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Soft Tissue Sarcomas and Military Service in Vietnam: A Case Comparison Group Analysis of Hospital Patients

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The possibility that exposure to Agent Orange or phenoxy herbicides may have increased the risk of soft tissue sarcomas has been of genuine concern to Vietnam veterans and their families. A hospital-based case comparison group study was undertaken to examine, through a comprehensive review of medical records and military personnel records, the association between previous military service in Vietnam and soft tissue sarcomas. The case group comprised 284 Vietnam-era veteran patients who served in the US military between 1964 and 1975 and were treated in one of the 172 VA hospitals between 1969 and 1983 with a diagnosis of soft tissue sarcoma. The comparison group consisted of 13,496 patients who were systematically sampled from the same Vietnam-era veteran patient population from which the cases were drawn. Military service information, in particular Vietnam service status, for each case and control patient was obtained from a review of the patient's military personnel records archived at the National Personnel Records Center in St Louis, Missouri. No significant association of soft tissue sarcomas and previous military service in Vietnam was observed: odds ratio was 0.83 with a 95% confidence interval of 0.63 to 1.09.

Two Swedish case-control studies have suggested that persons reporting exposure to phenoxy herbicides have a five- to sixfold higher risk of developing soft tissue sarcomas (STS) compared with persons without such exposure.^{1,2} In addition, several cases of soft tissue sarcomas have been reported in the US among workers involved in the manufacturing or use of phenoxy herbicides.³⁻⁵

These studies have generated much concern in the United States for Vietnam veterans—concern that, as a result of their exposure to Agent Orange in Vietnam, they may be at increased risk for soft tissue sarcomas in addition to several other medical and psychological problems. Agent Orange, a mixture of two commercial phenoxy herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), was the herbicide most commonly used by the US military in Vietnam. The principal concern over exposure to Agent Orange stems from the fact that during the manufacture of 2,4,5-T trace amounts of a highly toxic dioxin, 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD), appeared as a contaminant.

Agent Orange was sprayed in Vietnam for defoliation and crop destruction from 1965 to 1970 in a military operation named Ranch Hand. The aerial application of Agent Orange reached its peak in 1967, leveled off slightly in 1968 and 1969, and declined rapidly in 1970. During the five-year period the US Air Force sprayed more than 11 million gallons of Agent Orange in South Vietnam. Approximately 2 million US military personnel served 1-year tours during the same period.

Studies published subsequent to the Swedish studies have not yet demonstrated the association between soft tissue sarcomas and either exposure to phenoxy herbicides or military service in Vietnam.⁶⁻¹¹ Two of the seven industrial workers previously reported to be cases of STS were also found to have not sarcomas but carcinomas.¹²

In view of the public concern about potential health risk among Vietnam veterans and conflicting research findings in the scientific literature, a case comparison group analysis of hospital patients for soft tissue sarcomas was undertaken to determine the association between previous military service in Vietnam and soft tissue sarcomas.

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Materials and Methods

The Veterans Administration Patient Treatment File (PTF) was used to identify all Vietnam era veterans whose conditions were diagnosed as soft tissue sarcomas from 1969 through 1983. The PTF is a computerized hospital data base of inpatient records, including patients' demographic data, surgical and procedural transactions, and patient movement and diagnoses. A record is created for each inpatient discharged from one of the 172 VA medical centers. The Vietnam-era veterans are defined as veterans who served in the US military sometime during Aug 5, 1964, and May 7, 1975.

A total of 418 cases with International Classification of Diseases (ICD) 171 diagnosis, ie, malignant neoplasm of connective and other soft tissue, were identified by computer search of the PTF for Vietnam-era veterans who were hospitalized between 1969 and 1983. A pathology report for each ICD 171 case was requested from each treating VA medical center. A review of 394 pathology reports received for these cases was made by a pathologist (L.W.) who has particular interest and experience in this group of malignancies. During the review he had no knowledge of Vietnam service status of any of the patients.

