Table 3.9. Risk of Non-Hodgkin's Lymphoma Among Vietnam Veterans, by Number of Years Since Start of First Tour in Vietnam

Number of Years Since Start of First Tour in Vietnam[a]	Controls (N = 133) %[b]	(N)	Non-Hodgkin's Lymphoma Cases (N = 99) %[b]	(N)	Odds ratio[c] (95% Confidence Interval)	P-value[d]
<17	15.0	(20)	13.3	(13)	1.35 (0.64-2.82)	
17 to 18	30.8	(41)	30.6	(30)	1.51 (0.91-2.51)	0.75
19 to 21	41.4	(55)	39.8	(39)	1.40 (0.90-2.18)	
≥22	12.8	(17)	16.3	(16)	1.63 (0.80-3.32)	
Unknown	—	(0)	—	(1)		

[a] For cases, the end of the latency period is the date of diagnosis; for controls, it is the date the registry was notified of selection

[b] The percentage of control and case subjects who served in Vietnam in the specified category (unknowns excluded)

[c] Odds ratios estimate the relative risk of non-Hodgkin's lymphoma; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 3.3 (Model 3) by using unconditional logistic regression. Men with no military service in Vietnam form the referent group (1,643 controls and 1,058 cases)

[d] Test for a linear trend in the odds ratio as calculated from a logistic regression model

well as the case:control odds for each cell, are shown. For example, in the analyses for branch of military service, of the 19 Vietnam veterans who served in I Corps in the Army, 11 had NHL and 8 were controls.

Other characteristics show associations with NHL that are similar to those seen previously. After we controlled for location, we found no consistent trends in the summary ORs according to calendar year of service, age at beginning of first tour, years since first service in Vietnam, or any of the self-reported assessments of exposure to Agent Orange. The relative risk for NHL did tend to increase with duration of service in Vietnam, but the summary OR decreased among men who were in Vietnam for 2 years or more. The association between rank and NHL, however, was slightly stronger after adjustment for location, with an OR of 3.00 (95% CI 0.91-9.85) seen among officers. The highest case:control ratio was seen among officers in the blue-water Navy: five of the six men in this subgroup had NHL.

We then examined, simultaneously, three characteristics of military service in Vietnam — duration, location, and ending rank — in a logistic regression model that controlled for all characteristics shown in Model 3, Table 3.3. As the results shown in Table 3.11 indicate, although the relative risks for NHL among Vietnam veterans varied somewhat across subgroups, the differences were not statistically significant. Relative to other Vietnam veterans, the risk for NHL tended to be highest among men who (1) served in I Corps or the blue-water Navy, (2) were stationed in Vietnam for 1.5 to 1.9 years, and (3) were officers, but the observed differences were not statistically significant.

3.3.5 Sensitivity Analyses

The results of several sensitivity analyses are shown in Table 3.12. In general, our estimated relative risk of 1.47 varied only slightly according to various inclusion and exclusion criteria. For example, excluding the cases with proxy interviews yielded an OR of 1.47 and restricting the analyses to men whose interviews were rated as good or excellent slightly increased the OR to 1.49. The OR was slightly reduced by (1) excluding men whose self-reported military service in Vietnam could not be confirmed (OR = 1.40), (2) including men who were in Vietnam or off its coast, but not stationed there (OR = 1.35), and by (3) including the 1 control and 280 cases with AIDS or an AIDS-related condition (OR = 1.34). Regardless of the inclusions and exclusions, however, all ORs remained statistically significant.

Table 3.10. Association Between Selected Characteristics of Military Service in Vietnam and Non-Hodgkin's Lymphoma, by Location of Service[a]

Characteristics	Location of Service in Vietnam Corps				Blue-Water Navy	Mantel-Haenszel Summary Odds Ratio (95% Confidence Interval)[b]
	I	II	III	IV		
Overall	23:23[c]	19:30	19:40	2:4	28:25	
Branch of service in Vietnam						
Army	11: 8	14:22	16:34	1:2	–	1
Air Force	3: 3	5: 7	3: 3	0:0	–	1.20 (0.49-2.98)
Marines	6: 9	0: 0	0: 1	0:1	–	0.41 (0.10-1.60)
Navy	3: 3	0: 1	0: 2	1:0	28:25	–[d]
Duration of service in Vietnam (years)						
<1	15:18	11:19	9:25	2:2	5: 8	1
1 to 1.4	1: 4	4: 5	6: 5	0:1	6: 2	1.65 (0.76-3.58)
1.5 to 1.9	5: 0	0: 3	1: 3	0:1	9: 4	2.01 (0.75-5.38)
≥2	1: 1	3: 3	3: 7	0:0	8:10	1.34 (0.56-3.21)
Calendar years stationed in Vietnam						
Before 1966	3: 1	0: 1	2: 3	0:1	4: 3	1
1966 to 1969	16:20	18:21	13:35	2:1	19:18	0.76 (0.28-2.04)
After 1969	4: 2	0: 8	4: 2	0:2	5: 4	1.24 (0.31-4.86)
Age at beginning of first tour in Vietnam (years)						
<21	10:10	7:11	6:17	0:3	13:12	1
21-25	7: 8	4:15	7:15	1:1	11: 8	0.99 (0.52-1.89)
≥26	6: 5	7: 4	6: 8	1:0	4: 5	1.64 (0.81-3.35)
Rank at end of last tour in Vietnam[e]						
E1 to E3	3: 3	1: 8	1: 2	0:0	3: 6	1
E4 to E9	19:19	13:17	16:29	1:4	19:17	2.07 (0.84-5.07)
Officer	1: 1	4: 4	1: 8	1:0	5: 1	3.00 (0.91-9.85)
Type of unit in Vietnam						
Support	10:12	11:15	9:17	2:4	22:16	1
Combat support	4: 4	3:11	6:10	0:0	4: 6	0.70 (0.35-1.43)
Combat	6: 7	3: 4	2:12	0:0	2: 1	0.77 (0.33-1.77)
Years since first service in Vietnam						
<17	3: 3	0: 9	3: 1	0:2	5: 4	1
17 to 18	8: 8	6:10	6:13	1:1	5: 6	1.17 (0.47-2.90)
19 to 21	10:10	8:10	9:20	1:1	11: 9	1.35 (0.58-3.16)
≥22	2: 2	4: 1	1: 6	0:0	7: 6	1.26 (0.52-3.04)
Reported passing through a defoliated area						
No	11:17	13:13	12:23	1:3	25:24	1
Yes	11: 6	4:17	5:17	1:1	3: 1	0.88 (0.47-1.64)
Reported being present when others were spraying Agent Orange						
No	20:21	15:28	14:33	2:3	27:24	1
Yes	2: 2	2: 2	3: 7	0:1	1: 1	1.06 (0.40-2.75)
Reporting getting Agent Orange on skin or clothes						
No	20:20	14:29	16:38	2:4	27:23	1
Yes	2: 3	3: 1	1: 2	0:0	1: 2	1.20 (0.43-3.30)

[a] Men were excluded from the analysis if information on location of service or a certain characteristic was unknown. Location of service was unknown for 19 men (8 cases, 11 controls)

[b] Mantel-Haenszel summary odds ratio estimates the risk of non-Hodgkin's lymphoma among Vietnam veterans in a given category relative to the risk among Vietnam veterans in the first category of the characteristic. Estimates have been adjusted for location of military service in Vietnam

[c] N cases:N controls

[d] Not calculated because so few Navy veterans reported a location of service other than at sea

[e] In the Army, ranks of E1 to E3 correspond to the various levels of private, rank E4 to corporal, and ranks E5 to E9 to the various levels of sergeant

Table 3.11. Relative Risk of Non-Hodgkin's Lymphoma Among Subgroups of Vietnam Veterans as Estimated by Logistic Regression

Characteristic	Odds Ratio[a] (95% Confidence Interval)	P-value[b]
Duration of service in Vietnam (years)		
<1	1[c]	
1 to 1.4	1.82 (0.78-4.22)	
1.5 to 1.9	2.34 (0.88-6.22)	0.10
≥2	0.92 (0.35-2.41)	
Corps in Vietnam		
I	2.84 (1.18-6.84)	
II	1.53 (0.64-3.63)	
III	1[c]	0.10
IV	0.94 (0.14-6.16)	
Blue water Navy	2.57 (1.06-6.24)	
Rank at end of last tour in Vietnam[d]		
E1 to E3	1[c]	
E4 to E9	1.95 (0.74-5.19)	0.23
Officer	2.85 (0.82-9.83)	

[a] Twenty-seven Vietnam veterans were excluded from the analysis because information concerning duration, corps, or final rank was unknown. Odds ratios for each characteristic are adjusted for the other two characteristics and for all variables shown in Table 3.3 (Model 3)

[b] Null hypothesis: no difference in the odds ratio across subgroups

[c] Referent group. The subgroup shown in Table 3.7 as having the lowest relative risk was chosen as the referent group

[d] In the Army, ranks E1 to E3 correspond to the various levels of private, rank E4 to corporal, and ranks E5 to E9 to the various levels of sergeant

Table 3.12. Association Between Military Service in Vietnam and Non-Hodgkin's Lymphoma Among Selected Groups of Men

			Table 3.3, Model 3
	Controls	Non-Hodgkin's Lymphoma Cases	Odds Ratio (95% Confidence Interval)
Men in main analyses	1775	1156	1.47 (1.09-1.97)
Sensitivity Analyses[a]			
Additions to analyses:			
Men with AIDS or an AIDS-related condition	1776	1436	1.34 (1.01-1.79)
Men who were in Vietnam or off its coast, but not stationed there (include as exposed)	1802	1168	1.35 (1.02-1.78)
Deceased case-control subject pairs[b]	1869	1157	1.44 (1.08-1.92)
Exclusions from analyses:			
Men without a telephone in the household	1757	1129	1.44 (1.07-1.94)
Men interviewed in person	1751	1112	1.48 (1.10-1.99)
Men whose interview was not rated as good or excellent	1745	1130	1.49 (1.11-2.02)
Men who were 30 or older in 1968	1012	528	1.43 (1.03-2.00)
Case subjects with a proxy interview	1775	1037	1.47 (1.09-1.99)
Men whose Vietnam service could not be confirmed[c]	1768	1147	1.40 (1.03-1.90)

[a] Sensitivity analyses show the effect of adding (or removing) men to (or from) the main analysis. Each addition (or exclusion) is applied separately. Numbers of controls and cases are numbers remaining in analyses after additions or exclusions

[b] All case subjects were included in the analysis, regardless of vital status. If a deceased control subject did not meet the inclusion criteria listed in Table 2.1, he was not included. The model adjusts only for registry and age group in 1968 (Table 3.3, Model 1)

[c] Men who gave permission for military records review, whose records were located, and whose Vietnam service could not be confirmed were excluded

3.4 SUMMARY

These results suggest that Vietnam veterans have a roughly 50% increased risk of developing NHL about 15 to 25 years after military service in Vietnam relative to other men in the United States. The results do not show a similar increased risk among veterans who served in other locations during the Vietnam era, and therefore, the increased risk seems to be specific to military service in Vietnam. Few characteristics of military service were useful in identifying differences in risk *among* subgroups of Vietnam veterans. With only 99 men with NHL stationed in Vietnam, however, the power of the study is reduced for subgroup analyses. The relative risk tended to be higher among (1) men who were in Vietnam for 1.5 to 1.9 years (but was not higher among veterans who served for 2 or more years), (2) men who were stationed in I Corps or the blue-water Navy, and (3) officers. None of the differences among subgroups of Vietnam veterans, however, were statistically significant.

Bias must always be considered as a possible explanation for a relative risk of the magnitude (1.47) observed in this study. We were, however, not able to identify any substantial selection bias: all NHL cases from eight geographic regions were eligible for inclusion in the study, and controls were selected by random digit dialing. Restricting the cases to those with phones (a criterion for control selection) did not alter any of the results. Although failure to identify all Vietnam veterans in the control group might be postulated as an explanation for the observed association, several findings in our study argue against this possibility. Participation rates were high for this type of study, and 7.5% of the controls reported serving in Vietnam, a value very similar to what would be expected on the basis of national estimates (OASD, 1976; VA, 1981). In addition, in a previous study (CDC VES, 1988a; CDC VES 1989a), investigators found that Vietnam veterans selected from military records (most of whom were not ill) were somewhat more easily interviewed than were other Vietnam-era veterans. Our results show that Vietnam veterans are at increased risk for NHL even when compared with other veterans.

We discuss our results further in Chapter 9.

4. SOFT TISSUE AND OTHER SARCOMAS

4.1 BACKGROUND

Sarcomas are uncommon among men in the Vietnam service age range. The incidence in males aged 30 to 59 in the United States is 3.0 newly diagnosed cases per 100,000 men per year (Young et al., 1981). We included soft tissue and other sarcomas in the SCS because published evidence suggested an association with exposure to phenoxyherbicides or chlorophenols (IARC, 1986; Sterling and Arundel, 1986; Lilienfeld and Gallo, 1989). In a case-control study conducted in 1979, Hardell and Sandström (1979) studied men with soft tissue sarcomas and reported that previous occupational exposure to TCDD-contaminated phenoxyherbicides was associated with a fivefold increase in risk; this increased risk was later found to apply to uncontaminated phenoxyherbicides as well (Eriksson et al., 1981). Although some of the subsequent studies of occupationally exposed men have also yielded positive results (Lynge, 1985; Hardell and Eriksson, 1988; Reif et al., 1989), most investigators have reported no association between phenoxyherbicides and sarcomas (Balarajan and Acheson, 1984; Smith et al., 1984; Hoar et al., 1986; Vineis et al., 1986; Wiklund and Holm, 1986; Woods et al., 1987).

Because of the difficulty in measuring past exposure to Agent Orange, several investigators have examined the association between military service in Vietnam in general and soft tissue sarcomas. In each of these studies, the number of subjects was small. In two proportionate mortality studies, investigators found an increased number of deaths from soft tissue sarcomas among Vietnam veterans (Holmes et al., 1986; Kogan and Clapp, 1988). The results of four other such studies (Greenwald et al., 1984; Lawrence et al., 1985; Anderson et al., 1986; Breslin et al., 1988) and of two case-control studies (Kang et al., 1986; Kang et al., 1987), however, did not confirm these findings. Further, in an ongoing study of the health of men who served in the Air Force Ranch Hand group, which sprayed herbicide in Vietnam from fixed-wing aircraft, investigators have found only one Ranch Hand veteran with soft tissue sarcoma (Thomas et al., 1990). Problems in the diagnosis of soft tissue sarcomas make the study of this group of malignancies more difficult (Fingerhut et al., 1984; Lynge et al., 1987). In our study, we, like other researchers, focus on the risk of cancer after Vietnam service in general and only indirectly examine any possible association with herbicide exposure by investigating characteristics of service.

Most known and suspected risk factors for sarcoma are risk factors for a specific type of sarcoma, not for all sarcomas or all soft tissue sarcomas as a group (phenoxyherbicide exposure is an exception). Examples are bone sarcomas after radiation (Ron et al., 1988), hepatic angiosarcoma after medical use of Thorotrast (Falk et al., 1979), inorganic arsenicals (Popper et al., 1978), or exposure to vinyl chloride monomer (Popper et al., 1978).

4.2 METHODS

Chapter 2 provides an overview of the study's design, how it was conducted, and how the data were analyzed. Here we further discuss several topics discussed in Chapter 2.

4.2.1 Subjects and Sources of Data

Any case that had been definitively or tentatively diagnosed as a sarcoma (whether derived from connective tissue, viscera, or the skeletal system) was considered eligible for inclusion. Case eligibility was based on a list of more than 60 International Classification of Diseases for Oncology (ICD-O) morphology codes and subclassifications, including those previously noted

in studies on associations with phenoxyherbicides or chlorophenols (for eligible codes, see Appendix A). Men with a diagnosis of Kaposi's sarcoma or mesothelioma were not included. Because a classification by tumor site might have caused us to miss many cases that are morphologically classifiable as soft tissue sarcoma (Young et al., 1981; Berg, 1982; Lynge et al., 1987), we based our case inclusion criteria on morphology.

Personnel in eight participating tumor registries identified 612 men born between 1925 and 1953 who, between December 1, 1984, and November 30, 1988, had been diagnosed as having any of these sarcomas. During a telephone interview, trained personnel, using a standardized questionnaire, collected information on demographics, relevant medical history, occupations, and military service. At the subject's request, 21 men with sarcoma and 24 control subjects were interviewed in person. The participation rate for sarcoma case subjects was 85.1% and that for control subjects obtained by random digit dialing (RDD), 83.1% (Table 2.4). The most frequent reason for nonparticipation was the subject's or proxy's refusal to participate. Experts in sarcoma pathology attempted to confirm the diagnosis of all cases by independently reviewing microscope slides of tissue or tissue blocks. Specimens were obtained for 511 interviewed case subjects, and the experts confirmed 386 diagnoses.

Of the men with sarcoma who were stationed in Vietnam, 88% (23/26) (Table 2.8) gave permission for a record review by the U.S. Army and Joint Services Environmental Support Group (ESG). The ESG reviewed records without knowledge of the subject's case or control status. Records were located for all 23 men, and Vietnam service could be confirmed for 17 (74%). Vietnam service was confirmed for 92% of the controls whose records were located. Most analyses included men who reported Vietnam service in the interview. Those whose service was not confirmed after the record review were, however, excluded in sensitivity analyses.

