Author   Kang, Han

Corporate Author

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Soft Tissue Sarcoma and Military Service in Vietnam: A Case-Control Study [1]

Han Kang, Dr.P.H., [2,3] Franz Enziger, M.D., [4] Patricia Breslin, Sc.D., [2] Michael Feil, M.S., [2] Yvonne Lee, M.S., [2] and Barclay Shepard, M.D. [5,6]

ABSTRACT—A case-control study was conducted in men who were of draftable age during the Vietnam conflict to examine the association of soft tissue sarcomas (STSs) with military service in Vietnam as well as other host and environmental risk factors. A total of 217 STS cases selected from the Armed Forces Institute of Pathology were compared to 599 controls for Vietnam service, occupational and nonoccupational exposure to various chemicals, occupational history, medical history, and life-style (smoking, alcohol, coffee, etc.). Military service information was verified by a review of the patient's military personnel records. Other information was ascertained from a telephone interview with either subjects or their next of kin. Cases and controls were stratified on the basis of the hospital type (civilian, Veterans Administration, and military); the Mantel-Haenszel estimate of the odds ratio (OR), adjusted for the effects of the stratification variable, was calculated. Vietnam veterans in general did not have an increased risk of STS when compared to those men who had never been in Vietnam (OR, 0.85; 95% confidence interval, 0.54-1.36). Subgroups of Vietnam veterans who had higher estimated opportunities for Agent Orange exposure seemed to be at greater risk of STSs when their counterparts in Vietnam were taken as a reference group. However, this risk was not statistically significant.—JNCI 1987; 79:693-699.

There is much concern in the United States that many health problems in Vietnam veterans may be the result of exposure to Agent Orange during their military service in Vietnam. Their complaints range from psychological disorders to cancer. Agent Orange was the herbicide most commonly applied in Vietnam by the United States Air Force during the Vietnam conflict. It was a mixture of two commercial herbicides, 2,4-dichlorophenoxyacetic acid (CAS: 94-75-7) and 2,4,5-trichlorophenoxyacetic acid (CAS: 93-76-5). The 2,4,5-trichlorophenoxyacetic acid contained minute amounts of an extremely toxic chemical, dioxin [TCDD (CAS: 1746-01-6)], which contaminated the herbicide during the manufacturing process. TCDD is teratogenic and carcinogenic in some experimental animals (1-3). During the 5-year period from 1965 to 1970, the United States Air Force sprayed more than 11 million gallons of Agent Orange in South Vietnam (4). Approximately 2 million military personnel served in Vietnam during the same period.

The possibility that exposure to the herbicide may induce rare forms of cancer in humans such as STS has been suggested from studies in Sweden (5, 6). The Swedish studies have shown that persons reporting exposure to phenoxyherbicides have a fivefold to sixfold higher risk of developing STS as compared to persons without such exposure. A similar risk was reported by the Swedish investigators for malignant lymphoma (7).

Studies published subsequent to the Swedish studies have not demonstrated the association between STS and either exposure to phenoxyherbicides or military service in Vietnam (8-11). Several cases of STS have been reported, however, among workers involved in the manufacture or use of phenoxyherbicides (12-14). These industrial workers, in contrast to the herbicide applicators, are believed to have been exposed to relatively high levels of TCDD contaminant.

STSs are a complex and diverse group of malignant neoplasms that originate in extraskeletal supporting structures of the body, excluding the hematopoietic system, the glia, and supporting tissues of specific organs and tissues (15). STSs account for about 1% of all malignant neoplasms and for about 2% of all cancer deaths. The average annual age-adjusted incidence rate for white males is 3.82 per 100,000, and it is estimated that about 8,000 patients are diagnosed with STS each year in the United States (16).

Little is known about the etiology of STS. An excess

of STS has been reported in patients receiving immuno-suppression therapy for renal transplantation and other conditions (17, 18). A small fraction of STS is induced by heavy external radiation therapy for various benign disorders and malignant tumors. Nearly all cell types of STS have been described following radiation (19, 20). Some radioactive materials used for diagnostic or therapeutic purposes may induce sarcomas at or near sites of deposition (21, 22). The well-known examples of associations between specific chemicals and sarcomas of specific cell types are angiosarcoma of the liver and exposure to vinyl chloride and mesothelioma and exposure to asbestos (23, 24).