On the basis of the review of the pathology reports, 151 ICD 171 cases were excluded as not likely being soft tissue sarcomas because of miscoding or misclassification and nine ICD 171 cases were put in a doubtful STS category, leaving 234 diagnoses of STS. All diagnoses were classified according to the World Health Organization classification system for soft tissue sarcomas.¹³

The comparison group consisted of 14,931 patients who were systematically sampled from the same Vietnam-era veterans patient population from which the STS case subjects were identified. Vietnam-era veteran patients who have predetermined numbers in the last two digits of their social security numbers were selected among all Vietnam-era veteran patients.

Military service information, in particular Vietnam service status, for STS case subjects and control patients was obtained from a comprehensive review of the patient's military personnel records archived at the National Personnel Records Center (NPRC) in St Louis, Missouri. The General Services Administration (GSA), under an agreement with the Department of Defense,

maintains the military personnel records of veterans, including those from the Vietnam era. Military personnel records were located and abstracted for all of the 234 STS case subjects and 13,496 of the 14,931 (90%) control patients.

Results and Discussion

Eighty-six of the 234 STS cases, or 36.8%, had served in Vietnam. As Table 1 indicates there was no one predominant type of STS. Distribution of tumor type of the 234 STS cases was similar to the results from the recently published New York state study of 281 cases of soft tissue sarcoma and Vietnam service.⁷ Greenwald et al reported that percentage distribution of malignant tumor of muscle tissue, fibrous tissue, adipose tissue, and other soft tissue was 23.8, 17.8, 16.4, and 42.0, respectively, among the men with soft tissue sarcomas diagnosed from 1962 through 1980, who were between the ages of 18 and 29 years any time between 1962 and 1971 and in the New York State Cancer Registry.

Age distribution of STS case subjects was similar to the control group. No unusual influx of STS case subjects was observed at any interval as indicated by percent distribution of STS case subjects and control groups by hospitalization year (Table 2).

Of the sample of 13,469 PTF Vietnam-era patients, 5,544 or 41% had served in Vietnam (Table 3). No significant association of soft tissue sarcomas and previous military service in Vietnam was observed among the Vietnam-era veterans who had come to the VA hospital for inpatient medical care. The odds ratio was 0.83 with a 95% confidence interval of 0.63 to 1.09. This suggests that the chance of having a diagnosis of STS among Vietnam veteran patients was not greater than that among veteran patients who did not serve in Vietnam.

A differential ascertainment of military service status between the STS case subjects (100%) and the control patients (90%) should be noted. However, the difference is primarily a reflection of levels of efforts and man-hours allocated for the personnel record search rather than any difference in availability of the military records between STS case subjects and control patients, or Vietnam veterans and non-Vietnam veterans. For ex-

TABLE 1
Soft Tissue Sarcoma Type By Military Service Status

Type	Histology	Non-Vietnam Veteran	Vietnam Veteran	Total (%)
Tumors of muscle tissue	Rhabdomyosarcoma	18	8	26
	Leiomyosarcoma	8	12	20
Tumors of fibrous tissue	Fibrosarcoma	26	13	39 (16.7)
Tumors of synovial tissue	Synovial sarcoma	21	9	30 (12.8)
Tumors of adipose tissue	Liposarcoma	19	9	28 (12.0)
Tumors of vascular origin	Angiosarcoma	3	1	4
	Malignant hemangiopericytoma	10	2	12
Others		43	32	75 (32.0)
Total (%)		148 (63.2)	86 (36.8)	234 (100)

TABLE 2
Distribution by Age and Hospital Discharge Year for Soft Tissue Sarcoma Case Subjects and Comparison Group

Category	Percentage	
	STS Case Subjects	Comparison Group
Age group (yr)		
20-29	9	6
30-34	18	29
35-39	42	37
40-44	11	11
45-49	4	4
50-59	10	8
60+	6	5
Hospitalization (yr discharged)		
Before 1970	6	7
1971-1975	35	36
1976-1980	42	41
1981-1983	17	16

TABLE 3
Distribution of Soft Tissue Sarcoma Case Subjects and a Comparison Group of Patients by Vietnam Service Status*