We excluded men from the analysis if they reported a history of Von Recklinghausen's neurofibromatosis, a condition predisposing a person to sarcoma. We also excluded one man with a probable postirradiation osteosarcoma. Subjects were included in the sarcoma group regardless of vital status; however, the RDD control series was used for the main analyses. With these criteria, 342 cases (30 deceased) and 1,776 controls remained for analysis (Table 2.4), giving the study more than a 97% power to detect a twofold increase in risk for sarcoma among Vietnam veterans (Table 2.5).

4.2.2 Statistical Analyses

We assessed the strength of the association between sarcoma and Vietnam service by the odds ratio (OR), using conditional logistic regression. As noted in Chapter 2, we used three alternative choices for the nonexposed group.

In addition to those variables listed in Chapter 2 and considered as covariates for all six cancer investigations, in the sarcoma analysis we also accounted for cigarette smoking and prior work in a meat packing plant.

4.3 RESULTS

4.3.1 Overall Association

The distribution of case and control subjects across the 40 cells of the design matrix is shown in Table 4.1. Neither age nor registry (geographic area) modified the association of interest. Characteristics of cases were generally similar to those of controls, as summarized in Table 4.2. Relative to controls, more case subjects are non-Hispanic blacks and have less education. Differences in the reported use of herbicides in farming and nonfarming occupations are small. Fewer case subjects report occupational exposure to phenoxyherbicides, but more report possible exposure to chlorophenols or dioxin through a nonfarming occupation. Few study subjects reported other risk factors for sarcoma.

Table 4.1. Distribution of Men With Soft Tissue and Other Sarcomas and Distribution of Control Subjects, by Registry and Age in 1968

Registry	Age in 1968 (Years)					Total
	15-19	20-24	25-29	30-34	35-39	
1	3: 20[a]	9: 34	2: 35	8: 24	8: 29	30: 142
2	13: 37	11: 56	10: 49	5: 69	10: 74	49: 285
3	6: 39	9: 30	3: 58	6: 51	9: 69	33: 247
4	8: 31	4: 25	9: 36	5: 29	4: 45	30: 166
5	4: 17	2: 24	3: 14	9: 25	6: 22	24: 102
6	11: 89	12:102	13: 89	20: 80	14: 73	70: 433
7	11: 42	12: 46	17: 46	9: 41	18: 70	67: 245
8	9: 27	6: 37	10: 30	6: 30	8: 32	39: 156
Total	65:302	65:354	67:357	68:349	77:414	342:1776

[a] N cases:N controls

Table 4.2. Distribution of Selected Covariates[a] Among Men With Soft Tissue and Other Sarcomas and Among Control Subjects

	Controls (N = 1776)[b]		Soft Tissue and Other Sarcoma Cases (N = 342)[b]	
	%[c]	(N)	%[c]	(N)
Design Characteristics				
Registry				
1	8.0	(142)	8.8	(30)
2	16.0	(285)	14.3	(49)
3	13.9	(247)	9.6	(33)
4	9.3	(166)	8.8	(30)
5	5.7	(102)	7.0	(24)
6	24.4	(433)	20.5	(70)
7	13.8	(245)	19.6	(67)
8	8.8	(156)	11.4	(39)
Age in 1968 (years)				
15 to 19	17.0	(302)	19.0	(65)
20 to 24	19.9	(354)	19.0	(65)
25 to 29	20.1	(357)	19.6	(67)
30 to 34	19.7	(349)	19.9	(68)
35 to 39	23.3	(414)	22.5	(77)
Stationed in Vietnam or off the coast of Vietnam	7.5	(133)	7.6	(26)
Other reported characteristics				
Racial/ethnic group				
White non-Hispanic	84.3	(1497)	76.9	(263)
Black non-Hispanic	8.1	(143)	16.4	(56)
Hispanic	5.6	(99)	5.3	(18)
Asian	1.7	(31)	0.6	(2)
Other/unknown	0.3	(6)	0.9	(3)
Highest level of education completed				
Less than high school	11.3	(200)	15.9	(54)
High school, technical school	29.5	(523)	27.9	(95)
1 to 3 years of college	20.6	(366)	23.2	(79)
4 or more years of college	38.6	(686)	32.9	(112)
Smoked cigarettes regularly	66.8	(1186)	69.0	(236)
Drank alcohol regularly	71.7	(1262)	73.4	(251)
Never married	7.3	(129)	9.9	(34)
Lived or worked on a farm or ranch	44.8	(796)	41.8	(143)
Sprayed or mixed any herbicide on a farm or ranch	9.6	(170)	8.5	(29)

Table 4.2. Distribution of Selected Covariates[a] Among Men With Soft Tissue and Other Sarcomas and Among Control Subjects — Continued

	Controls (N = 1776)[b]		Soft Tissue and Other Sarcoma Cases (N = 342)[b]	
	%[c]	(N)	%[c]	(N)
Contact with herbicides on a farm or ranch, 21 or more days per year, 5 or more years before the date of diagnosis[d]	2.4	(43)	1.8	(6)
Sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work	7.3	(129)	9.4	(32)
Occupational exposure to phenoxyherbicides	5.9	(105)	4.4	(15)
Occupational exposure to chlorophenols	11.3	(200)	15.5	(53)
Occupational exposure to 2,4,5-T	0.9	(16)	0.3	(1)
Occupational exposure to 2,4-D	5.8	(103)	4.4	(15)
Worked in a meat packing or processing plant	5.9	(104)	8.5	(29)
Worked in a leather tanning plant	0.5	(8)	0.6	(2)
Worked in a pulp, saw, or planing mill	5.7	(101)	8.2	(28)
Worked with or around wood preservatives	11.8	(209)	12.0	(41)
Worked with or around cutting oils	20.5	(364)	19.9	(68)
Had an immune disease other than AIDS 3 or more years before the date of diagnosis[d]	0.1	(2)	—	(0)
Had Gardner's syndrome	0.1	(1)	0.3	(1)
Had hemochromatosis	—	(0)	—	(0)
Had Paget's disease of bone	0.1	(1)	—	(0)
Had malaria	1.4	(25)	1.2	(4)
Took drugs to suppress the immune system	0.1	(1)	0.3	(1)
Took clofibrate or a related compound	0.7	(13)	0.3	(1)
Took androgenic steroids	1.7	(30)	2.0	(7)
Took medication to treat or prevent malaria	11.4	(202)	11.7	(40)

[a] The covariates are described in the text
[b] Information on education for one control subject and two case subjects was missing. None were Vietnam veterans
[c] Percentage of cases or controls with the specified characteristic
[d] For controls, 5 or more years before the date the registry was notified of selection

Case and control subjects reported military service in Vietnam with similar frequency. Adjusted for age and registry, the risk among Vietnam veterans relative to that among other men is 1.02 (95% CI 0.65-1.61) (Table 4.3, Model 1). Controlling for additional risk factors (Models 2 and 3) did not alter the estimate. In another analysis, we combined data on 22 deceased control subjects and on their matching deceased case subjects with data on the RDD controls and on the remaining cases. After we adjusted the results for the design variables, the OR was 1.00 (95% CI 0.63-1.58). This estimate is nearly identical to that obtained when we used RDD controls only. To assure control of confounding, in subsequent analyses we controlled for all covariates listed in Model 3 (OR = 1.00, 95% CI 0.63-1.58).

We also examined the association of Vietnam service with sarcoma, using the three alternative referent groups as shown in Table 4.4. The risk of sarcoma among Vietnam veterans relative to that among men who served in the military but not in Vietnam was 0.88 (95% CI 0.51-1.52). The risk for Vietnam veterans relative to that of other Vietnam-era veterans (men in service between 1964 and 1972) was 0.74 (95% CI 0.39-1.41) and the risk in relation to men with no active U.S. military duty was 1.05 (95% CI 0.64-1.71).

Analyses in Tables 4.3 and 4.4 incorporate all confirmed cases of sarcoma, including (1) those arising in the skeletal system and (2) those classified as dermatofibrosarcoma

Table 4.3. Association Between Military Service in Vietnam and Soft Tissue and Other Sarcomas

Model[a]	Odds Ratio[b] (95% Confidence Interval)
1. Adjusted for registry and age group in 1968	1.02 (0.65-1.61)
2. Adjusted for registry, age group in 1968, racial/ethnic group, and education	1.01 (0.64-1.60)
3. Adjusted for— all variables in Model 2 reported exposure to pesticides and chlorophenols —sprayed or mixed any herbicide on a farm or ranch —sprayed or mixed any herbicide in right-of-way maintenance, lawn care, or forestry work —occupational exposure to phenoxyherbicides —occupational exposure to chlorophenols reported occupational or lifestyle characteristics —history of smoking cigarettes —worked in a meat packing or processing plant	1.00 (0.63-1.58)

[a] One control and two cases were excluded from all models because level of education was not known
[b] Odds ratios estimate the relative risk and were calculated by using conditional logistic regression. The referent group is composed of men who did not serve in Vietnam

Table 4.4. Risk of Soft Tissue and Other Sarcomas Among Vietnam Veterans Relative To the Risk Among Four Referent Groups

Risk Group	Controls (N = 1776) %[a]	Controls (N = 1776) (N)	Soft Tissue and Other Sarcoma Cases (N = 342) %[a]	Soft Tissue and Other Sarcoma Cases (N = 342) (N)	Odds Ratio[b] (95% Confidence Interval)
Exposed group Subjects who served in Vietnam	7.5	(133)	7.6	(26)	
Referent groups Men who did not serve in Vietnam	92.5	(1643)	92.4	(316)	1.00 (0.62-1.59)
Men who served in the military but not in Vietnam	38.4	(682)	35.4	(121)	0.88 (0.51-1.52)
Men who served at any time from 1964 to 1972 in the military but not in Vietnam[c]	11.4	(203)	12.0	(41)	0.74 (0.39-1.41)
Men who never served in the military	54.1	(961)	57.0	(195)	1.05 (0.64-1.71)

[a] The percentage of controls or cases in the indicated exposed or referent group
[b] Odds ratios estimate the risk of soft tissue and other sarcomas for the exposed group relative to the risk for the indicated referent group; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 4.3 (Model 3) by using unconditional logistic regression
[c] The exposed group is restricted to men who served in the military in Vietnam at any time from 1964 to 1972 (130 controls and 24 cases)

protuberans, an indolent cutaneous tumor that rarely metastasizes (Enzinger and Weiss, 1983). When we excluded these two groups to more closely match the apparent definition of cases included in other studies, the OR for the resulting soft tissue sarcoma group (N=252) was 0.94 (95% CI 0.55-1.61) (Table 4.10). We examined sarcoma cases by histologic subclassification, as shown in Table 4.5. No one type of sarcoma shows any apparent association with service in Vietnam. The distribution of fibromatous, lipomatous, myomatous, and other soft tissue sarcomas did not differ between Vietnam veterans and other men ($p = 0.82$).

Table 4.5. Histologic Classification of Malignancies Among Men With Soft Tissue and Other Sarcomas, by Military Service in Vietnam

Classification	ICD-O Code[a]	Stationed in Vietnam or off the Coast of Vietnam: No %[b]	No (N)	Yes %[b]	Yes (N)
Dermatofibrosarcoma protuberans (Total)	88323	12.0	(38)	19.2	(5)
Sarcoma of bone and chondrosarcoma (Total)		13.3	(42)	11.5	(3)
Sarcoma of bone (Subtotal)		5.1	(16)	—	(0)
Sarcoma of bone, NOS[c]	XXXXX[d]	1.9	(6)	—	(0)
Osteosarcoma, NOS	91803	1.9	(6)	—	(0)
Chondroblastic osteosarcoma	91813	0.6	(2)	—	(0)
Juxtacortical osteosarcoma	91903	0.6	(2)	—	(0)
Chondrosarcoma (Subtotal)		6.3	(20)	11.5	(3)
Chondrosarcoma, NOS	92203	6.3	(20)	7.7	(2)
Osteochondroma with chondrosarcoma change	92XXX[d]	—	(0)	3.8	(1)
Chordoma	93703	1.6	(5)	—	(0)
Round cell sarcoma	88033	0.3	(1)	—	(0)
Soft tissue sarcoma and sarcoma, NOS (Total)		74.7	(236)	69.2	(18)
Sarcoma, NOS	88003	12.3	(39)	7.7	(2)
Malignant tumor, most likely sarcoma	8800X[d]	3.5	(11)	7.7	(2)
Spindle cell sarcoma	88013	2.2	(7)	3.8	(1)
Round cell sarcoma	88033	1.0	(3)	—	(0)
Fibromatous (Subtotal)		11.4	(36)	3.8	(1)
Fibrosarcoma, NOS	88103	0.3	(1)	—	(0)
Fibromyxosarcoma	88113	1.6	(5)	3.8	(1)
Fibrous hystiocytoma, malignant	88303	9.2	(29)	—	(0)
Fibroxanthoma, malignant	88313	0.3	(1)	—	(0)
Lipomatous (Subtotal)		14.9	(47)	11.5	(3)
Liposarcoma, NOS	88503	2.8	(9)	3.8	(1)
Liposarcoma, well differentiated	88513	4.1	(13)	—	(0)
Myxoid liposarcoma	88523	4.1	(13)	3.8	(1)
Round cell liposarcoma	88533	0.3	(1)	—	(0)
Pleomorphic liposarcoma	88543	1.0	(3)	3.8	(1)
Mixed type liposarcoma	88553	0.6	(2)	—	(0)
Liposarcoma, dedifferentiated	885X3[d]	1.9	(6)	—	(0)
Myomatous (Subtotal)		21.2	(67)	19.2	(5)
Leimyosarcoma, NOS	88903	18.4	(58)	19.2	(5)
Epithelioid leimyosarcoma	88913	2.2	(7)	—	(0)
Rhabdomyosarcoma, NOS	89003	0.3	(1)	—	(0)
Mixed type rhabdomyosarcoma	89023	0.3	(1)	—	(0)
Synovial sarcoma, NOS	90403	0.6	(2)	7.7	(2)
Synovial sarcoma, spindle cell type	90413	0.3	(1)	—	(0)
Synovial sarcoma, epitheliod type	90423	0.3	(1)	—	(0)
Clear cell sarcoma of tendons and aponeuroses	90443	0.6	(2)	—	(0)
Hemangiosarcoma	91203	1.9	(6)	—	(0)
Hemangioendothelial sarcoma	91303	—	(0)	3.8	(1)
Chondrosarcoma, NOS, ES[e]	92203	1.3	(4)	—	(0)
Mesenchymal chondrosarcoma, ES	92403	0.3	(1)	—	(0)
Malignant giant cell tumor of soft parts	92513	0.6	(2)	—	(0)
Meningioma, malignant	95303	0.3	(1)	—	(0)
Neurilemmoma, malignant	95603	1.9	(6)	3.8	(1)
All soft tissue and other sarcomas (Total)		100.0	(316)	100.0	(26)

[a] International Classification of Diseases for Oncology, 1976
[b] Percentage of cases in each Vietnam service category with the indicated histology
[c] Not otherwise specified
[d] There is no ICD-O code for these categories
[e] Extraskeletal site

4.3.2 Characteristics of Military Service in Vietnam

The association between military service and sarcoma for both Vietnam veterans and veterans who served elsewhere (Table 4.6) shows only nonsignificant variation by branch. Other aspects of military service for the 26 men with sarcoma and the 133 controls who were stationed in Vietnam (Table 4.7) are not significantly associated with sarcoma risk. The preponderance of both case and control subjects served at some time during 1968 to 1969, when Agent Orange was most heavily used. Both groups were similar in age at the first tour of duty. Risk was not associated with duration of service, nor with the type of unit. Small differences in risk by region of service (with the risk for I Corps highest) were not significant.

Self-perceived contact with Agent Orange or other herbicides was not significantly associated with sarcoma among Vietnam veterans (Table 4.8). Only one case subject reported being present when others were spraying or that he got Agent Orange on his skin or clothing. No case subject reported that he had sprayed Agent Orange. Although 10 of the 26 Vietnam veterans with sarcoma reported that they had passed through a defoliated area (OR = 1.60, 95% CI 0.63-4.12), the association was not statistically significant.

The range of latency periods that we could analyze was narrow, but we found no trend in risk by time elapsed between the start of the first tour in Vietnam and the diagnosis of cancer (Table 4.9).

4.3.3 Sensitivity Analyses

The results of additional sensitivity analyses are shown in Table 4.10. Broadening the definition of exposure to include men who were in, or off the coast of, Vietnam, but not stationed there, had little effect on the OR (1.11, 95% CI 0.73-1.68). Similarly, restricting the analysis to those with a telephone had little effect (OR = 1.01, 95% CI 0.63-1.61). Neither restricting the analysis to those men whose interview quality was rated as good or excellent or to those who were interviewed in person had an appreciable effect on the outcome. Restricting the study group to those who were between the ages of 15 and 29 in 1968 yielded an OR of 1.06 (95% CI 0.64-1.75). Excluding men whose Vietnam service was not confirmed after record review yielded an OR of 0.82 (95% CI 0.49-1.36).

4.4 SUMMARY

The results of this study provide no evidence that men who served in the U.S. military in Vietnam have a higher risk for sarcoma. This was true whether the Vietnam veterans were compared with other military veterans, other Vietnam-era veterans, or nonveterans. We found no increased risk when we restricted the case subjects to a group representing only soft tissue sarcoma. Finally, the results do not indicate that any subgroup of Vietnam veterans is at a higher risk for sarcoma.