In view of the concern raised by many veterans that their contact with Agent Orange during Vietnam service may increase the risk of developing STS and conflicting research findings in the scientific literature regarding association between exposure to phenoxyherbicides or military service in Vietnam and STS, a case-control study of STSs among men of draftable ages during the Vietnam conflict was conducted.

SUBJECTS AND METHODS

Selection of cases and controls.—Cases were drawn from soft tissue tumor files of the AFIP. The AFIP offered a unique resource to contribute to this study. The AFIP routinely provides consultation services for civilian and military pathologists throughout the United States, especially for conditions such as STS that present special diagnostic problems. Almost one-quarter to one-third of the STSs occurring in the United States are being sent to the AFIP for review. Thus the AFIP is one of the largest single registries in the world for this group of tumors. The uniformity of diagnoses at the AFIP gives it an added advantage as a resource for epidemiologic studies.

Selection of STS cases was restricted to men who were diagnosed at the AFIP as STS patients between January 1, 1975, and December 31, 1980, and who were born between 1940 and 1955. These eligibility criteria were established to restrict the study to individuals who were potentially at risk of exposure to Agent Orange and to reduce selection bias. These individuals would have been between 18 and 25 years of age during the Vietnam conflict, and their specimens would have been referred for diagnostic evaluation to the AFIP before the publicity appeared on Vietnam service, Agent Orange exposure, and the risk of STS.

Controls were selected from the patient logs of referring pathologists or their pathology department. This was to duplicate the selective factors (e.g., socioeconomic status, area of residency, etc.) that bring people to these hospitals or clinics. Excluded from consideration as controls were patients with diagnoses of STS, non-Hodgkin's lymphoma, and Hodgkin's disease. The latter two conditions have been associated with exposure to phenoxyacetic acid herbicides, chlorophenols, or their contaminants (7). For each STS case, a pathologist in

each referring pathology unit was asked to select the 3 male patients who would have been born between 1940 and 1955. Controls were not matched to the STS case by race or vital status.

A total of 440 STS cases was identified from the AFIP soft tissue tumor registry as potentially eligible cases. A letter was sent to each of the 368 hospitals representing the potential cases requesting their cooperation in the study. One hundred and nineteen hospitals (32%) did not respond positively because they were either unable or unwilling to retrieve and review the requisite medical records for selection of controls. These medical records could be as old as 10 years. Ultimately, 249 hospitals nationwide cooperated in the study and contributed 279 STS cases and 808 controls.

Interviews.—A letter was then sent to attending physicians of the STS cases and controls indicating our intent to approach the study subjects or the next of kin for a telephone interview unless the physician believed that there was strong medical contraindication for their participation in the interview. When negative responses were not received from the physician, an introductory letter was sent to each study subject or the next of kin to solicit his participation in a telephone interview. In the letter the purpose of the study was described simply as a national health study of adult men who were treated in various hospitals throughout the United States. No specific mention was made of cancer, STS, Agent Orange, or service in Vietnam.

The telephone interview averaged approximately 40 minutes and elicited information on occupational exposures, medical history, life-style including alcohol and tobacco consumption, and socio-demographic factors.

Interviews were successfully conducted for 217 of 279 cases (78%) and 599 of 808 controls (74%). Reasons for unsuccessful interviews included inability to locate study subjects or their next of kin (17% of cases and 17% of controls) and refusal to be interviewed (5% of cases and 9% of controls). In an attempt to minimize interviewer bias, a two-interview approach was taken. The first interviewer asked questions on medical history, and the second interviewer administered the remaining questions on occupational exposure, life-style, and military history. The interviewers had no opportunity to know the case or control status of the respondent. Interviews were obtained directly from the study subjects for 120 of 217 cases (55%) and 527 of 599 controls (88%). Military and Vietnam service for all study subjects was documented by reviewing the existing military personnel records stored at various locations.

Measure for herbicide exposure.—Although desirable, a valid and precise estimate of the exposure of each Vietnam veteran to Agent Orange is not considered feasible based on either military records or self-reported exposure. In this study the probability of opportunity for exposure was determined in several different ways with varying degrees of likelihood of exposure: service in the Army or Marine Corps, military occupation, broad geographical location of the individual's unit in

Vietnam at the time of his service, or a combination of the above.

