Southeast Asia service in Comparison US Air Force Vietnam veterans by quartile of years in Southeast Asia.

			Years in Southeast Asia			
Site			0.3-1.3	1.3-2.1	2.1-3.6	3.6-15.6
All sites[1]		255 (16.4)	52 (12.9)	46 (11.3)	77 (20.9)	80 (21)
	RR	1.1	1.0	1.1	1.2	1.3
	95% CI	1 to 1.2	Referent	0.7 to 1.8	0.8 to 1.9	0.9 to 2.0
	p-value	0.08		0.67	0.30	0.21
All SEER sites[1]		151 (9.3)	19 (4.6)	22 (5.2)	45 (11.7)	65 (16)
	RR	1.2	1.0	1.2	1.9	3.0
	95% CI	1.1 to 1.3	Referent	0.6 to 2.7	1 to 3.6	1.6 to 5.5
	p-value	<0.001		0.56	0.06	<0.001
Digestive system[2]		26 (1.6)	3 (0.7)	7 (1.6)	5 (1.3)	11 (2.7)
	RR	1.2	1.0	2.4	1.4	3.4
	95% CI	1 to 1.4	Referent	0.6 to 9.4	0.3 to 6.5	0.8 to 13.8
	p-value	0.03		0.2	0.66	0.09
Prostate[1]		60 (3.6)	2 (0.5)	7 (1.6)	21 (5.4)	30 (7.2)
	RR	1.2	1.0	3.4	6.4	8.7
	95% CI	1.1 to 1.4	Referent	0.7 to 16.9	1.5 to 27.8	2 to 37.1
	p-value	<0.001		0.13	0.01	0.003

1. Adjusted for military occupation, year of birth, BMI at the qualifying tour, race, and baseline smoking history (pack-years).
2. Adjusted for military occupation, and year of birth and BMI at the qualifying tour.