We discuss our results further in Chapter 9.

Table 4.6. Association Between Branch of Military Service and Soft Tissue and Other Sarcomas, by Vietnam Veteran Status

	Non-Vietnam Veterans					Vietnam Veterans					
	Controls (N = 682)[a]		Soft Tissue and Other Sarcoma Cases (N = 121)		Odds Ratio[c] (95% Confidence Interval)	Controls (N = 133)		Soft Tissue and Other Sarcoma Cases (N = 26)[a]		Odds Ratio[c] (95% Confidence Interval)	
Branch of Service	%[b]	(N)	%[b]	(N)		%[b]	(N)	%[b]	(N)		P-value
Army	52.5	(358)	54.5	(66)	0.89 (0.64-1.25)	52.6	(70)	38.5	(10)	0.70 (0.35-1.43)	
Air Force	18.2	(124)	12.4	(15)	0.58 (0.32-1.04)	13.5	(18)	19.2	(5)	1.40 (0.49-3.99)	
Marines	5.7	(39)	5.8	(7)	0.85 (0.36-1.99)	9.8	(13)	19.2	(5)	1.71 (0.57-5.15)	0.52[d]
Navy	17.0	(116)	22.3	(27)	1.25 (0.77-2.01)	23.3	(31)	19.2	(5)	0.83 (0.30-2.24)	
Coast Guard	0.7	(5)	0.8	(1)	1.35 (0.15-12.2)	0.8	(1)	—	(0)	—[e]	

[a] The sum of the subjects in all branches is less than N because information about branch of service was missing for 46 men

[b] Percentage of controls or cases in the specified branch

[c] Odds ratios estimate the risk of soft tissue and other sarcomas for a given category relative to the risk among men with no military service (961 controls and 195 cases); they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 4.3 (Model 3) by using unconditional logistic regression

[d] Null hypothesis: no difference in the odds ratio across branches among Vietnam veterans

[e] Odds ratio and confidence interval were not calculated because of a zero cell

Table 4.7. Association Between Selected Characteristics of Military Service in Vietnam and Soft Tissue and Other Sarcomas

Characteristic	Controls (N = 1776) %[a]	Controls (N = 1776) (N)	Soft Tissue and Other Sarcoma Cases (N = 342) %[a]	Soft Tissue and Other Sarcoma Cases (N = 342) (N)	Odds Ratio[b] (95% Confidence Interval)	P-value[c]
No military service in Vietnam	—	(1643)	—	(316)	Referent	
Military service in Vietnam	—	(133)	—	(26)	1.00 (0.63-1.58)	
Duration of service in Vietnam (years)						
<1	59.8	(79)	50.0	(12)	0.77 (0.41-1.47)	
1 to 1.4	13.6	(18)	20.8	(5)	1.28 (0.45-3.66)	0.80
1.5 to 1.9	9.8	(13)	8.3	(2)	0.92 (0.20-4.26)	
≥2	16.7	(22)	20.8	(5)	1.24 (0.44-3.45)	
Unknown	—	(1)	—	(2)		
Calendar years stationed in Vietnam						
Before 1966	7.5	(10)	4.0	(1)	0.46 (0.05-3.93)	
1966 to 1969	78.2	(104)	76.0	(19)	0.95 (0.56-1.62)	0.66
After 1969	14.3	(19)	20.0	(5)	1.30 (0.45-3.69)	
Unknown	—	(0)	—	(1)		
Age at beginning of first tour in Vietnam (years)						
<21	42.9	(57)	40.0	(10)	0.97 (0.47-2.01)	
21 to 25	37.6	(50)	48.0	(12)	1.34 (0.68-2.66)	0.26
≥26	19.5	(26)	12.0	(3)	0.44 (0.13-1.52)	
Unknown	—	(0)	—	(1)		
Rank at end of last tour in Vietnam[d]						
E1 to E3	16.2	(21)	12.0	(3)	0.67 (0.19-2.35)	
E4 to E9	73.1	(95)	80.0	(20)	1.11 (0.65-1.89)	0.66
Officer	10.8	(14)	8.0	(2)	0.69 (0.15-3.22)	
Unknown	—	(3)	—	(1)		
Type of unit in Vietnam						
Support	53.5	(69)	47.6	(10)	0.76 (0.37-1.53)	
Combat Support	26.4	(34)	33.3	(7)	1.03 (0.44-2.41)	0.85
Combat	20.2	(26)	19.0	(4)	0.76 (0.25-2.28)	
Unknown	—	(4)	—	(5)		
Corps in Vietnam						
I	18.9	(23)	42.1	(8)	1.61 (0.69-3.76)	
II	24.6	(30)	21.1	(4)	0.74 (0.25-2.18)	0.33
III	32.8	(40)	21.1	(4)	0.50 (0.17-1.44)	
IV	3.3	(4)	—	(0)	—.[e]	
Blue water Navy[e]	20.5	(25)	15.8	(3)	0.64 (0.18-2.21)	
Unknown	—	(11)	—	(7)		
Ever in III Corps in Vietnam						
No	36.8	(46)	52.4	(11)	1.15 (0.57-2.32)	
Yes	43.2	(54)	33.3	(7)	0.67 (0.30-1.54)	0.73
Blue water Navy[e]	20.0	(25)	14.3	(3)	0.63 (0.18-2.20)	
Unknown	—	(8)	—	(5)		
Land vs. sea duty in Vietnam						
All land-based men	81.2	(108)	88.5	(23)	1.07 (0.65-1.76)	
All branches other than Navy	76.7	(102)	80.8	(21)	1.03 (0.62-1.73)	
Navy—shore	3.0	(4)	7.7	(2)	2.67 (0.46-15.4)	0.41[f]
Navy—brown water	1.5	(2)	—	(0)	—[g]	
Sea-based blue water Navy	18.8	(25)	11.5	(3)	0.64 (0.18-2.21)	

[a] Percentage of case or control subjects who served in Vietnam with the specified characteristic (unknowns excluded)
[b] Odds ratios estimate the risk of soft tissue and other sarcomas for a given category of men relative to the risk among men who did not serve in Vietnam; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 4.3 (Model 3) by using unconditional logistic regression
[c] Null hypothesis: no difference in the odds ratio across subgroups
[d] In the Army, ranks E1 to E3 correspond to the various levels of private, rank E4 to corporal, and ranks E5 to E9 to the various levels of sergeant
[e] Corps does not apply to Navy men stationed on ocean-going vessels
[f] Null hypothesis: no difference in the odds ratio between all land-based men combined and sea-based blue water Navy men
[g] Odds ratio and confidence interval were not calculated because of a zero cell

Table 4.8. Association Between Self-Reported Possible Contact With Agent Orange[a] and Soft Tissue and Other Sarcomas Among Men Who Served in the Military in Vietnam

Characteristic	Category	Controls (N = 133) %[b]	(N)	Soft Tissue and Other Sarcoma Cases (N = 26) %[b]	(N)	Odds Ratio[c] (95% Confidence Interval)
Reported passing through a defoliated area	No	65.4	(87)	54.5	(12)	
	Yes	34.6	(46)	45.5	(10)	1.60 (0.63-4.12)
	Unknown	—	(0)	—	(4)	
Reported any possible contact with Agent Orange[d]	No	74.4	(99)	77.3	(17)	
	Yes	25.6	(34)	22.7	(5)	0.68 (0.23-2.05)
	Unknown	—	(0)	—	(4)	
Reported being present when others were spraying Agent Orange	No	89.5	(119)	95.5	(21)	
	Yes	10.5	(14)	4.5	(1)	0.38 (0.05-3.11)
	Unknown	—	(0)	—	(4)	
Reported getting Agent Orange on skin or clothes	No	92.5	(123)	95.5	(21)	
	Yes	7.5	(10)	4.5	(1)	0.52 (0.06-4.39)
	Unknown	—	(0)	—	(4)	
Reported handling equipment or containers that had been used with Agent Orange	No	97.7	(130)	100.0	(22)	
	Yes	2.3	(3)	—	(0)	—[e]
	Unknown	—	(0)	—	(4)	
Reported spraying Agent Orange	No	98.5	(131)	100.0	(22)	
	Yes	1.5	(2)	—	(0)	—[e]
	Unknown	—	(0)	—	(4)	

[a] Includes other herbicides
[b] Percentage of case or control subjects who served in the military in Vietnam with the specified characteristic (unknowns excluded). Information on possible contact with Agent Orange was not obtained from proxy respondents for four deceased men
[c] Odds ratios estimate the risk of soft tissue and other sarcomas relative to the risk among men who did not report the specific exposure but who served in the military in Vietnam; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 4.3 (Model 3) by using unconditional logistic regression
[d] Includes all contacts listed below as well as any other mention of Agent Orange
[e] Odds ratio and confidence interval were not calculated because of a zero cell

Table 4.9. Risk of Soft Tissue and Other Sarcomas Among Vietnam Veterans, by Number of Years Since Start of First Tour in Vietnam

Number of Years Since Start of First Tour in Vietnam[a]	Controls (N = 133) %[b]	(N)	Soft Tissue and Other Sarcoma Cases (N = 26) %[b]	(N)	Odds ratio[c] (95% Confidence Interval)	P-value[d]
<17	15.0	(20)	28.0	(7)	1.80 (0.72-4.50)	
17-18	30.8	(41)	12.0	(3)	0.34 (0.10-1.14)	0.12
19-21	41.4	(55)	56.0	(14)	1.38 (0.73-2.60)	
≥22	12.8	(17)	4.0	(1)	0.28 (0.04-2.22)	
Unknown	—	(0)	—	(1)		

[a] For cases, the end of the latency period is the date of diagnosis; for controls, it is the date the registry was notified of selection
[b] The percentage of control or case subjects who served in Vietnam in the specified category (unknowns excluded)
[c] Odds ratios estimate the relative risk of soft tissue and other sarcomas; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 4.3 (Model 3) by using unconditional logistic regression. Men with no military service in Vietnam form the referent group (1,643 controls and 316 cases)
[d] Test for a linear trend in the odds ratios as calculated from a logistic regression model

Table 4.10. Association Between Military Service in Vietnam and Soft Tissue and Other Sarcomas Among Selected Groups of Men

	Controls	Soft Tissue and Other Sarcoma Cases	Table 4.3, Model 3 Odds Ratio (95% Confidence Interval)
Men in main analyses	1775	340	1.00 (0.63-1.58)
Sensitivity Analyses[a]			
Additions to analyses:			
Men with AIDS or an AIDS-related condition	1776	343	0.99 (0.63-1.58)
Men who were in Vietnam or off its coast, but not stationed there (include as exposed)	1802	348	1.11 (0.73-1.68)
Case subjects whose diagnosis was not confirmed because a specimen was not obtained or was deemed inadequate for review	1775	351	1.04 (0.67-1.64)
Deceased case-control subject pairs[b]	1797	340	1.00 (0.63-1.58)
Exclusions from analyses:			
Men without a telephone in the household	1757	321	1.01 (0.63-1.61)
Men interviewed in person	1751	319	1.00 (0.62-1.60)
Men whose interview was not rated as good or excellent	1745	333	1.04 (0.65-1.65)
Men who were 30 or older in 1968	1012	196	1.06 (0.64-1.75)
Case subjects with a proxy interview	1775	310	0.93 (0.57-1.53)
Men whose Vietnam service could not be confirmed[c]	1768	334	0.82 (0.49-1.36)
Case subjects with other than soft tissue sarcoma	1775	252	0.94 (0.55-1.61)

[a] Sensitivity analyses show the effect of adding (or removing) men to (or from) the main analysis. Each addition (or exclusion) is applied separately. Numbers of controls and cases are numbers remaining in analyses after additions or exclusions

[b] All case subjects were included in the analysis, regardless of vital status. If a deceased control subject did not meet the inclusion criteria listed in Table 2.1, he was not included. The model adjusts only for registry and age group in 1968 (Table 4.3, Model 1)

[c] Men who gave permission for military records review, whose records were located, and whose Vietnam service could not be confirmed were excluded

5. HODGKIN'S DISEASE

5.1 BACKGROUND

The annual incidence of Hodgkin's disease, a malignant lymphoma, among 30- to 59-year-old men in the United States is about 4 per 100,000 (Young et al., 1981). Results of animal studies conducted in the early 1970s suggested that rodents' exposure to 2,4,5-T during pregnancy could result in malformations in offspring (Courtney et al., 1970). Moreover, evidence suggests that TCDD, a contaminant of the 2,4,5-T component of Agent Orange, is carcinogenic in animals (IARC, 1986).

Concern over a possible association between exposure to Agent Orange and Hodgkin's disease was first raised in a 1979 report from Sweden of a cluster of patients with histiocytic lymphoma and previous exposure to phenoxyherbicides or chlorophenols (Hardell, 1979). In a later case-control study (Hardell et al., 1981) of 60 cases of Hodgkin's disease and 105 cases of non-Hodgkin's lymphoma (NHL), researchers found that occupational exposure to phenoxyherbicides was associated with a 5-fold increased risk for malignant lymphoma (95% CI 2.9-8.1). They did not present the results of separate analyses for Hodgkin's disease and NHL, but they stated that the relative risks for each were similar. Results of a later analysis of the 60 cases of Hodgkin's disease (Hardell and Bengtsson, 1983) indicated that 10% of the control subjects and 32% of the case subjects reported exposure to phenoxyherbicides or chlorophenols.

In a proportionate mortality study in the United States, researchers reported a moderate (20%-30%) excess in deaths from Hodgkin's disease among farmers (Burmeister, 1981), but few researchers have found any association between potential exposure to phenoxyherbicides and Hodgkin's disease (Wiklund, 1983; Pearce et al., 1985; Hoar et al., 1986; Brownson et al., 1989). Furthermore, in a population-based, case-control study, Hoar and coworkers (1986) reported a twofold increased risk for NHL among farmers who reported using phenoxyherbicides and an estimated relative risk for Hodgkin's disease of 0.9. Historical cohort studies are limited by small numbers of subjects and short periods of follow-up; however, results of these studies have not shown an excess of Hodgkin's disease among persons who were potentially exposed to phenoxyherbicides (Riihimäki et al., 1982; Lynge, 1985).

The etiology of Hodgkin's disease has been the subject of numerous epidemiologic investigations (reviewed in Grufferman and Delzell, 1984; Mueller, 1987), and its bimodal incidence with age has received much attention. Several characteristics related to social class and childhood environment, such as a small number of siblings, high levels of maternal education, and being raised in the Jewish religion, have also been related to an increased risk for Hodgkin's disease in adulthood. A higher risk for Hodgkin's disease has also been reported among persons who live in rural areas, smoke cigarettes, have had a tonsillectomy, or have had infectious mononucleosis. In several case reports, investigators have noted the occurrence of Hodgkin's disease among patients with HIV infection, but one investigator reported no increase in the incidence of Hodgkin's disease among single males in San Francisco from 1979 through 1987 (Kaplan, 1988).

Because measuring past exposure to Agent Orange is so difficult, investigators have studied the herbicide's possible effect on cancer among Vietnam veterans only indirectly by comparing the occurrence of cancer among Vietnam veterans with that in other groups. Results of proportionate mortality studies have varied, with the number of deaths from Hodgkin's disease among Vietnam veterans showing an increase in a study in West Virginia (Bailey et al., 1986) but not in others (Anderson et al., 1986; Breslin et al., 1988). In a historical cohort study of Australian troops, no deaths from Hodgkin's disease were observed among

19,000 men who served in Vietnam, whereas three such deaths were observed among 26,000 men who served elsewhere (Fett et al., 1987).

We, like others, focus on the risk of Hodgkin's disease after Vietnam service in general. We only indirectly assess a possible association between exposure to Agent Orange and Hodgkin's disease by investigating characteristics of military service in Vietnam, such as region and time period, that might be associated with greater exposure to Agent Orange.

5.2 METHODS

5.2.1 Subjects and Sources of Data

The design and conduct of the Selected Cancers Study (SCS) are described in detail in Chapter 2. Eligible for inclusion in the Hodgkin's disease case group were all males who (1) were born between 1929 and 1953, (2) were diagnosed with non-Hodgkin's lymphoma, Hodgkin's disease, or "lymphoma, not otherwise specified" between December 1, 1984, and November 30, 1988, and (3) lived in an area covered by one of eight collaborating tumor registries. Experts in lymphoma pathology reviewed specimens and determined the final classifications of the diagnoses. The primary source of exposure data was a standardized questionnaire administered by telephone.

As Table 2.4 shows, 2,073 (88%) of the 2,354 identified case subjects with lymphoma (NHL and Hodgkin's disease combined) were interviewed, and microscope slides or blocks were obtained for 2,004. A lymphoma diagnosis was confirmed for 93% of these men, with 343 classified as having Hodgkin's disease. Population-based controls were selected through random digit dialing (RDD) (Waksberg, 1978) and were frequency matched (by registry and 5-year date-of-birth interval) to all lymphoma cases. Of the 2,299 control subjects selected for enrollment in the SCS, 1,910 (83%) were interviewed. The same control group was used in the analyses of all six malignancies.