It has been suggested that ground troops (Army or Marines) in Vietnam, by the nature of their military operations through defoliated zones and the practice of base perimeter spraying, might have a higher probability of direct or indirect contact with Agent Orange than other Vietnam veterans. Furthermore, it has been suggested that, among ground troops, those engaged in combat were more likely to be placed in herbicide-sprayed areas than individuals who were not in combat. In the military personnel records, there was no single data element applicable to all veterans that would indicate whether they actually had been in combat. As an alternative measure, the proportion of individuals with combat-related MOSCs was determined for both STS cases and controls. Combat-related MOSCs were those occupations where primary duties involved direct offensive and defensive action against an armed hostile force. Examples of combat MOSCs include rifleman, field artillery man, and tank crew member.

As another surrogate measure for herbicide exposure, the broad geographic location of the individual's military unit in reference to recorded herbicide spray missions was also determined. Initially, an elaborate computer matching of troop location to recorded aerial spray missions (Ranch Hand HERB and Service HERB tapes) was planned. However, an expert government panel (25) has subsequently determined that military records alone could not be used to locate troops with enough precision to allow a scientifically valid estimate of the likelihood of exposure to herbicides. For example, it cannot be determined in many instances whether a man was within 2 km of a spray tract on the day of a Ranch Hand spray mission.

According to maps developed by the National Research Council of the National Academy of Sciences from recorded spray missions, areas of defoliation and crop destruction were most extensive in military region III (26). There were 3,487 spray missions carried out in military region III for the purposes of crop destruction, defoliation, and clearance of base perimeters and supply lines from 1964 to 1971 (25). During the same period the number of spray missions recorded within military regions I, II, and IV were 2,015, 2,406, and 825, respectively. Army units were classified as located in regions I, II, III, or IV. Almost all Marine units were located in military region I.

Statistical analysis.—The measure of association between the risk of STS and the various exposure factors that included military service in Vietnam was the RR, as approximated by the OR. Tests of significance were derived by the Mantel-Haenszel chi-square statistic, and 95% CIs were calculated using Cornfield's method (27, 28).

The confounding variable of hospital type (civilian, Veterans Administration, and military) was evaluated by stratified techniques. The Mantel-Haenszel procedure was used to estimate the OR and calculate the 95% CI (27).

Since matching was employed in the study design and cases and controls were not replaced when the interview was not completed because of inability to locate them or refusal to participate, analysis was also conducted using a logistic approach for matched data with unequal number of controls per case (29). The results were similar to those derived from the unmatched stratified analysis. For this reason, the results from the unmatched stratified analysis were chosen for presentation.

RESULTS

The distribution of cases and controls by age, accession year, and type of hospital for controls is shown in table 1. Demographic characteristics for cases and controls were almost identical with respect to marital status, religion, race, and level of education (table 2).

There were 45 of 217 STS cases and 145 of 599 controls who had a record of military service in Vietnam. No statistically significant positive association was found between STS and military service in Vietnam on a crude and adjusted basis. The crude OR was 0.82, with a 95% CI of 0.55-1.21. The Mantel-Haenszel OR adjusted for the effect of hospital type was 0.85, with a 95% CI of 0.54-1.36 (table 3). Distribution of histologic type of STS reported among Vietnam veterans was similar to that reported among non-Vietnam veterans. No particular anatomic site or histologic type was predominant in either group.

Notwithstanding the assumption that ground troops were more likely to be exposed to Agent Orange than non-ground troops, table 4 indicates that ground troops in Vietnam as a group showed a lower RR of STS when compared to men who had never been in Vietnam or Vietnam veterans in general. However, it appears that subgroups of ground troops who had higher estimated opportunities for Agent Orange exposure experienced greater risk of STS. For example, the OR was 0.61 (95% CI, 0.32-1.13) for Army Vietnam veterans, whereas the OR increased to 1.06 (95% CI, 0.42-2.59) for a subgroup of Army Vietnam veterans who were likely to

TABLE 1.—*Distribution of STS cases and control patients by age, accession year, and hospital type*