Vietnam Service	STS Case Subjects (%)	Comparison Group (%)	Total
Yes	86 (37)	5,544 (41)	5,630
No	148 (63)	7,952 (59)	8,100
Total	234 (100)	13,496 (100)	13,730

* Odds ratio: 0.83 (95% confidence interval 0.63 to 1.09); χ^2 : 1.78 ($P > .1$)

ample, when the same levels of record search efforts made for the control patients were employed for the STS case subjects, the military record searchers at the NPRC were able to locate 214 of the 234 STS cases (91%); the yield for the control patients was 13,496 of the 14,931 (90%). Additional time-consuming manual tracking efforts were made for the 20 STS case subjects whose Vietnam service status was not determined because their personnel folders were misplaced, missing, or on loan to other agencies. Of the 20 STS case subjects, 12 did not serve in Vietnam and eight did serve in Vietnam: a ratio of 5:3.3. Prior to this exhaustive manual search the ratio among the 214 STS case subjects was 5:2.9.

Even if one makes an extreme assumption, that is, that all of the remaining 10% of the control patients (1,435) whose military personnel records were not located did not serve in Vietnam, the conclusion of the study would not be altered. This assumption results in the odds ratio of 0.98. The other extreme assumption, that is, that all of the 1,435 control patients had served in Vietnam, results in the odds ratio of 0.66.

There seems to be no propensity of ground troops (Army or Marines) among the STS case subjects compared with the comparison group (Table 4). It has been suggested that ground troops in Vietnam, by nature of their military operation through defoliated zones and by practice of base perimeter spraying, might have a higher probability of direct or indirect contact with Agent Orange than Air Force or Navy personnel.

TABLE 4
Distribution of Soft Tissue Sarcoma Case Subjects and Comparison Group of Patients by Branch of Service in Vietnam

Branch	STS Case Subjects (%)	Comparison Group (%)
Army	45 (52)	3,528 (64)
Air Force	6 (7)	367 (7)
Marines	14 (16)	921 (16)
Navy	21 (24)	721 (13)
Coast Guard	—	7 (<1)
Total	86 (100)	5,544 (100)

The findings of this study are consistent with a case control study recently published by Greenwald et al.⁷ Greenwald et al reported no significant association between STS among Vietnam-era veteran-age males and military service in Vietnam.

Other studies of Vietnam-era veterans published to date also have failed to find an excess of STS among Vietnam veterans. A study of Ranch Hand personnel, a group of approximately 1,260 men who conducted the fixed-wing aerial herbicide spraying missions in Vietnam from 1962 through 1971, did not reveal a single death from STS.¹⁰ A proportionate mortality analysis of deaths among New York State Vietnam-era veterans between 1965 and 1980, exclusive of 1968 and 1969, also failed to show excess STS deaths among Vietnam veterans.¹⁴ Two of the 555 deaths reported among Vietnam veterans were due to cancer of connective and soft tissue (ICD 171), whereas three of 941 deaths among non-Vietnam veterans resulted from the same type of cancer. The mortality odds ratio (MOR) was 1.09 with a 95% confidence interval of 0.18 to 6.70. A mortality study of Australian Vietnam-era veterans reported 260 deaths among 19,205 Vietnam veterans and 263 deaths among 25,677 non-Vietnam veterans when followed from the end of their military service to Jan 1, 1982. There was no statistically significant difference in the death rates from STS.¹¹ However, in all three mortality studies, it should be recognized that the design of the study is such that only very high risks for STS were likely to be detected: the number of person-years followed or number of deaths available for analysis was too small to detect moderately elevated relative risks of STS from Vietnam service.

The absence of positive association between STS and Vietnam service might be a 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. More than 80% of STS case subjects in the 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 amounts that the conventional epidemiologic study cannot detect the excess risk resulting from Agent Orange exposure in Vietnam. Or there is the possibility that Agent Orange does not induce STS in humans after all.

In conclusion, a study of STS case subjects and a comparison patients group in VA hospitals did not reveal a statistically significant positive association between STS and previous military service in Vietnam.

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