Subjects were excluded from the analyses if (1) their military service in Vietnam was unknown, (2) they were in Vietnam or off its coast, but were not stationed there, (3) they had AIDS, a condition possibly increasing the risk for Hodgkin's disease, or an AIDS-related illness, or (4) they were not residents of the United States before 1969. These restrictions resulted in 310 men with Hodgkin's disease and 1,776 controls. Because of unknown values, one control subject was deleted from analyses involving education, and two control subjects were deleted from analyses that included the number of siblings as a covariate.

The U.S. Army and Joint Services Environmental Support Group (ESG) performed a "blinded" review of military records of the men who reported being stationed in Vietnam. As Table 2.8 shows, of the Vietnam veterans, 86% (24/28) of the men with Hodgkin's disease and 74% (98/133) of the control subjects gave permission for their records to be reviewed. For these men, records were located for 92% (22) of the cases and 87% (85) of the controls. Military service in Vietnam could be corroborated by information in the records of 95% (21) of the case subjects and 92% (78) of the control subjects for whom records could be found. Unless otherwise specified, we classified military service in Vietnam according to interview response. We conducted supplemental analyses to assess the sensitivity of our results to these assumptions, as well as to several inclusion and exclusion criteria.

5.2.2 Statistical Analyses

We assessed whether men who served in the U.S. military in Vietnam are at greater risk for developing Hodgkin's disease compared with other men. Details on the analytic methods are in Chapter 2. Although we had several possible choices for the nonexposed (referent) group, unless otherwise specified, the nonexposed group consists of all men who were not in the military in Vietnam, regardless of their other military service.

Because we wanted to be able to assess the possibility that an observed association between military service in Vietnam and a particular malignancy might be due to a characteristic unrelated to military service in Vietnam, we obtained information on several characteristics (potential confounders) that have been reported to increase the risk of Hodgkin's disease (Grufferman and Delzell, 1984; Mueller, 1987). In addition to age, covariates in the analyses included racial or ethnic group, educational achievement, a history of spraying or mixing any herbicide other than in Vietnam, any exposure to phenoxyherbicides, possible exposure to chlorophenols or dioxin in various occupations, a history of infectious mononucleosis, medical irradiation, chemotherapy, appendectomy, tonsillectomy, cigarette smoking, marital status, having been raised in the Jewish religion, number of siblings, and having been raised in an urban setting.

Unconditional logistic regression with 39 indicator variables (representing the 40 date-of-birth and registry strata) was used in multivariable analyses. This method yielded results that are almost identical to those obtained with the Mantel-Haenszel summary odds ratio (OR) and conditional logistic regression. We assessed the homogeneity of the association between Vietnam service and Hodgkin's disease across strata of age, registry, and other characteristics, using the test statistic described by Breslow and Day (1980); in logistic regression models, we used likelihood ratio tests. The influence of potential confounders or the association between military service in Vietnam and Hodgkin's disease was assessed in logistic regression models that controlled for several covariates simultaneously. As Table 2.5 shows, we had about a 50% power to detect a 1.5-fold increased risk among Vietnam veterans and a 96% power to detect a twofold increase. All reported p-values are two-sided.

We also examined whether the risk for Hodgkin's disease among Vietnam veterans differed according to branch of service, duration of service, calendar years of service, age at beginning of first tour in Vietnam, rank at end of last tour, type of unit, military region, and number of years since start of first tour in Vietnam. Although we were aware of the large potential for misclassification (CDC VHS, 1988; CDC VHS, 1989), we also evaluated the association between several self-reported assessments of exposure to Agent Orange and Hodgkin's disease.

5.3 RESULTS

5.3.1 Overall Association

The distribution of cases and controls across the 40 cells defined by the frequency-matched design is shown in Table 5.1. As Table 5.2 shows, case subjects were younger than control subjects (mean ages of 25 and 27 years in 1968, respectively) but were more likely to

Table 5.1. Distribution of Men With Hodgkin's Disease and Distribution of Control Subjects, by Registry and Age in 1968

Registry	Age in 1968 (Years)					Total
	15-19	20-24	25-29	30-34	35-39	
1	6: 20[a]	3: 34	6: 35	2: 24	6: 29	23: 142
2	23: 37	14: 56	7: 49	13: 69	9: 74	66: 285
3	15: 39	9: 30	9: 58	6: 51	9: 69	48: 247
4	12: 31	8: 25	2: 36	4: 29	8: 45	34: 166
5	7: 17	3: 24	2: 14	4: 25	1: 22	17: 102
6	21: 89	9:102	7: 89	3: 80	11: 73	51: 433
7	12: 42	9: 46	5: 46	7: 41	7: 70	40: 245
8	10: 27	8: 37	9: 30	2: 30	2: 32	31: 156
Total	106:302	63:354	47:357	41:349	53:414	310:1776

[a] N cases:N controls

Table 5.2. Distribution of Selected Covariates[a] Among Men With Hodgkin's Disease and Among Control Subjects

	Controls (N = 1776)[b]		Hodgkin's Disease Cases (N = 310)[b]	
	%[c]	(N)	%[c]	(N)
Design Characteristics				
Registry				
1	8.0	(142)	7.4	(23)
2	16.0	(285)	21.3	(66)
3	13.9	(247)	15.5	(48)
4	9.3	(166)	11.0	(34)
5	5.7	(102)	5.5	(17)
6	24.4	(433)	16.5	(51)
7	13.8	(245)	12.9	(40)
8	8.8	(156)	10.0	(31)
Age in 1968 (years)				
15 to 19	17.0	(302)	34.2	(106)
20 to 24	19.9	(354)	20.3	(63)
25 to 29	20.1	(357)	15.2	(47)
30 to 34	19.7	(349)	13.2	(41)
35 to 39	23.3	(414)	17.1	(53)
Stationed in Vietnam or off the coast of Vietnam	7.5	(133)	9.0	(28)
Other reported characteristics				
Racial/ethnic group				
White non-Hispanic	84.3	(1497)	88.7	(275)
Black non-Hispanic	8.1	(143)	7.4	(23)
Hispanic	5.6	(99)	2.9	(9)
Asian	1.7	(31)	1.0	(3)
Other/unknown	0.3	(6)	—	(0)
Highest level of education completed				
Less than high school	11.3	(200)	12.6	(39)
High school, technical school	29.5	(523)	33.2	(103)
1 to 3 years of college	20.6	(366)	23.5	(73)
4 or more years of college	38.6	(686)	30.6	(95)
Smoked cigarettes regularly	66.8	(1186)	70.3	(218)
Drank alcohol regularly	71.1	(1262)	69.0	(214)
Mother's education				
Less than high school	35.0	(568)	26.7	(74)
High school, technical school	45.9	(746)	56.0	(155)
1 to 3 years of college	8.7	(142)	7.9	(22)
4 or more years of college	10.3	(168)	9.4	(26)
Raised in the Jewish religion	3.0	(53)	4.8	(15)
Number of siblings in household while growing up				
0	9.0	(159)	7.1	(22)
1 or 2	45.9	(814)	47.1	(146)
3 to 5	31.3	(555)	34.8	(108)
6 to 25	13.9	(246)	11.0	(34)
Raised in an urban environment	53.9	(957)	55.8	(173)
Never married	7.3	(129)	7.1	(22)
Lived or worked on a farm or ranch	44.8	(796)	40.0	(124)
Sprayed or mixed any herbicide on a farm or ranch	9.6	(170)	8.4	(26)
Had contact with herbicides on a farm or ranch 21 or more days per year, 5 or more years before the date of diagnosis[d]	2.4	(43)	1.3	(4)
Sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work	7.3	(129)	7.7	(24)
Occupational exposure to phenoxyherbicides	5.9	(105)	5.2	(16)

Table 5.2. Distribution of Selected Covariates[a] Among Men With Hodgkin's Disease and Among Control Subjects — Continued

	Controls (N = 1776)[b]		Hodgkin's Disease Cases (N = 310)[b]	
	%[c]	(N)	%[c]	(N)
Occupational exposure to chlorophenols	11.3	(200)	12.6	(39)
Occupational exposure to 2,4,5-T	0.9	(16)	0.6	(2)
Occupational exposure to 2,4-D	5.8	(103)	5.2	(16)
Worked in a leather tanning plant	0.5	(8)	1.0	(3)
Worked in a pulp, saw, or planing mill	5.7	(101)	6.1	(19)
Worked in a meat packing or processing plant	5.9	(104)	6.8	(21)
Worked with or around wood preservatives	11.8	(209)	13.2	(41)
Worked with or around cutting oils	20.5	(364)	18.1	(56)
Exposure to medical radiation 5 or more years before the date of diagnosis[c]	2.6	(47)	2.6	(8)
Had mononucleosis	6.5	(115)	10.0	(31)
Had a tonsillectomy	47.5	(843)	47.7	(148)
Had an appendectomy	16.0	(285)	17.1	(53)
Had chicken pox	84.4	(1499)	85.5	(265)
Had allergies	29.8	(530)	24.2	(75)
Had rheumatoid arthritis	3.6	(64)	2.3	(7)
Had multiple sclerosis	0.5	(8)	—	(0)
Took amphetamines (prescribed or illicit)	13.3	(236)	11.8	(36)
Took phenytoin or related compounds for epilepsy or seizures	1.0	(17)	0.6	(2)

[a] The covariates are described in the text

[b] Information on education for one non-Vietnam veteran control was missing. Information on dwelling while growing up for six controls (one Vietnam veteran) and two cases (one Vietnam veteran) was missing; information on mother's education level for 152 controls (seven Vietnam veterans) and 33 cases (two Vietnam veterans) was missing; information on number of siblings lived with for two non-Vietnam veteran controls was missing; and information on amphetamine use for five non-Vietnam veteran cases was missing

[c] Percentage of cases or controls with the specified characteristic

[d] For controls, 5 or more years before the date the registry was notified of selection

report having had infectious mononucleosis than were controls. Of the men with Hodgkin's disease, 9% (28) reported having served in the military in Vietnam — a slightly larger percentage than that for controls (7.5%).

After adjustment for the design characteristics (Table 5.3, Model 1), the relative risk estimate was 1.20 (95% CI 0.76-1.90), consistent with no association ($p=0.43$). Additional analyses (Models 2 and 3), in which we controlled for several additional characteristics, yielded similar results (Model 3, OR = 1.14), with a 95% CI ranging from 0.71 to 1.83. In all subsequent analyses, we controlled for covariates included in Model 3.

Choice of referent (nonexposed) group had little effect on the relative risk estimate for Hodgkin's disease (Table 5.4). The risk for Hodgkin's disease among Vietnam veterans relative to that among men who served in the military but not in Vietnam was 1.09 (95% CI 0.62-1.91), and the risk among Vietnam veterans relative to men with military service from 1964 to 1972 was 1.23 (95% CI 0.65-2.36). None of the observed associations were statistically significant.

The distribution of histologic types of Hodgkin's disease among men who were stationed in Vietnam was similar to that of men who were not stationed there (Table 5.5). About two-thirds of the men in each group were classified as having nodular sclerosing histology, with mixed cellularity being the second most common histologic type.

Table 5.3. Association Between Military Service in Vietnam and Hodgkin's Disease

Model[a]	Odds Ratio[b] (95% Confidence Interval)
1. Adjusted for registry and age group in 1968	1.20 (0.76-1.90)
2. Adjusted for registry, age group in 1968, racial/ethnic group, and education	1.17 (0.74-1.86)
3. Adjusted for—	
all variables in Model 2	
reported exposure to pesticides and chlorophenols	
—sprayed or mixed any herbicide on a farm or ranch	
—sprayed or mixed any herbicide in right-of-way maintenance, lawn care, or forestry work	
—occupational exposure to phenoxyherbicides	
—occupational exposure to chlorophenols	
reported medical history/drugs	
—infectious mononucleosis[c]	
—medical irradiation[c]	
—chemotherapy[c]	
—appendectomy	
—tonsillectomy	
reported demographic and lifestyle characteristics	
—history of smoking cigarettes	
—marital status	
—raised in the Jewish religion	
—number of siblings raised with	
—raised in an urban setting	1.14 (0.71-1.83)

[a] One control was excluded from all models because level of education was not known. Two controls were excluded from all models because number of siblings was not known

[b] Odds ratios estimate the relative risk and were calculated by using unconditional logistic regression. The referent group is composed of men who did not serve in Vietnam

[c] For cases, reported 5 or more years before the date of diagnosis; for controls, reported 5 or more years before the date the registry was notified of selection

Table 5.4. Risk of Hodgkin's Disease Among Vietnam Veterans Relative To the Risk Among Four Referent Groups

Risk Group	Controls (N = 1776) %[a]	Controls (N = 1776) (N)	Hodgkin's Disease Cases (N = 310) %[a]	Hodgkin's Disease Cases (N = 310) (N)	Odds Ratio[b] (95% Confidence Interval
Exposed group					
Men who served in Vietnam	7.5	(133)	9.0	(28)	
Referent groups					
Men who did not serve in Vietnam	92.5	(1643)	91.0	(282)	1.14 (0.71-1.83)
Men who served in the military but not in Vietnam	38.4	(682)	34.5	(107)	1.09 (0.62-1.91)
Men who served at any time from 1964 to 1972 in the military but not in Vietnam[c]	11.4	(203)	11.3	(35)	1.23 (0.65-2.36)
Men who never served in the military	54.1	(961)	56.5	(175)	1.17 (0.71-1.92)

[a] The percentage of controls or cases in the indicated exposed or referent group

[b] Odds ratios estimate the risk of Hodgkin's disease for the exposed group relative to the risk for the indicated referent group; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 5.3 (Model 3). Odds ratios were calculated by using unconditional logistic regression

[c] The exposed group is restricted to men who served in the military in Vietnam at any time from 1964 to 1972 (130 controls and 26 cases)

Table 5.5. Histologic Classification of Malignancies Among Men With Hodgkin's Disease, by Military Service in Vietnam

Classification	ICD-0 Code[a]	Stationed in Vietnam or off the Coast of Vietnam: No %[b]	No (N)	Yes %[b]	Yes (N)
Hodgkin's disease, NOS[c]	96503	2.5	(7)	10.7	(3)
Hodgkin's disease, lymphocytic predominance	96513	8.9	(25)	7.1	(2)
Hodgkin's disease, mixed cellularity	96523	23.0	(65)	14.3	(4)
Hodgkin's disease, nodular sclerosis	96563	65.6	(185)	67.9	(19)
All Hodgkin's disease cases (Total)		100.0	(282)	100.0	(28)

[a] International Classification of Diseases for Oncology, 1976
[b] Percentage of cases in each Vietnam service category with the indicated histology
[c] Not otherwise specified

5.3.2 Characteristics of Military Service in Vietnam

As Table 5.6 shows, the estimated risk of Hodgkin's disease by both branch of service and place of service relative to that for men who never served in the U.S. military fluctuates only modestly. The estimated risks were somewhat higher for men who served in Vietnam in the Air Force or Marines (and for Marines who did not serve in Vietnam), but none were statistically different from 1.0. The variation in relative risks across branch of service for Vietnam veterans lacked statistical significance.