Characteristic	Cases (n = 217)		Controls (n = 599)	
	No.	Percent	No.	Percent
Age at accession, yr				
≤26	30	14	77	13
26-35	165	76	476	79
≥35 or more	22	10	46	8
Accession year				
1975 or earlier	37	17	98	16
1976-77	64	29	159	27
1978-79	73	34	205	34
1980 or later	43	20	137	23
Type of hospital				
Civilian	163	75	431	72
Veterans Administration	26	12	86	14
Military	28	13	82	14

TABLE 2.—*Distribution of selected demographic characteristics for STS cases and control patients*

Characteristic[a]	Cases (n = 217)		Controls (n = 599)	
	No.	Percent	No.	Percent
Marital status				
Married	154	71	409	68
Divorced	18	8	62	10
Never married	45	21	125	21
Other-DK	0	0	3	<1
Religion				
None	7	3	26	4
Catholic	52	24	176	29
Protestant	146	67	361	60
Others	12	6	36	6
Race				
White	178	82	511	85
Black	31	14	62	10
Hispanic	6	3	17	3
Other	2	1	9	2
Education				
<11th grade	22	10	63	11
High school	62	29	175	29.
Vocational school	11	5	22	4
Some college	60	28	148	25
4-yr college	34	16	81	14
Post college	28	13	108	18
DK	0	0	2	<1

[a] DK = Do not know.

have been involved in combat. For this reason, the ORs were calculated for Army and Marine veterans with combat-related MOSCs by military region where their units were stationed, taking their non-combat counterparts in each military region as reference groups (table 5). Army Vietnam veterans who had a combat-related MOSC showed a 2.6 times elevated risk of STS as compared to their non-combat counterparts in Vietnam (OR, 2.57; 95% CI, 0.72–9.36). The risk of STS was even greater (OR, 8.64; 95% CI, 0.77–111.84) when the location of their units was within military region III, the area where Agent Orange spray was reported to be extensive. In both instances, however, these increased risks were not statistically significant.

In this study the power to detect moderate increases in RR of STS among the entire group with Vietnam service is fairly good. The study had an estimated

TABLE 4.—*ORs for STSs in relation to various categories of estimated Agent Orange exposure likelihood for all study subjects*

Exposure group[a]	STS cases	Controls	OR	95% CI
Never in Vietnam	172	454	1.00	
Ever in Vietnam	45	145	0.82	0.55–1.21
Army, all	15	65	0.61	0.32–1.13
Combat MOSCs	8	20	1.06	0.42–2.59
MR I	7	15	1.23	0.45–3.29
MR I and combat MOSCs	3	6	1.32	<0.01–6.00
MR III	6	30	0.53	0.19–1.36
MR III and combat MOSCs	5	11	1.20	0.36–3.80
Marine, all	5	24	0.54	0.18–1.55
Combat MOSCs	3	13	0.61	0.08–2.32

[a] Combat MOSCs include the following career groups: infantry, combat engineering, field artillery, special operations, and armor. MR refers to military region. South Vietnam was divided into four regions. The regions were denoted by I, II, III, and IV. They went from north to south.

65% chance of detecting a 1.5 times increase in the risk of STS and a 98% chance of detecting a twofold increase in the risk of STS for Vietnam veterans in general. It must be noted, however, that the study had a very low power to detect greater increased risks for subgroups of Vietnam veterans who had higher estimated opportunities for Agent Orange exposure. There was a 10% chance of detecting a 1.5 times increase in the risk of STS, a 23% chance of detecting a twofold increase, and an approximately 80% chance of detecting a fivefold increase in the risk of STS for Army combat veterans when non-combat Army Vietnam veterans were taken as a reference group.