Several attributes of military service in Vietnam, shown in Table 5.7, were not associated with differences in risk. Risks did not significantly vary according to calendar year of service, age at first tour in Vietnam, rank at the end of the first tour, or service in III Corps (the region most heavily sprayed with Agent Orange). Neither was there a consistent trend in risk with duration of service. Although the men who were in Vietnam for 1 to 1.4 years tended to have

Table 5.6. Association Between Branch of Military Service and Hodgkin's Disease, by Vietnam Veteran Status

Branch of Service	Non-Vietnam Veterans: Controls (N = 682)[a] %[b]	(N)	Hodgkin's Disease Cases (N = 107)[a] %[b]	(N)	Odds Ratio[c] (95% Confidence Interval)	Vietnam Veterans: Controls (N = 133) %[b]	(N)	Hodgkin's Disease Cases (N = 28) %[b]	(N)	Odds Ratio[c] (95% Confidence Interval)	P value
Army	52.5	(358)	35.6	(38)	0.78 (0.52-1.17)	52.6	(70)	42.9	(12)	1.00 (0.51-1.97)	
Air Force	18.2	(124)	21.5	(23)	1.36 (0.81-2.29)	13.5	(18)	17.9	(5)	1.69 (0.58-4.89)	0.80[d]
Marines	5.7	(39)	11.2	(12)	1.77 (0.86-3.63)	9.8	(13)	14.3	(4)	1.73 (0.51-5.88)	
Navy	17.0	(116)	22.4	(24)	1.34 (0.81-2.24)	23.3	(31)	25.0	(7)	1.06 (0.43-2.59)	
Coast Guard	0.7	(5)	—	(0)	—[e]	0.8	(1)	—	(0)	—[e]	

[a] The sum of the subjects in all branches is less than N because information concerning branch of service was missing for 50 men
[b] Percentage of controls or cases in the specified branch
[c] Odds ratios estimate the risk of Hodgkin's disease for a given category relative to the risk among men with no military service (961 controls and 175 cases); they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 5.3 (Model 3) by using unconditional logistic regression
[d] Null hypothesis: no difference in the odds ratio across branches among Vietnam veterans
[e] Odds ratio and confidence interval were not calculated because of a zero cell

Table 5.7. Association Between Selected Characteristics of Military Service in Vietnam and Hodgkin's Disease

Characteristic	Controls (N = 1776) %[a]	Controls (N = 1776) (N)	Hodgkin's Disease Cases (N = 310) %[a]	Hodgkin's Disease Cases (N = 310) (N)	Odds Ratio[b] (95% Confidence Interval)	P-value[c]
No military service in Vietnam	—	(1643)	—	(282)	Referent	
Military service in Vietnam	—	(133)	—	(28)	1.14 (0.71-1.83)	
Duration of service in Vietnam (years)						
<1	59.9	(79)	46.4	(13)	0.86 (0.45-1.65)	
1 to 1.4	13.6	(18)	28.6	(8)	2.43 (0.98-5.99)	0.33
1.5 to 1.9	9.9	(13)	10.7	(3)	1.14 (0.30-4.37)	
⩾2	16.7	(22)	14.3	(4)	1.11 (0.36-3.45)	
Unknown	—	(1)	—	(0)		
Calendar years stationed in Vietnam						
Before 1966	7.5	(10)	3.6	(1)	0.41 (0.05-3.44)	
1966 to 1969	78.2	(104)	67.9	(19)	1.11 (0.64-1.93)	0.42
After 1969	14.3	(19)	28.6	(8)	1.63 (0.66-4.02)	
Unknown	—	(0)	—	(0)		
Age at beginning of first tour in Vietnam (years)						
<21	42.9	(57)	53.6	(15)	1.15 (0.61-2.18)	
21 to 25	37.6	(50)	32.1	(9)	1.06 (0.49-2.29)	0.95
⩾26	19.6	(26)	14.3	(4)	1.31 (0.42-4.10)	
Unknown	—	(0)	—	(0)		
Rank at end of last tour in Vietnam[d]						
E1 to E3	16.2	(21)	17.9	(5)	1.07 (0.37-3.04)	
E4 to E9	73.1	(95)	75.0	(21)	1.19 (0.70-2.04)	0.97
Officer	10.8	(14)	7.1	(2)	1.33 (0.28-6.26)	
Unknown	—	(3)	—	(0)		
Type of unit in Vietnam						
Support	53.5	(69)	71.4	(20)	1.58 (0.90-2.77)	
Combat Support	26.4	(34)	10.7	(3)	0.50 (0.14-1.76)	0.17
Combat	20.2	(26)	17.9	(5)	0.94 (0.34-2.59)	
Unknown	—	(4)	—	(0)		
Corps in Vietnam						
I	18.9	(23)	25.9	(7)	1.67 (0.67-4.18)	
II	24.6	(30)	11.1	(3)	0.52 (0.15-1.81)	0.59
III	32.8	(40)	33.3	(9)	1.25 (0.57-2.75)	
IV	3.3	(4)	3.7	(1)	0.93 (0.09-9.82)	
Blue water Navy[e]	20.5	(25)	25.9	(7)	1.39 (0.56-3.46)	
Unknown	—	(11)	—	(1)		
Ever in III Corps in Vietnam						
No	36.8	(46)	35.7	(10)	1.27 (0.60-2.67)	
Yes	43.2	(54)	39.3	(11)	1.12 (0.55-2.27)	0.92
Blue Water Navy[e]	20.0	(25)	25.0	(7)	1.42 (0.57-3.52)	
Unknown	—	(8)	—	(0)		
Land vs. sea duty in Vietnam						
All land-based Men	81.2	(108)	75.0	(21)	1.08 (0.64-1.82)	
All branches other than Navy	76.7	(102)	75.0	(21)	1.18 (0.70-2.00)	
Navy—shore	3.0	(4)	—	(0)	—[f]	0.61[g]
Navy—brown water	1.5	(2)	—	(0)	—[f]	
Sea-based blue water Navy	18.8	(25)	25.0	(7)	1.41 (0.57-3.50)	

[a] Percentage of case or control subjects who served in Vietnam with the specified characteristic (unknowns excluded
[b] Odds ratios estimate the risk of Hodgkin's disease for a given category of men relative to the risk among men who did not serve in Vietnam; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 5.3 (Model 3) by using unconditional logistic regression
[c] Null hypothesis: no difference in the odds ratio across subgroups
[d] In the Army, ranks E1 to E3 correspond to the various levels of private, rank E4 to corporal, and ranks E5 to E9 to the various levels of sergeant
[e] Corps does not apply to Navy men stationed on ocean-going vessels
[f] Odds ratio and confidence interval were not calculated because of a zero cell
[g] Null hypothesis: no difference in the odds ratio between all land-based men combined and sea-based blue water Navy men

a higher estimated risk than men who did not serve in Vietnam, (OR=2.43, 95% CI 0.98-5.99), risks were very close to 1.0 for men who served for longer periods (1.5-1.9 years or ≥2 years). Small differences in risk by type of unit (combat, combat support, or support), region of duty in Vietnam, or type of Navy duty (shore, brown water, blue water) were also not significant.

When we examined the association between self-perceived contact with Agent Orange and Hodgkin's disease among Vietnam veterans (Table 5.8), we did not find any characteristic to be associated with an increased risk. For example, the men who reported that they had passed through a defoliated area in Vietnam did not have a higher risk for Hodgkin's disease relative to other Vietnam veterans (OR=0.65, 95% CI 0.25-1.67). Only 1 of the 28 Vietnam veterans with Hodgkin's disease reported getting Agent Orange on his skin or clothes, and none reported handling equipment or containers used with Agent Orange or spraying Agent Orange.

Table 5.8. Association Between Self-Reported Possible Contact With Agent Orange[a] and Hodgkin's Disease Among Men Who Served in the Military in Vietnam

Characteristic	Category	Controls (N = 133) %[b]	Controls (N = 133) (N)	Hodgkin's Disease Cases (N = 28) %[b]	Hodgkin's Disease Cases (N = 28) (N)	Odds Ratio[c] (95% Confidence Interval)
Reported passing through a defoliated area	No	65.4	(87)	71.4	(20)	
	Yes	34.6	(46)	28.6	(8)	0.65 (0.25-1.67)
Reported any possible contact with Agent Orange[d]	No	74.4	(99)	75.0	(21)	
	Yes	25.6	(34)	25.0	(7)	0.76 (0.28-2.07)
Reported being present when others were spraying Agent Orange	No	89.5	(119)	92.9	(26)	
	Yes	10.5	(14)	7.1	(2)	0.74 (0.15-3.67)
Reported getting Agent Orange on skin or clothes	No	92.5	(123)	96.4	(27)	
	Yes	7.5	(10)	3.6	(1)	0.47 (0.06-3.99)
Reported handling equipment or containers that had been used with Agent Orange	No	97.7	(130)	100.0	(28)	
	Yes	2.3	(3)	—	(0)	—[e]
Reported spraying Agent Orange	No	98.5	(131)	100.0	(28)	
	Yes	1.5	(2)	—	(0)	—[e]

[a] Includes other herbicides
[b] Percentage of case or control subjects who served in the military in Vietnam with the specified characteristic
[c] Odds ratios estimate the risk of Hodgkin's disease relative to the risk among men who did not report the specific exposure but who served in the military in Vietnam; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 5.3 (Model 3) by using unconditional logistic regression
[d] Includes all contacts listed below as well as any other mention of Agent Orange
[e] Odds ratio and confidence interval were not calculated because of a zero cell

We studied the pattern of risk over the time since service in Vietnam (Table 5.9), although the relatively short time span of the study and of the extensive American involvement in Vietnam resulted in a narrow distribution of latency periods. Within the confines of this study (periods of <17 years to ≥22 years), however, there was no evidence that the risk of Hodgkin's disease varies with the time since service in Vietnam.

5.3.3 Sensitivity Analyses

The results of various sensitivity analyses are shown in Table 5.10. In general, our estimated relative risk of 1.14 varied only slightly according to various inclusion and exclusion criteria, and none of the ORs was statistically significant. The highest relative risk was seen after we excluded men who were 30 years of age and older in 1968 (OR=1.24, 95% CI 0.76-2.02).

Table 5.9. Risk of Hodgkin's Disease Among Vietnam Veterans, by Number of Years Since Start of First Tour in Vietnam

Number of Years Since Start of First Tour in Vietnam[a]	Controls (N = 133) %[b]	(N)	Hodgkin's Disease Cases (N = 28) %[b]	(N)	Odds Ratio[c] (95% Confidence Interval)	P-value[d]
<17	15.0	(20)	21.4	(6)	1.12 (0.43-2.96)	
17 to 18	30.8	(41)	21.4	(6)	0.68 (0.27-1.74)	0.99
19 to 21	41.4	(55)	50.0	(14)	1.73 (0.90-3.33)	
≥22	12.8	(17)	7.1	(2)	0.68 (0.15-3.18)	

[a] For cases, the end of the latency period is the date of diagnosis; for controls, it is the date the registry was notified of selection

[b] The percentage of controls and cases who served in Vietnam in the specified category

[c] Odds ratios estimate the relative risk of Hodgkin's disease; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 5.3 (Model 3) by using unconditional logistic regression. Men with no military service in Vietnam form the referent group (1,643 controls and 282 cases)

[d] Test for a linear trend in the odds ratio as calculated from a logistic regression model

Table 5.10. Association Between Military Service in Vietnam and Hodgkin's Disease Among Selected Groups of Men

	Controls	Hodgkin's Disease Cases	Table 5.3, Model 3 Odds Ratio (95% Confidence Interval)
Men in main analyses	1773	310	1.14 (0.71-1.83)
Sensitivity Analyses[a]			
Additions to analyses:			
Men with AIDS or an AIDS-related condition	1774	327	1.08 (0.68-1.72)
Men who were in Vietnam or off its coast, but not stationed there (include as exposed)	1800	311	0.99 (0.63-1.56)
Exclusions from analyses:			
Men without a telephone in the household	1755	300	1.08 (0.67-1.74)
Men interviewed in person	1749	304	1.06 (0.66-1.72)
Men whose interview was not rated as good or excellent	1743	308	1.16 (0.73-1.86)
Men who were 30 or older in 1968	1010	216	1.24 (0.76-2.02)
Case subjects with a proxy interview	1773	305	1.15 (0.72-1.84)
Men whose Vietnam service could not be confirmed[b]	1766	309	1.16 (0.72-1.88)

[a] Sensitivity analyses show the effect of adding (or removing) men to (or from) the main analysis. Each addition (or exclusion) is applied separately. Numbers of controls and cases are numbers remaining in analyses after additions or exclusions

[b] Men who gave permission for military records review, whose records were located, and whose Vietnam service could not be confirmed were excluded

5.4 SUMMARY

Our results indicate that Vietnam veterans are not at higher risk for Hodgkin's disease compared with (1) men who did not serve in Vietnam, (2) men who served in the military, but not in Vietnam, and (3) men who did not serve in the military. Furthermore, we found no attributes of military service that identify subgroups of Vietnam veterans with a higher risk of Hodgkin's disease. The relative risk did not vary according to branch, calendar year, duration, location, rank, age at the beginning of service in Vietnam, or several self-reported assessments of exposure to Agent Orange. In addition, there were no significant differences in the risk among Vietnam veterans relative to that among other men from 15 to 25 years after the beginning of their military service in Vietnam. Although a negative study raises the question of statistical power, we had a power of 96% for detecting a relative risk of 2.0 (Table 2.5).

We discuss these results further in Chapter 9.

6. NASAL CANCER

6.1 BACKGROUND

Nasal cancer is extremely rare; the average annual incidence among men ages 30 to 59 years (the age range included in this study) is only 0.8 per 100,000 persons (Young et al., 1981). Peak rates of this malignancy occur among persons between the ages of 65 and 75 years (Redmond et al., 1982).

There is some concern that exposure to Agent Orange (and its contaminant 2,3,7,8-TCDD) in Vietnam has increased the risk of cancer of the sinonasal cavities among Vietnam veterans. Although animal experiments have shown that TCDD causes tumors of the nasal turbinate in rats (IARC, 1987), evidence linking TCDD or phenoxyherbicides with cancer of this site in humans is weak. Early studies of agricultural workers reported nonsignificant deficits in nasal cancers (Williams et al., 1977; Wiklund et al., 1981). In 1982, however, Hardell and coworkers reported, for a combined nasal and nasopharyngeal cancer case group, an increased risk estimate of 2.1 (95% CI 0.9-4.7) for exposure to phenoxyherbicides for at least 1 day (Crude odds ratios provided for the cancers separately were 1.8 (nasal) and 2.0 (nasopharyngeal).) Although Gallagher and coworkers (1984) reported a nonsignificant increase among British Columbia farmers, the results of most later studies showed no association between suspected agricultural exposures to phenoxyherbicides and cancer of the sinonasal cavity (Hernberg et al., 1983; Milham, 1983).

In 1986, Coggon and coworkers examined mortality and cancer incidence among manufacturers and sprayers of the phenoxyherbicide, 2 methyl-4 chlorophenoxyacetic acid (a phenoxyherbicide that is not contaminated with TCDD). Nasal cancer was the cause of death for 3 of the 5,754 men whose cases were followed from 1947 through 1983 (0.7 deaths were expected). All 3 men were at high potential for exposure to phenoxyherbicides; the duration of exposure, however, was only between 1 and 6 months. Because of the small numbers and the lack of nasal cancer cases among men exposed for longer periods, these results must be interpreted cautiously.

Because of the difficulty in measuring past exposure to Agent Orange, its possible effect on cancer among Vietnam veterans has been studied only indirectly by comparing cancer occurrence among Vietnam veterans with that in other groups. An increase in deaths for nasal cancer has been reported (Lawrence et al., 1985); however, the results were based on only three deaths among Vietnam veterans. In other studies of Vietnam veterans, researchers have not reported results specific for this anatomical site (Anderson et al., 1986; Bailey et al., 1986; Breslin et al., 1988; Thomas et al., 1990).

Numerous factors affect the risk of nasal cancer. Excesses in this type of cancer have been reported among workers who manufacture chrome pigment, mustard gas, isopropyl alcohol, textiles and clothing (cotton and wool), boots and shoes, and petrochemicals; among workers in nickel refineries, among workers whose jobs involve cutting oils; among radium dial painters; and among wood workers in various industries (Redmond et al., 1982; Acheson, 1986). Cigarette smoking (Elwood, 1981; Brinton et al., 1984; Hirayama, 1984; Hayes et al., 1987), chronic sinusitis and previous nasal problems (Shimizu et al., 1989), and low socioeconomic status (Redmond et al., 1982) have been positively associated with this malignancy. In addition, the incidence of nasal cancer is increased among Hawaiians, American Indians, and Chinese Americans (Redmond et al., 1982).

In 1983, acting on the recommendations of reviewers, researchers in the Selected Cancers Study added cancer of the sinonasal cavities to the group of malignancies to be included in the study. During the study we focused on the risk of this cancer after Vietnam service in

general and reviewed the characteristics of military service in Vietnam, some of which may be indicative of greater potential for exposure to Agent Orange.

6.2 METHODS

Chapter 2 provides an overview of the study's design, how it was conducted, and how the data were analyzed. Here we further discuss several topics discussed in Chapter 2.

6.2.1 Subjects and Sources of Data

Nasal cancer was defined to include malignancies of the sinus or nasal cavities (Appendix A shows the ICD-O codes that were eligible for the study.) Eight participating tumor registries identified 89 men, born between 1929 and 1953, who had malignancies diagnosed between December 1, 1984, and November 30, 1988. Ninety percent of the eligible case subjects were interviewed by using a standardized questionnaire, and pathology specimens were obtained for all but two (Table 2.4). Because we used a site-specific definition for nasal cancer, our case group included various histologic types that differ in their sensitivity to risk factors. Known risk factors for nasal cancer are related specifically to the carcinomas. For example, wood working is associated with adenocarcinoma, smoking is associated with squamous cell carcinoma, and shoe manufacturing and repair is associated with both. Therefore, we restricted most analyses of nasal malignancies to carcinomas. Our case group includes 74% of the 70 men whose malignancy was confirmed by an expert nasal and nasopharyngeal pathology panel.

As discussed in Chapter 2, the category of men with confirmed malignancies comprises two groups: those with definite nasal carcinoma and those with probable nasal carcinoma. The latter group consists of one man whose cancer was diagnosed by the pathology panel as "consistent with a nasal primary" on the basis of a histologic review of a metastatic tumor. We included this probable case in our analyses.

Twenty-two men were excluded from most analyses either because they did not have carcinoma or because they met the other exclusion criteria defined in Chapter 2 (not a confirmed malignancy, military service unknown, in Vietnam but not stationed there, had AIDS or an AIDS-related condition, or not a resident of the United States before 1969). Excluding these men left only 48 subjects with cases of nasal carcinoma for comparison with 1,776 random digit dialing (RDD) control subjects. (Chapter 2 contains a thorough explanation of our methods for selecting a control group. Table 2.4 shows the number of men identified, interviewed, and included in our analyses.) The sensitivity of our results to the inclusion and exclusion criteria was assessed in supplemental analyses.

6.2.2 Statistical Analyses

Because of the study's matched design and small number of cases, we used conditional logistic regression to calculate the risk estimates presented in this chapter. To facilitate interpretation, we limited the number of potential confounders in the final model to the following factors: racial or ethnic group, education, history of cigarette smoking, and occupational exposure to wood dust. When possible, we calculated exact 95% mid-p confidence intervals (SERC, 1990) for the association between Vietnam service and carcinoma. We did not assess effect modification because of the sparsity of data.

In most analyses the referent group consisted of men who did not serve in Vietnam. These analyses had an 80% power to detect an increased OR of about 2.8. (Table 2.5 shows the power estimates for detecting risk estimates of 1.5, 2.0, and 4.0 for this cancer.) We also examined the effect of using other definitions of *nonexposed*. We did not perform subgroup analyses of military characteristics because only 2 of the 48 nasal carcinoma subjects

reported having been stationed in Vietnam. For both of these men, the U.S. Army and Joint Services Environmental Support Group (ESG) confirmed military service in Vietnam.

6.3 RESULTS

6.3.1 Overall Association

The distribution of case and control subjects among each of the 40 registry and age-in-1968 cells is shown in Table 6.1. The overall ratio of the number of nasal carcinoma subjects to the number of control subjects was about 1:37.

As Table 6.2 shows, compared with men in the control group, men with nasal carcinoma were older, were more likely to be black, had less formal education, and were more likely to have smoked cigarettes. In exposure to herbicides and chlorophenols, we observed only minor differences between the two groups. Few case or control subjects reported exposure to several occupational risk factors. For example, 8% (4/48) of men with nasal carcinoma and 5.7% (101/1,776) of control subjects reported having worked in a pulp, saw, or planing mill.

Table 6.1. Distribution of Men With Nasal Carcinoma and Distribution of Control Subjects, by Registry and Age in 1968

Registry	Age in 1968 (Years)					Total
	15-19	20-24	25-29	30-34	35-39	
1	1: 20[a]	0: 34	1: 35	1: 24	1: 29	4: 142
2	0: 37	0: 56	1: 49	6: 69	3: 74	10: 285
3	0: 39	1: 30	2: 58	2: 51	1: 69	6: 247
4	1: 31	0: 25	0: 36	0: 29	3: 45	4: 166
5	0: 17	0: 24	0: 14	3: 25	0: 22	3: 102
6	0: 89	1:102	0: 89	3: 80	3: 73	7: 433
7	0: 42	3: 46	2: 46	1: 41	4: 70	10: 245
8	0: 27	0: 37	2: 30	0: 30	2: 32	4: 156
Total	2:302	5:354	8:357	16:349	17:414	48:1776

[a] N cases:N controls

Table 6.2. Distribution of Selected Covariates[a] Among Men With Nasal Carcinoma and Among Control Subjects

	Controls (N = 1776)[b]		Nasal Carcinoma Cases (N = 48)[b]	
	%[c]	(N)	%[c]	(N)
Design characteristics				
Registry				
1	8.0	(142)	8.3	(4)
2	16.0	(285)	20.8	(10)
3	13.9	(247)	12.5	(6)
4	9.3	(166)	8.3	(4)
5	5.7	(102)	6.3	(3)
6	24.4	(433)	14.6	(7)
7	13.8	(245)	20.8	(10)
8	8.8	(156)	8.3	(4)
Age in 1968 (years)				
15 to 19	17.0	(302)	4.2	(2)
20 to 24	19.9	(354)	10.4	(5)
25 to 29	20.1	(357)	16.7	(8)
30 to 34	19.7	(349)	33.3	(16)
35 to 39	23.3	(414)	35.4	(17)

Table 6.2. Distribution of Selected Covariates[a] Among Men With Nasal Carcinoma and Among Control Subjects — Continued

	Controls (N = 1776)[b]		Nasal Carcinoma Cases (N = 48)[b]	
	%[c]	(N)	%[c]	(N)
Stationed in Vietnam or off the coast of Vietnam	7.5	(133)	4.2	(2)
Other reported characteristics				
Racial/ethnic group				
White non-Hispanic	84.3	(1497)	79.2	(38)
Black non-Hispanic	8.1	(143)	14.6	(7)
Hispanic	5.6	(99)	2.1	(1)
Asian	1.7	(31)	2.1	(1)
Other/unknown	0.3	(6)	2.1	(1)
Highest level of education completed				
Less than high school	11.3	(200)	20.8	(10)
High school, technical school	29.5	(523)	39.6	(19)
1 to 3 years of college	20.6	(366)	25.0	(12)
4 or more years of college	38.6	(686)	14.6	(7)
Smoked cigarettes regularly	66.8	(1186)	85.4	(41)
Drank alcohol regularly	71.1	(1262)	87.5	(42)
Never married	7.3	(129)	6.3	(3)
Lived or worked on a farm or ranch	44.8	(796)	37.5	(18)
Sprayed or mixed any herbicide on a farm or ranch	9.6	(170)	10.4	(5)
Contact with herbicides on a farm or ranch, 21 or more days per year, 5 or more years, before the date of diagnosis[d]	2.4	(43)	2.1	(1)
Sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work	7.3	(129)	6.3	(3)
Occupational exposure to phenoxy-herbicides	5.9	(105)	6.3	(3)
Occupational exposure to chloro-phenols	11.3	(200)	10.4	(5)
Occupational exposure to 2,4,5-T	0.9	(16)	4.2	(2)
Occupational exposure to 2,4-D	5.8	(103)	6.3	(3)
Worked in leather tanning	0.5	(8)	2.1	(1)
Worked around shoe or leather dust	1.4	(25)	—	(0)
Worked in a pulp, saw, or planing mill	5.7	(101)	8.3	(4)
Worked with or around wood preservatives	11.8	(209)	8.3	(4)
Worked with or around wood dust	26.7	(474)	29.2	(14)
Worked with or around plywood	23.8	(422)	25.0	(12)
Worked in metal plating	3.4	(61)	4.2	(2)
Worked with or around nickel	6.7	(119)	4.2	(2)
Worked with or around chromium	6.1	(109)	2.1	(1)
Worked with or around radiation	12.6	(223)	12.5	(6)
Worked with wood in a hobby	24.6	(437)	18.8	(9)
Worked with or around cutting oils	20.5	(364)	20.8	(10)

Table 6.2. Distribution of Selected Covariates[a] Among Men With Nasal Carcinoma and Among Control Subjects — Continued

	Controls (N = 1776)[b]		Nasal Carcinoma Cases (N = 48)[b]	
	%[c]	(N)	%[c]	(N)
Had sinus infections in previous 5 years with first occurrence 5 or more years before the date of diagnosis[d]	6.6	(117)	2.1	(1)
Had other sinus problems in previous 5 years with first occurrence 5 or more years before the date of diagnosis[d]	2.9	(51)	2.1	(1)
Had nose bleeds 5 or more years before the date of diagnosis[d]	5.9	(105)	—	(0)
Had nasal polyps 5 or more years before the date of diagnosis[d]	1.5	(27)	—	(0)
Used nasal drops or sprays 5 or more years before the date of diagnosis[d]	4.1	(72)	4.2	(2)

[a] The covariates are described in the text
[b] Information on education was missing for one non-Vietnam veteran control
[c] Percentage of cases or controls with the specified characteristic
[d] For controls, 5 or more years before the date the registry was notified of selection

Only 4% (2/48) of men with nasal carcinoma served in Vietnam compared with 7.5% (133/1776) of the men in the control group. After we controlled for the design factors, the OR was 0.70 (exact 95% CI 0.08-2.95) (Table 6.3). Further adjustment for racial or ethnic group, education, history of cigarette smoking, and occupational exposure to wood dust produced little change in this association (OR=0.66, 95% CI 0.15-2.91). Occupational exposure to phenoxyherbicides, chlorophenols, or farming or nonfarming herbicides did not confound this relationship; adding all of these factors to Model 3 (Table 6.3) resulted in an OR of 0.67 (95% CI 0.15-2.98). None of these results indicates that men who served in Vietnam had a higher risk for nasal carcinoma. The covariates included in Model 3 (Table 6.3) are controlled for in all subsequent analyses.

Because of the relatively small number of men with nasal carcinoma, the use of different referent (nonexposed) groups resulted in different risk estimates, but in no instance were Vietnam veterans at significantly increased risk (Table 6.4). For example, restricting the referent group to the 710 men who served in the military in places other than Vietnam (of whom 28 had nasal carcinoma), yielded an OR of 0.37 (95% CI 0.08-1.83), and restricting it to men who had no active military service (of whom only 18 had nasal carcinoma), yielded an OR of 1.38 (95% CI 0.28-6.81).

Table 6.3. Association Between Military Service in Vietnam and Nasal Carcinoma

Model[a]	Odds Ratio[b] (95% Confidence Interval)
1. Adjusted for registry and age group in 1968	0.70 (0.08-2.95)[c]
2. Adjusted for registry, age group in 1968, racial/ethnic group[d], and education	0.67 (0.15-2.96)
3. Adjusted for— all variables in Model 2 reported occupational or lifestyle characteristics —history of smoking cigarettes —occupational exposure to wood dust	0.66 (0.15-2.91)

[a] One control was excluded from all models because level of education was not known
[b] Odds ratios estimate the relative risk and were calculated by using conditional logistic regression. The referent group is composed of men who did not serve in Vietnam
[c] Exact confidence interval
[d] White, black, other

Table 6.4. Risk of Nasal Carcinoma Among Vietnam Veterans Relative To the Risk Among Four Referent Groups

Risk Group	Controls (N = 1776) %[a]	Controls (N = 1776) (N)	Nasal Carcinoma Cases (N = 48) %[a]	Nasal Carcinoma Cases (N = 48) (N)	Odds Ratio[b] (95% Confidence Interval)
Exposed group					
Men who served in Vietnam	7.5	(133)	4.2	(2)	
Referent groups					
Men who did not serve in Vietnam	92.5	(1643)	95.8	(46)	0.66 (0.15-2.91)
Men who served in the military but not in Vietnam	38.4	(682)	58.3	(28)	0.37 (0.08-1.83)
Men who served at any time from 1964 to 1972 in the military but not in Vietnam[c]	11.4	(203)	16.7	(8)	0.31 (0.04-2.20)
Men who never served in the military	54.1	(961)	37.5	(18)	1.38 (0.28-6.81)

[a] The percentage of controls or cases in the indicated exposed or referent group

[b] Odds ratios estimate the risk of nasal carcinoma for the exposed group relative to the risk for the indicated referent group; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 6.3 (Model 3). Odds ratios were calculated by using conditional logistic regression

[c] The exposed group is restricted to men who served in the military in Vietnam at any time from 1964 to 1972 (130 controls and 2 cases)

The two Vietnam veterans with nasal carcinoma served in the Army for 1 year or less. Both men served in support units in III Corps. Neither reported direct contact with Agent Orange though one case reported passing through a defoliated area. When the case series was expanded to include all malignancies, we identified one additional Vietnam veteran—a Navy veteran who served off the coast of Vietnam for 26 months. A reanalysis that included all malignancies altered the OR only slightly (OR = 0.72, 95% CI 0.21-2.44).

Table 6.5 provides the histologic classification of malignancies among men in the expanded case group by Vietnam service status. The distribution of cancers is comparable with what would be expected on the basis of the distribution of histologic types in the general population.

6.3.2 Sensitivity Analyses

Because we decided to exclude case subjects who fit specific criteria before analyzing the data, we performed sensitivity analyses to assess the effect of these exclusions on our risk estimate. Table 6.6 presents the results of these analyses. We evaluated the potential for information bias as a result of our using only certain interview data in some of these analyses (data on men whose interview was rated good or excellent, data on men who were interviewed by phone only, or data that were self-reported). Model 3 (Table 6.3) was used for all analyses. Differences in the risk estimates were negligible. Similarly, changes in the case definition, based on pathology information, did not affect the risk estimate. An analysis that included only case and control men in the three youngest age groups changed the direction of the association; however, the risk estimate was based on only 16 nasal carcinoma cases and was highly unstable (95% CI 0.25-6.51).

6.4 SUMMARY

No association was found between military service in Vietnam and nasal carcinoma, regardless of referent group. Nor did changes in the case definition significantly affect this result. The small numbers of cases, however, limits our ability to detect small increases in risk.

We discuss our results further in Chapter 9.

Table 6.5. Histologic Classification of Malignancies Among Men With Nasal Cancer, by Military Service in Vietnam

Classification	ICD-0 Code[a]	Stationed in Vietnam or off the Coast of Vietnam: No %[b]	No (N)	Yes %[b]	Yes (N)
Malignant neoplasm, NOS[c]	80003	1.7	(1)	—	(0)
Carcinoma (Total)		78.0	(46)	66.7	(2)
Carcinoma, undifferentiated	80203	1.7	(1)	—	(0)
Small cell carcinoma, NOS	80413	1.7	(1)	—	(0)
Mucoepidermoid carcinoma	84303	1.7	(1)	—	(0)
Squamous cell carcinoma (Subtotal)		59.3	(35)	66.7	(2)
Squamous cell carcinoma, keratinizing	80713	52.5	(31)	66.7	(2)
Squamous cell carcinoma, nonkeratinizing	80733	6.8	(4)	—	(0)
Adenocarcinoma (Subtotal)		13.6	(8)	—	(0)
Adenocarcinoma, NOS	81403[d]	5.1	(3)	—	(0)
Adenoid cystic carcinoma	82003	5.1	(3)	—	(0)
Mucinous adenocarcinoma	84803	1.7	(1)	—	(0)
Mucin-producing adenocarcinoma	84813	1.7	(1)	—	(0)
Sarcoma (Total)		8.5	(5)	—	(0)
Sarcoma, NOS	88003	1.7	(1)	—	(0)
Chondrosarcoma, NOS	92203	1.7	(1)	—	(0)
Esthesioneuroblastoma	95223	5.1	(3)	—	(0)
Lymphoma (Total)		11.9	(7)	33.3	(1)
Malignant lymphoma, NOS	95903	10.2	(6)	33.3	(1)
Malignant lymphoma, diffuse, large cell	96403	1.7	(1)	—	(0)
All nasal cancer cases (Total)		100.0	(59)	100.0	(3)

[a] International Classification of Diseases for Oncology, 1976
[b] Percentage of cases in each Vietnam service category with the indicated histology
[c] Not otherwise specified
[d] One case was diagnosed on the basis of a metastatic tumor consistent with a nasal primary

Table 6.6. Association Between Military Service in Vietnam and Nasal Carcinoma Among Selected Groups of Men

	Controls	Nasal Carcinoma Cases	Table 6.3, Model 3 Odds Ratio (95% Confidence Interval)
Men in main analyses	1775	48	0.70 (0.16-3.05)
Sensitivity Analyses[a]			
Additions to analyses:			
Men with AIDS or an AIDS-related condition	1776	49	0.64 (0.14-2.81)
Men who were in Vietnam or off its coast, but not stationed there (include as exposed)	1802	49	0.87 (0.25-3.00)
Case subjects whose diagnosis was not confirmed because a specimen was not obtained or was deemed inadequate for review	1775	49	0.64 (0.14-2.81)
Case subjects with any malignancy of a sinonasal site (includes lymphomas and sarcomas)	1775	62	0.72 (0.21-2.44)
Exclusions from analyses:			
Men without a telephone in the household	1757	45	0.69 (0.15-3.03)
Men interviewed in person	1751	47	0.67 (0.15-2.98)
Men whose interview was not rated as good or excellent	1745	44	0.78 (0.17-3.46)
Men who were 30 or older in 1968	1012	16	1.27 (0.25-6.51)[b]
Case subjects with a proxy interview	1775	42	0.79 (0.18-3.52)
Case subjects with other than definite nasal carcinoma	1775	47	0.71 (0.16-3.14)

[a] Sensitivity analyses show the effect of adding (or removing) men to (or from) the main analysis. Each addition (or exclusion) is applied separately. Numbers of controls and cases are numbers remaining in analyses after additions or exclusions
[b] Excludes 18 of 133 Vietnam veteran control subjects and no Vietnam veteran case subjects

7. NASOPHARYNGEAL CANCER

7.1 BACKGROUND

Nasopharyngeal cancer is an extremely rare malignancy, occurring in the United States at a rate of about 1.2 per 100,000 among men ages 30 to 59 (Young et al., 1981). The incidence rate of this malignancy tends to rise in younger age groups, and, unlike the incidence for many cancers, does not increase sharply in older age groups. The incidence rates are similar for blacks and whites, except that the rate has a minor peak among young blacks (Shanmugaratnam, 1982).

Concerns that exposure to Agent Orange (and its contaminant 2,3,7,8-TCDD) may have increased the risk of this malignancy among men who served in the military in Vietnam were raised in 1982 by the results of a Swedish case-control study. In this investigation, Hardell and coworkers reported a nonsignificant twofold increase in risk (odds ratio (OR) = 2.1, 95% CI 0.9-4.7) for nasal and nasopharyngeal cancers combined among men reporting exposure to phenoxy herbicides for at least 1 day. (Crude ORs provided for the cancers separately were 1.8 (nasal) and 2.0 (nasopharyngeal).)

The results of other epidemiologic research lend little support to the findings of Hardell and coworkers (1982). Only indirect evidence of an association between exposure to phenoxy-herbicides and nasopharyngeal cancer can be hypothesized from results in a 1981 report (Yu et al.) that showed increased standardized incidence ratios for male and female farmhands (standardized incidence ratio = 2.7 and 4.5, respectively, p-values not provided) in Hong Kong. In mortality studies of herbicide manufacturers (Lynge, 1985; Coggon et al., 1986), investigators have not reported doing analyses of the association between phenoxyherbicide exposures and nasopharyngeal cancer. Because this cancer is so rare, these investigators, in their reports, have grouped it with other cancers of the pharynx or with all cancers of the oral cavity.

Because of the difficulty in measuring past exposure to Agent Orange, its possible effect on cancer among Vietnam veterans has been studied only indirectly by comparing cancer occurrence among Vietnam veterans with that in other groups. As with studies of herbicide manufacturers, results of analyses specific to cancer of the nasopharynx have not been reported (Bailey et al., 1986; Breslin et al., 1988; Thomas et al., 1990).