No statistically significant association was found between STS and other study variables, including histories of viral infections, tropical diseases, skin problems, use of certain medications, organ transplantation, artificial joints, trauma, cancer other than STS, immune deficiency, chronic edema, radiation therapy, blood transfusion, and cancer in the family; smoking, alcohol drinking, and coffee drinking; work in certain occupations or industries that might involve herbicide, pesticide, and other toxic chemical exposure; exposure to specific chemicals such as asbestos, arsenic, herbicides,

TABLE 3.—*Distribution of STS cases and control patients by Vietnam service status[a]*

Vietnam service	Hospital type							
	Civilian		Veterans Administration		Military		Total	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Yes	20	66	11	43	14	36	45	145
No	143	365	15	43	14	46	172	454
Total	163	431	26	86	28	82	217	599
OR	0.77		0.73		1.27		0.82	
95% CI	0.43–1.36		0.27–1.94		0.50–3.29		0.55–1.21	

[a] The Mantel-Haenszel estimate of the OR adjusted for the effects of the stratification variable = 0.85; 95% CI = 0.54–1.36.

TABLE 5.—ORs for STSs in relation to combat and military region among Vietnam veterans[a]

Combat MOSC	Military region[b]							
	I		II		III		Total	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Army Vietnam veterans								
Yes	3	7	0	3	5	11	8	20
No	4	9	2	17	1	19	7	45
Total	7	15	2	20	6	30	15	65
OR	1.13		0		8.64		2.57	
95% CI	0.13-9.85				0.77-111.84		0.72-9.36	
Marine Vietnam veterans								
Yes	3	13					3	13
No	2	11					2	11
Total	5	24					5	24
OR	1.27						1.27	
95% CI	0.13-7.90						0.13-7.90	

[a] The Mantel-Haenszel estimate of the OR adjusted for the effects of the military region for Army personnel = 2.32; 95% CI = 0.47-11.41.
[b] South Vietnam was divided into four military regions. No Army Vietnam veterans in the study served in military region IV. Almost all Marine units were located in military region I.

degreasing chemicals, insecticides or pesticides, and vinyl chloride or polyvinyl chloride; and occupational exposure to radiation (table 6).

The STS cases were also compared to control patients with cancer ($n = 132$) for study variables. No statistically significant association was found for any variable. This was also true when taking only the study subjects who responded directly (120 cases and 527 controls), with one exception. Men who had a history of topical tar ointment application had an OR of 2.72, with a 95% CI of 1.25-5.85. This finding is of interest in that crude coal tar contains chemical substances that can cause benign and malignant neoplasms in animals and a case-control study reported that patients with high exposure to tar and UV radiation had a 2.4 times increase in the risk of skin cancer as compared with those patients lacking the high exposure (30).

DISCUSSION

The results of the present study do not support a strong positive association between Vietnam service and the occurrence of STS. These findings are consistent with the results of several other case-control studies of STSs. Greenwald and co-workers in 1984 (8) reported no significant association between STS and military service in Vietnam or Agent Orange-2,4,5-trichlorophenoxyacetic acid exposure. Of 281 STS cases, 10 men had mili-

TABLE 6.—ORs for STSs for various host and environmental factors[a]

Factors	Cases (n=217)	Controls (n=599)	OR	95% CI
Manufacture or repair of electrical transformers	11	20	1.52	0.60-3.82
Work with asbestos	53	151	0.97	0.44-2.11
Work with arsenic	6	21	0.81	0.13-4.87
Work with herbicides	17	77	0.62	0.32-1.21
Work with vinyl chloride-polyvinyl chloride	14	35	1.13	0.36-3.57
Work with x-ray	22	61	0.99	0.86-1.14
Apply herbicides on farm or ranch	12	61	0.51	0.19-1.37
Work at incinerator for waste materials	3	12	0.69	0.05-10.24
Work in lumbering, logging, or forestry	13	45	0.79	0.35-1.76
Use herbicides in yard work	60	157	1.08	0.68-1.70
Cigarette smoking	126	401	0.71	0.51-0.99
Coffee drinking	131	371	0.92	0.63-1.35
Drinking alcoholic beverages	193	559	0.66	0.36-1.20
Angioma	13	19	1.95	0.87-4.36
Psoriasis	5	10	1.43	0.19-10.81
Neurofibromatosis	4	2	6.00	0.89-40.39
Radiotherapy	9	28	0.99	0.83-1.18
Tar ointment	15	23	1.85	0.89-3.86
Close relative with cancer	70	159	1.31	0.92-1.87

[a] ORs were calculated using the Mantel-Haenszel procedure controlling for the effect of hospital type.