Both environmental and genetic factors appear to play a role in the occurrence of nasopharyngeal cancer. In certain populations, such as the Chinese and Vietnamese, the incidence of this malignancy is high (Shanmugaratnam, 1982), and familial clustering of this cancer has been reported among whites born in the United States (Gajwani et al., 1980), among Alaska Natives (Ireland et al., 1988), and among persons of Chinese origin (Shanmugaratnam, 1982). These findings indicate that the disease has a genetic component. Results of studies of migrants indicate that the environment also plays a role; however, strong evidence linking this cancer to specific environmental agents is lacking. Occupational exposures to fumes, chemicals, or smoke or to wood dust, a diet including Cantonese-style salted fish, previous sinonasal illnesses, Epstein-Barr virus infection (Gastpar et al., 1981; Shanmugaratnam, 1982), heavy cigarette smoking (Hammond, 1966; Lin et al., 1973), and exposure to formaldehyde (Vaughan et al., 1986a; Vaughan et al., 1986b) have been examined as risk factors for cancer of the nasopharynx, and the results have been inconsistent. Socioeconomic status is known to have an inverse relationship with this cancer (Fedder and Gonzalez, 1985).

In 1983, acting on the recommendations of committees reviewing the Agent Orange Projects' protocol, researchers in the Selected Cancers Study added cancer of the nasopharynx to the group of malignancies to be included in the study (CDC, 1983b). Like other

research efforts, our study focuses on the risk of this cancer after Vietnam service in general. Characteristics of military service in Vietnam, some of which may indicate a greater potential for Agent Orange exposure, are reviewed.

7.2 METHODS

Chapter 2 provides an overview of the study's design, how it was conducted, and how the data were analyzed. Here we further discuss several topics discussed in Chapter 2.

7.2.1 Subjects and Sources of Data

Our definition of nasopharyngeal cancer includes all malignancies of the nasopharynx (Appendix A shows the ICD-O codes for diseases considered eligible for the study). Personnel in eight participating tumor registries identified 131 men born between 1929 and 1953 who had this malignancy diagnosed between December 1, 1984, and November 30, 1988. About 87% of the eligible case subjects were interviewed by using a standardized questionnaire, and, for all but two of them, pathology specimens were obtained for review by our nasal and nasopharyngeal pathology panel (Table 2.4).

Because we used a site-specific definition for nasopharyngeal cancer, our case group includes squamous cell carcinomas, malignant tumors of the glandular epithelium (adenoid cystic carcinoma), malignant lymphomas, and other malignant tumors. These various histologic types differ in their sensitivity to risk factors; therefore, we restricted most analyses of nasopharyngeal malignancies to carcinomas. This group includes 90% of the 113 men whose malignancies were confirmed by pathology review.

As discussed in the methods chapter, the category of confirmed malignancies comprises two groups: those men with "definite" nasopharyngeal carcinoma, and those men with "probable" nasopharyngeal carcinoma. This latter group consists of men for whom only cervical lymph node biopsy material was available for review by our pathology panel. (Nasopharyngeal carcinoma usually involves early and extensive cervical node disease (Zagars and Norante, 1983).) Because the pathology panel was able to classify these cases as "consistent with a nasopharyngeal primary" on the basis of histologic and clinical record review, we included "probable" cases in most analyses. We excluded them in sensitivity analyses to determine the effect of this decision on our odds ratio.

We excluded 33 case subjects from most analyses because they did not have carcinoma or because they met the other exclusion criteria defined in Chapter 2 (not a confirmed malignancy, military service unknown, in Vietnam but not stationed there, had AIDS or an AIDS-related condition, or not a resident of the United States before 1969). This left 80 cases of nasopharyngeal carcinoma for analysis. We compared these cases with 1,776 controls obtained by random digit dialing. (Chapter 2 contains a thorough explanation of how we selected controls. Table 2.4 shows the number of men identified, interviewed, and included in the analyses.) We assessed the sensitivity of our results to the inclusion and exclusion criteria in supplemental analyses.

7.2.2 Statistical Analyses

Because of the matched design and the small number of cases, we used conditional logistic regression to calculate the risk estimates presented in this chapter. To facilitate interpretation, in the final model we limited the number of potential confounders; we included racial or ethnic group, years of education, cigarette smoking, occupational exposure to chlorophenols, and a history of infectious mononucleosis 5 or more years before the reference date. When possible, exact 95% mid-p confidence intervals (SERC, 1990) were calculated for the association between Vietnam service and carcinoma. Because of the sparsity of data, we did not assess effect modification.

In most analyses, the referent group consisted of all men who did not serve in Vietnam. These analyses had an 80% power to detect about a 2.4-fold increase in risk (Table 2.5 shows the power of this study to detect risk estimates of 1.5, 2.0, and 4.0). We also examined the effect of using other definitions of "nonexposed," but we did not perform subgroup analyses of military characteristics because only 3 of 80 nasopharyngeal carcinoma subjects reported being stationed in Vietnam. For all three cases, the U.S. Army and Joint Services Environmental Support Group (ESG) confirmed the Vietnam service.

7.3 RESULTS

7.3.1 Overall Association

Table 7.1 shows the distribution of carcinoma cases and controls in each of the 40 registry and age-in-1968 cells. The overall ratio of number of nasopharyngeal carcinoma subjects: number of control subjects was about 1:22.

The occurrence of specific characteristics in the study population is summarized in Table 7.2. Men with nasopharyngeal carcinoma tended to be older than controls, had less formal education, were more likely to have smoked cigarettes regularly and to have reported previous sinus problems, and were less likely to have had infectious mononucleosis (a surrogate for Epstein-Barr virus infection). Although men with nasopharyngeal carcinoma were more likely to have been exposed to chlorophenols (17.5% of cases vs. 11.3% of controls), a larger proportion of control subjects reported exposure to phenoxyherbicides, outside of Vietnam (1.2% of cases vs. 5.9% of controls). Only small differences were observed between cases and controls in the other examined risk factors for nasopharyngeal carcinoma.

Table 7.1. Distribution of Men With Nasopharyngeal Carcinoma and Distribution of Control Subjects, by Registry and Age in 1968

	Age in 1968 (Years)					
Registry	15-19	20-24	25-29	30-34	35-39	Total
1	1: 20[a]	1: 34	2: 35	3: 24	1: 29	8: 142
2	0: 37	1: 56	3: 49	3: 69	2: 74	9: 285
3	0: 39	0: 30	2: 58	3: 51	4: 69	9: 247
4	0: 31	0: 25	0: 36	1: 29	3: 45	4: 166
5	0: 17	0: 24	2: 14	1: 25	0: 22	3: 102
6	5: 89	4:102	6: 89	1: 80	8: 73	24: 433
7	2: 42	2: 46	4: 46	2: 41	5: 70	15: 245
8	0: 27	0: 37	3: 30	1: 30	4: 32	8: 156
Total	8:302	8:354	22:357	15:349	27:414	80:1776

[a] N cases:N controls

Men with nasopharyngeal carcinoma were less likely to have served in Vietnam (4%, 3/80) than were controls (7.5%). Controlling for the design characteristics yielded an OR of 0.60 (Table 7.3, Model 1). When we adjusted for racial or ethnic group, education, occupational exposure to chlorophenols, infectious mononucleosis, and cigarette smoking (Model 3), the OR for the association between military service in Vietnam and nasopharyngeal carcinoma was 0.52 (95% CI 0.15-1.75). Occupational exposure to phenoxyherbicides, farming herbicides, nonfarming herbicides, or any combination of these three factors did not confound this relationship; adding all of these to Model 3 decreased the OR only slightly (OR = 0.48, 95% CI 0.14-1.64). Thus, Model 3 (Table 7.3) was used in all subsequent analyses.

The use of different referent (nonexposed) groups—men who served in the military but not in Vietnam, Vietnam-era veterans, and men who never served on active duty in the U.S. military—did not alter the association between military service in Vietnam and carcinoma of the nasopharynx (Table 7.4).

Table 7.2. Distribution of Selected Covariates[a] Among Men With Nasopharyngeal Carcinoma and Among Control Subjects

	Controls (N = 1776)[b]		Nasopharyngeal Carcinoma Cases (N = 80)[b]	
	%[c]	(N)	%[c]	(N)
Design characteristics				
Registry				
1	8.0	(142)	10.0	(8)
2	16.0	(285)	11.2	(9)
3	13.9	(247)	11.2	(9)
4	9.3	(166)	5.0	(4)
5	5.7	(102)	3.7	(3)
6	24.4	(433)	30.0	(24)
7	13.8	(245)	18.8	(15)
8	8.8	(156)	10.0	(8)
Age in 1968 (years)				
15 to 19	17.0	(302)	10.0	(8)
20 to 24	19.9	(354)	10.0	(8)
25 to 29	20.1	(357)	27.5	(22)
30 to 34	19.7	(349)	18.8	(15)
35 to 39	23.3	(414)	33.7	(27)
Stationed in Vietnam or off the coast of Vietnam	7.5	(133)	3.7	(3)
Other reported characteristics				
Racial/ethnic group				
White non-Hispanic	84.3	(1497)	65.0	(52)
Black non-Hispanic	8.1	(143)	12.5	(10)
Hispanic	5.6	(99)	5.0	(4)
Asian	1.7	(31)	17.5	(14)
Other/unknown	0.3	(6)	—	(0)
Highest level of education completed				
Less than high school	11.3	(200)	23.7	(19)
High school, technical school	29.5	(523)	36.2	(29)
1 to 3 years of college	20.6	(366)	16.2	(13)
4 or more years of college	38.6	(686)	23.7	(19)
Smoked cigarettes regularly	66.8	(1186)	81.3	(65)
Drank alcohol regularly	71.7	(1262)	65.0	(52)
Never married	7.3	(129)	10.0	(8)
Lived or worked on a farm or ranch	44.8	(796)	43.8	(35)
Sprayed or mixed any herbicide on a farm or ranch	9.6	(170)	8.7	(7)
Contact with herbicides on a farm or ranch, 21 or more days per year, 5 or more years before the date of diagnosis[d]	2.4	(43)	6.3	(5)
Sprayed or mixed any herbicides for right-of-way maintenance, lawn care, or forestry work	7.3	(129)	8.7	(7)
Occupational exposure to phenoxyherbicides	5.9	(105)	1.2	(1)
Occupational exposure to chlorophenols	11.3	(200)	17.5	(14)
Occupational exposure to 2,4,5-T	0.9	(16)	—	(0)
Occupational exposure to 2,4-D	5.8	(103)	1.2	(1)
Worked in a pulp, saw, or planing mill	5.7	(101)	6.3	(5)
Worked with or around wood preservatives	11.8	(209)	12.5	(10)
Worked with or around wood dust	26.7	(474)	28.7	(23)
Worked with or around plywood	23.8	(422)	22.5	(18)
Worked with or around insulating materials	18.6	(330)	20.0	(16)
Worked with or around formaldehyde	8.0	(142)	6.3	(5)

Table 7.2. Distribution of Selected Covariates[a] Among Men With Nasopharyngeal Carcinoma and Among Control Subjects — Continued

	Controls (N = 1776)[b]		Nasopharyngeal Carcinoma Cases (N = 101)[b]	
	%[c]	(N)	%[c]	(N)
Blood relative had nasopharyngeal cancer	—	(0)	1.2	(1)
Had infectious mononucleosis 5 or more years before the date of diagnosis[d]	6.3	(112)	2.5	(2)
Had sinus infections in previous 5 years with first occurrence 5 or more years before the date of diagnosis[d]	6.6	(117)	12.5	(10)
Had other sinus problems in previous 5 years with first occurrence 5 or more years before the date of diagnosis[d]	2.9	(51)	6.3	(5)
Used nasal drops or sprays 5 or more years before the date of diagnosis[d]	4.1	(72)	5.0	(4)

[a] The covariates are described in the text
[b] Information on education was missing for one non-Vietnam veteran control
[c] Percentage of cases or controls with the specified characteristic
[d] For controls, 5 or more years before the date the registry was notified of selection

Table 7.3. Association Between Military Service in Vietnam and Nasopharyngeal Carcinoma

Model[a]	Odds Ratio[b] (95% Confidence Interval)
1. Adjusted for registry and age group in 1968	0.60 (0.12-1.33)[c]
2. Adjusted for registry, age group in 1968, racial/ethnic group[d], and education	0.57 (0.17-1.33)
3. Adjusted for— all variables in Model 2 occupational exposure to chlorophenols reported medical history or lifestyle characteristics —infectious mononucleosis[e] —history of smoking cigarettes	0.52 (0.15-1.75)

[a] One control was excluded from all models because level of education was not known
[b] Odds ratios estimate the relative risk and were calculated by using conditional logistic regression The referent group is composed of men who did not serve in Vietnam
[c] Exact confidence interval
[d] White and other
[e] For cases, reported 5 or more years before the date of diagnosis; for controls, reported 5 or more years before the date the registry was notified of selection

The three Vietnam veterans with nasopharyngeal carcinoma are distributed between the Air Force (n = 1) and the Navy (n = 2) and served in Vietnam from 1 to 3 years. All three men served in support units, none served in III Corps, and one reported contact with Agent Orange but not spraying Agent Orange. When we expanded our case definition to include lymphomas and other malignancies, we identified only one other Vietnam veteran. Table 7.5 presents the distribution of histologic classification by Vietnam service status. Of the four case subjects (representing all morphologies) who served in Vietnam, two had squamous cell carcinoma; one, an adenocarcinoma; and one, a malignant lymphoma. The most common histologic subtypes among the 85 case subjects who had not served in Vietnam were squamous cell carcinoma (73%) and lymphoma (8%). In a reanalysis that included all malignancies rather than just carcinomas, the OR increased slightly (0.61, 95% CI 0.21-1.76).

Table 7.4. Risk of Nasopharyngeal Carcinoma Among Vietnam Veterans Relative to the Risk Among Four Referent Groups

Risk Group	Controls (N = 1776) %[a]	Controls (N = 1776) (N)	Nasopharyngeal Carcinoma (N = 80) %[a]	Nasopharyngeal Carcinoma (N = 80) (N)	Odds Ratio[b] (95% Confidence Interval)
Exposed group					
Men who served in Vietnam	7.5	(133)	3.8	(3)	
Referent groups					
Men who did not serve in Vietnam	92.5	(1643)	96.3	(77)	0.52 (0.15-1.75)
Men who served in the military but not in Vietnam	38.4	(682)	35.0	(28)	0.68 (0.18-2.65)
Men who served at any time from 1964 to 1972 in the military but not in Vietnam[c]	11.4	(203)	10.0	(8)	—[d]
Men who never served in the military	54.1	(961)	61.3	(49)	0.48 (0.14-1.71)

[a] The percentage of controls or cases in the indicated exposed or referent group
[b] Odds ratios estimate the risk of nasopharyngeal carcinoma for the exposed group relative to the risk for the indicated referent group; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 7.3 (Model 3). Odds ratios were calculated by using conditional logistic regression
[c] The exposed group is restricted to men who served in the military in Vietnam at any time from 1964 to 1972 (130 controls and 3 cases)
[d] Conditional estimate could not be calculated

Table 7.5. Histologic Classification of Malignancies Among Men With Nasopharyngeal Cancer, by Military Service in Vietnam

Classification	ICD-0 Code[a]	Stationed in Vietnam or off the Coast of Vietnam: No %[b]	No (N)	Yes %[b]	Yes (N)
Carcinoma (Total)		90.6	(77)	75.0	(3)
Carcinoma, NOS[c]	80103[d]	2.4	(2)	—	(0)
Carcinoma, undifferentiated, NOS	80203[d]	15.3	(13)	—	(0)
Squamous carcinoma (Subtotal)		72.9	(62)	50.0	(2)
Squamous cell carcinoma NOS	80703	1.2	(1)	—	(0)
Squamous cell carcinoma, keratinizing	80713	12.9	(11)	25.0	(1)
Squamous cell carcinoma, nonkeratinizing	80733[d]	58.8	(50)	25.0	(1)
Adenocarcinoma (Subtotal)		—	(0)	25.0	(1)
Adenoid cystic carcinoma	82003	—	(0)	25.0	(1)
Malignant melanoma	87203[d]	1.2	(1)	—	(0)
Lymphoma (Total)		8.2	(7)	25.0	(1)
Malignant lymphoma, NOS	95903	5.9	(5)	25.0	(1)
Malignant lymphoma, diffuse, large cell	96403	1.2	(1)	—	(0)
Hodgkin's disease, mixed cellularity	96523	1.2	(1)	—	(0)
All nasopharyngeal cancer cases (Total)		100.0	(85)	100.0	(4)

[a] International Classification of Diseases for Oncology, 1976
[b] Percentage of cases in each Vietnam service category with the indicated histology
[c] Not otherwise specified
[d] Some cases in each of these categories were diagnosed on the basis of a tumor metastatic to a cervical lymph node consistent with a nasopharyngeal primary

7.3.2 Sensitivity Analyses

Because we reasoned that we should exclude case subjects who fit specific criteria, we performed sensitivity analyses to assess the effect of these exclusions on our risk estimate. Table 7.6 presents the results of these analyses. We evaluated the potential for information bias as a result of our using, in some of these analyses, only certain interview data (data on men whose interview was rated as good or excellent, data on men who were interviewed by phone only, or data that were self-reported). Model 3 (Table 7.3) was used for all analyses. Differences in the risk estimates were negligible. Similarly, changes in the case definition, based on pathology information, did not affect the risk estimate.