tary service in Vietnam; in contrast, of 281 live controls, 18 had served in Vietnam. The OR was 0.5, with a 95% CI of 0.21-1.31. The OR associated with Agent Orange exposure as reported by the subjects was 0.70, with a 95% CI of 0.17-2.92. Smith and co-workers (*9*), in studying 82 STS cases and 92 controls for their potential exposure to phenoxyherbicides, did not observe a statistically significant positive association. The estimate of RR was 1.3, with a 90% CI of 0.6-2.5. In a recent paper, Hoar and co-workers (*10*) confirmed the non-positive association between STS and herbicide exposure. They reported that neither STS nor Hodgkin's disease was associated with herbicide exposure. Of the 133 STS cases, 95 men reported having worked or lived on farmland as compared with 662 of 948 controls, yielding an OR of 1.00, with a 95% CI of 0.7-1.6. Twenty-two of the STS cases reported farm herbicide use as compared to 192 of the controls. The OR was 0.9, with a 95% CI of 0.5-1.6. However, Hoar et al. reported a strong association between non-Hodgkin's lymphoma and farm herbicide use.

The absence of an increased risk of STS in Vietnam veterans as a group when compared to those men who had never been in Vietnam cannot be explained by possible differential referral patterns to the AFIP with respect to the presence of study factors such as Vietnam service or Agent Orange exposure. The hospital pathologist referring STS cases to the AFIP seldom has that information. Furthermore, selection of STS cases was restricted to the cases referred to the AFIP in 1980 or earlier, before the publicity appeared on Vietnam service, Agent Orange exposure, and the risk of STS. Preferential referral of Vietnam veteran STS cases to the AFIP, however, would have introduced a bias toward overestimating the risk of STS for Vietnam veterans. Selection of controls from the hospital that referred the STS case to the AFIP does not appear to have introduced either an overrepresentation or an underrepresentation of men who were unlikely to have been in the military because of their chronic illness. The whole spectrum of diagnoses reflecting acute and chronic conditions was recorded for the control patients in the hospital records. However, it is unknown what the recorded health status of the STS cases as well as the controls was as far back as 15 years ago, during their draftable age. Interview data show that the proportions of cases and controls reporting as having had any physical conditions that might have prevented them from serving in the military during their draftable age were similar: 24% of the STS cases and 23% of the controls. Had bias been introduced, it would have created a spurious positive association by underrepresenting veterans in controls.

Several mortality studies of Vietnam veterans found no statistically significant excess deaths from STS, with the exception of the Massachusetts State study (*31-34*). The Massachusetts study found 9 deaths from STS among Vietnam veterans as compared to only 1 expected death from STS. The results of the mortality studies reported to date are difficult to interpret since there are some limitations, which include the small number of

deaths available for analysis (lack of adequate statistical power), the varying quality and accuracy of the death certificate coding, possible misdiagnosis of this malignancy, and lack of verification of Vietnam service.

The absence of a possible positive association between STS and Vietnam service might be the result of insufficient observation time since Agent Orange exposure in Vietnam. In general, it takes more than a decade for cancer to manifest itself if it is induced by a chemical carcinogen. Over 80% of the STS cases in this study were observed less than 10 years after the last troops were exposed to Agent Orange in Vietnam. Another possibility is that, although Agent Orange or dioxin can induce STS, Vietnam veterans as a group were exposed to such small doses or only a very small fraction of Vietnam veterans might have been exposed to Agent Orange that the present study does not have an adequate statistical power to detect the excess risk.

In summary, Vietnam veterans as a group as well as subgroups of those veterans who were categorized as having had higher opportunities for Agent Orange exposure by virtue of their military occupation or location of their units in Vietnam did not have a statistically significant increased risk of STS when compared to men who had never been in Vietnam. However, within Vietnam veterans, those who had higher opportunities for Agent Orange exposure appear to have greater risk of STS. The conclusion for subgroups of Vietnam veterans is based on considerably weaker study power than the conclusion about Vietnam veterans in general. Therefore, the possibility of a modestly increased risk of STS associated with Agent Orange exposure in Vietnam among select groups of Vietnam veterans can be neither confirmed nor ruled out in this study. Additional studies using better characterization of exposure are needed to answer this question.

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