7.4 SUMMARY

No association was found between military service in Vietnam and nasopharyngeal carcinoma, regardless of the referent group. The small number of cases, however, limits our ability to detect a small-to-moderate increase in risk.

We discuss our results further in Chapter 9.

Table 7.6. Association Between Military Service in Vietnam and Nasopharyngeal Carcinoma Among Selected Groups of Men

			Table 7.3, Model 3	
	Controls	Nasopharyngeal Carcinoma Cases	Odds Ratio (95% Confidence Interval)	
Men in main analyses	1775	80	0.52	(0.15-1.78)
Sensitivity Analyses[a]				
Additions to analyses:				
Men with AIDS or an AIDS-related condition	1776	80	0.52	(0.15-1.75)
Men who were in Vietnam or off its coast, but not stationed there (include as exposed)	1802	81	0.59	(0.20-1.71)
Case subjects whose diagnosis was not confirmed because a specimen was not obtained or was deemed inadequate for review	1775	82	0.53	(0.16-1.78)
Case subjects with any malignancy of the nasopharynx (includes lymphomas and sarcomas)	1775	90	0.61	(0.21-1.76)
Exclusions from analyses:				
Men without a telephone in the household	1757	77	0.51	(0.15-1.71)
Men interviewed in person	1751	74	0.37	(0.09-1.59)
Men whose interview was not rated as good or excellent	1745	76	0.57	(0.17-1.93)
Men who were 30 or older in 1968	1012	38	0.45	(0.10-1.97)
Case subjects with a proxy interview	1775	75	0.58	(0.17-1.96)
Case subjects with other than definite nasopharyngeal carcinoma	1775	66	0.45	(0.10-1.95)

[a] Sensitivity analyses show the effect of adding (or removing) men to (or from) the main analysis. Each addition (or exclusion) is applied separately. Numbers of controls and cases are numbers remaining in analyses after additions or exclusions

8. PRIMARY LIVER CANCER

8.1 BACKGROUND

Among young and middle-aged men in the United States, primary liver cancer is rare. In the 30- to 59-year age range, the incidence is about 2.3 cases per 100,000 per year (Young et al., 1981).

Relatively few studies provide evidence of an association between exposure to phenoxyherbicides and primary liver cancer in humans. Tung (1973) reported an increase in the proportion of all cancers diagnosed as primary liver cancer at one hospital in Hanoi between the periods 1955 to 1961 and 1962 to 1968; he attributed this increase to dioxin exposure. In a case-control study at the same hospital (Vân, 1984), an investigator found an association between reported exposure to herbicides and primary liver cancer. Male farm laborers in the United States have also been reported to be at increased risk for liver cancer (Stemhagen et al., 1983). In contrast, Hardell and coworkers (1984) found little association between exposure to phenoxyherbicides and this disease.

Because past exposure to Agent Orange is difficult to measure, its possible effect on cancer among Vietnam veterans has been studied only indirectly by comparing the occurrence of cancer among Vietnam veterans with that in other groups. Investigators have not reported significant increases in deaths from liver cancer among Vietnam veterans (Lawrence et al., 1985; Breslin et al., 1988).

In this component of the SCS, we examine the association between military service in Vietnam and primary liver cancer. This malignancy was added, on the recommendation of non-CDC reviewers, to a study of lymphomas and sarcomas. Like other researchers we focus on the risk of cancer after Vietnam service in general and only indirectly examine any possible association with herbicide exposure by investigating characteristics of service.

The most consistently noted risk factor for primary liver cancer is prior infection with the hepatitis B virus (Popper et al., 1982). Other possible risk factors include alcohol consumption and preexisting cirrhosis (Tuyns, 1979). The disease is more common in the African and Chinese populations than in other populations (Waterhouse et al., 1976); the higher incidence may be related to environmental factors, including the prevalence of hepatitis B infection.

8.2 METHODS

Chapter 2 provides an overview of the study's design, how it was conducted, and how the data were analyzed. Here we further discuss several topics discussed in Chapter 2.

8.2.1 Subjects and Sources of Data

Men with primary liver cancer were considered eligible participants on the basis of the site of the primary origin of their malignancy. Any morphologic diagnosis primary to the liver was included in the case list (see Appendix A). Personnel in the eight participating tumor registries identified 310 men born between 1929 and 1953 whose malignancies were diagnosed between December 1, 1984, and November 30, 1988. Experts in liver cancer pathology attempted to confirm the diagnosis of all cases by independently reviewing microscope slides or tissue blocks. Pathology confirmation rates, along with the number of men included in the study, are shown in Table 2.4.

Because of the limitations of the material available for review, the review panel could not always make a definitive diagnosis, and we categorized 45 cases as "probable carcinoma primary to the liver." We obtained specimens for 89% of the 263 men identified as having

primary liver cancer who were interviewed, and the confirmation rate ("definites" and "probables" combined) was 72% (168 cases). The panel reported that the majority of the unconfirmed tumors had metastasized to the liver.

Only eight men with primary liver cancer reported that they had been stationed in Vietnam, and of the six men whose records were located, Vietnam service was confirmed for five. The man whose reported service in Vietnam was not confirmed after the record review was not included in sensitivity analyses.

Before we performed the analyses, we applied several exclusions (Table 2.4). The resulting study group included 130 men with primary liver cancer and 1,776 control subjects.

In studying primary liver cancer, we generally included men with a "definite" or "probable" diagnosis, but in sensitivity analyses, we excluded case subjects with a probable diagnosis.

We included all cases regardless of vital status and, in most analyses, used only controls obtained by random digit dialing (RDD). A supplemental analysis included both RDD and deceased control subjects.

8.2.2 Statistical Analyses

We assessed the strength of the association between liver cancer and Vietnam service by the odds ratio (OR), using unconditional logistic regression. As noted in Chapter 2, we used three alternative choices for the nonexposed group.

The power of the study to detect a twofold increase in liver cancer was 75%. It had a greater than 99% power to detect a fourfold increase in risk associated with Vietnam service (Table 2.5).

In addition to the variables listed in Chapter 2 and considered as covariates for all six cancer investigations, we also accounted for the use of androgenic steroids, prior hepatitis or cirrhosis, prior work in a dry cleaning establishment, and prior work with or around chemical solvents.

8.3 RESULTS

8.3.1 Overall Association

The distribution of cases and controls across the 40 cells of the design matrix is shown in Table 8.1. There were no statistically significant differences in risk across the five age categories or the eight registries at the .01 level. Compared with control subjects, men with primary liver cancer were older and had less formal education, and more were black or Asian and had smoked cigarettes (Table 8.2). Men with primary liver cancer also reported a history of hepatitis or cirrhosis and the use of androgenic steroids more frequently than control subjects.

Table 8.1. Distribution of Men With Primary Liver Cancer and Distribution of Control Subjects, by Registry and Age in 1968

	Age in 1968 (Years)					
Registry	15-19	20-24	25-29	30-34	35-39	Total
1	0: 20[a]	2: 34	0: 35	5: 24	4: 29	11: 142
2	3: 37	1: 56	5: 49	4: 69	7: 74	20: 285
3	0: 39	0: 30	1: 58	3: 51	3: 69	7: 247
4	0: 31	0: 25	2: 36	0: 29	3: 45	5: 166
5	2: 17	2: 24	0: 14	3: 25	3: 22	10: 102
6	1: 89	6:102	8: 89	9: 80	17: 73	41: 433
7	4: 42	1: 46	7: 46	5: 41	10: 70	27: 245
8	0: 27	1: 37	2: 30	2: 30	4: 32	9: 156
Total	10:302	13:354	25:357	31:349	51:414	130:1776

[a] N cases:N controls

Table 8.2. Distribution of Selected Covariates[a] Among Men With Primary Liver Cancer and Among Control Subjects

	Controls (N = 1776)[b]		Liver Cancer Cases (N = 130)[b]	
	%[c]	(N)	%[c]	(N)
Design characteristics				
Registry				
1	8.0	(142)	8.5	(11)
2	16.0	(285)	15.4	(20)
3	13.9	(247)	5.4	(7)
4	9.3	(166)	3.8	(5)
5	5.7	(102)	7.7	(10)
6	24.4	(433)	31.5	(41)
7	13.8	(245)	20.8	(27)
8	8.8	(156)	6.9	(9)
Age in 1968 (years)				
15 to 19	17.0	(302)	7.7	(10)
20 to 24	19.9	(354)	10.0	(13)
25 to 29	20.1	(357)	19.2	(25)
30 to 34	19.7	(349)	23.8	(31)
35 to 39	23.3	(414)	39.2	(51)
Stationed in Vietnam or off the coast of Vietnam	7.5	(133)	6.2	(8)
Other reported characteristics				
Racial/ethnic group				
White non-Hispanic	84.3	(1497)	59.2	(77)
Black non-Hispanic	8.1	(143)	17.7	(23)
Hispanic	5.6	(99)	8.5	(11)
Asian	1.7	(31)	13.8	(18)
Other/unknown	0.3	(6)	0.8	(1)
Highest level of education completed				
Less than high school	11.3	(200)	21.8	(27)
High school, technical school	29.5	(523)	37.9	(47)
1 to 3 years of college	20.6	(366)	21.0	(26)
4 or more years of college	38.6	(686)	19.4	(24)
Smoked cigarettes regularly	66.8	(1186)	83.1	(108)
Drank alcohol regularly	71.1	(1262)	76.2	(99)
Never married	7.3	(129)	10.0	(13)
Lived or worked on a farm or ranch	44.8	(796)	29.2	(38)
Sprayed or mixed any herbicide on a farm or ranch	9.6	(170)	2.3	(3)
Contact with herbicides on a farm or ranch, 21 or more days per year, 5 or more years before the date of diagnosis[d]	2.4	(43)	—	(0)
Sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work	7.3	(129)	3.8	(5)
Occupational exposure to phenoxyherbicides	5.9	(105)	—	(0)
Occupational exposure to chlorophenols	11.3	(200)	6.2	(8)
Occupational exposure to 2,4,5-T	0.9	(16)	—	(0)
Occupational exposure to 2,4-D	5.8	(103)	—	(0)
Worked with chemical solvents	41.4	(736)	20.8	(27)
Worked in a dry cleaning plant	2.9	(52)	2.3	(3)
Worked in a leather tanning plant	0.5	(8)	—	(0)
Worked in a pulp, saw, or planing mill	5.7	(101)	0.8	(1)
Worked in a meat packing or processing plant	5.9	(104)	3.9	(5)
Worked with or around wood preservatives	11.8	(209)	3.9	(5)
Worked with or around cutting oils	20.5	(364)	14.6	(19)

Table 8.2. Distribution of Selected Covariates[a] Among Men With Primary Liver Cancer and Among Control Subjects — Continued

	Controls (N = 1776)[b]		Liver Cancer Cases (N = 130)[b]	
	%[c]	(N)	%[c]	(N)
Had hepatitis 3 or more years before the date of diagnosis[e]	5.3	(94)	21.5	(28)
Had cirrhosis 3 or more years before the date of diagnosis[e]	0.2	(4)	13.1	(17)
Had hemochromatosis	—	(0)	—	(0)
Took androgenic steroids	1.7	(30)	3.1	(4)

[a] The covariates are described in the text
[b] Information on education for one control and six liver cancer cases was missing. None were Vietnam veterans
[c] Percentage of cases or controls with the specified characteristic
[d] For controls, 5 or more years before the date the registry was notified of selection
[e] For controls, 3 or more years before the date the registry was notified of selection

Only 6% (8) of the men with primary liver cancer served in Vietnam, compared with 7.5% of control subjects. After we controlled for the design factors (Table 8.3, Model 1), the OR was 1.22. This estimate changed only slightly after we adjusted for several additional characteristics (Models 2 and 3). The estimated relative risk for Model 3 is 1.16, with a 95% confidence interval (CI) of 0.50 to 2.68.

Sixty-four percent of the primary liver cancer case subjects had died, necessitating the use of a proxy respondent. We conducted an analysis that combined data on 62 deceased control subjects and on their matching deceased case subjects with data on the RDD controls and on

Table 8.3. Association Between Military Service in Vietnam and Primary Liver Cancer

Model[a]	Odds Ratio[b] (95% Confidence Interval)
1. Adjusted for registry and age group in 1968	1.22 (0.55-2.67)[c]
2. Adjusted for registry, age group in 1968, racial/ethnic group, and education	1.27 (0.56-2.89)[c]
3. Adjusted for— all variables in Model 2 reported exposure to pesticides and chlorophenols —sprayed or mixed any herbicide on a farm or ranch —sprayed or mixed any herbicide in right-of-way maintenance, lawn care, or forestry work —occupational exposure to chlorophenols reported medical history/drugs —androgenic steroids —liver disease[d] other than hepatitis or cirrhosis reported demographic and lifestyle characteristics —history of smoking cigarettes —history of drinking alcohol reported occupations and exposures —worked in a dry cleaning establishment —worked with or around solvents	1.16 (0.50-2.68)
4. Adjusted for— all variables in Model 3 reported medical history —cirrhosis[d] —hepatitis[d]	0.85 (0.34-2.09)

[a] One control and six cases were excluded from all models because level of education was not known
[b] Odds ratios estimate the relative risk and were calculated by using unconditional logistic regression. The referent group is composed of men who did not serve in Vietnam
[c] By using conditional logistic regression, the odds ratio (95% confidence interval) for Model 1 was calculated to be 1.21 (0.56-2.63), and for Model 2, 1.26 (0.56-2.84)
[d] For cases, reported 3 or more years before the date of diagnosis; for controls, reported 3 or more years before the date the registry was notified of selection

the remaining cases. When we controlled for the design characteristics, the OR was 1.25 (95% CI 0.52-2.97) (Table 8.6). This estimate is similar to that obtained when we used only RDD controls (Table 8.3, Model 1).

Vietnam veterans reported histories of hepatitis and cirrhosis more frequently than other men, and case subjects reported such histories more frequently than control subjects. Controlling for these liver diseases (Table 8.3, Model 4) reduced the OR for military service in Vietnam to 0.85. Because these diseases may have been a result of service in Vietnam, in subsequent analyses we used the model that did not include these risk factors (Model 3).

The estimated risk of primary liver cancer among Vietnam veterans did not significantly differ relative to that for any alternative referent group (Table 8.4). The risk for Vietnam veterans was slightly lower (OR = 0.87) than for men who served elsewhere in the military, but the risk for Vietnam veterans was slightly higher (OR = 1.34) than for men who had no active service. All CIs, however, were wide and included 1.0. Of the eight Vietnam veterans with primary liver cancer, four were in the Navy and three were in the Army; for one, the proxy respondent did not know the branch of service. All four veterans for whom duration of service was known had spent 1 year or less in Vietnam.

Of the eight men with primary liver cancer who had served in Vietnam, seven had histology classified as hepatocellular carcinoma (four as "definites"), and one had histology classified as probable sclerosing adenocarcinoma (Table 8.5). Among the 122 case subjects who had not served in Vietnam, 100 (82%) had histology classified as hepatocellular carcinoma, 17 (14%) as cholangiocarcinoma, and 4 (3%) as sclerosing adenocarcinoma.

8.3.2 Sensitivity Analyses

The results of additional sensitivity analyses are shown in Table 8.6. Broadening the definition of exposure to include men who were in or off the coast of Vietnam but not stationed there had little effect on the OR. Similarly, restricting the analysis to those men with a telephone had little effect. Neither restricting the analysis to those men whose interview was rated as good or excellent in quality nor excluding those men interviewed in person had an appreciable effect on the outcome. Excluding men with a proxy respondent did result in a drop

Table 8.4. Risk of Primary Liver Cancer Among Vietnam Veterans Relative To the Risk Among Four Referent Groups

Risk Group	Controls (N = 1776) %[a]	Controls (N = 1776) (N)	Primary Liver Cancer Cases (N = 130) %[a]	Primary Liver Cancer Cases (N = 130) (N)	Odds Ratio[b] (95% Confidence Interval)
Exposed group					
Men who served in Vietnam	7.5	(133)	6.2	(8)	
Referent groups					
Men who did not serve in Vietnam	92.5	(1643)	93.8	(122)	1.16 (0.50-2.68)
Men who served in the military but not in Vietnam	38.4	(682)	46.2	(60)	0.87 (0.33-2.28)
Men who served at any time from 1964 to 1972 in the military but not in Vietnam[c]	11.4	(203)	13.8	(18)	0.53 (0.14-1.94)
Men who never served in the military	54.1	(961)	47.7	(62)	1.34 (0.52-3.44)

[a] The percentage of controls or cases in the indicated exposed or referent group

[b] Odds ratios estimate the risk of primary liver cancer for the exposed group relative to the risk for the indicated referent group; they have been adjusted for registry, age group in 1968, and the other risk factors listed in Table 8.3 (Model 3). Odds ratios were calculated by using unconditional logistic regression

[c] The exposed group is restricted to men who served in the military in Vietnam at any time from 1964 to 1972 (130 controls and 7 cases)

Table 8.5 Histologic Classification of Malignancies Among Men With Primary Liver Cancer, by Military Service in Vietnam

Classification	ICD-0 Code[a]	Stationed in Vietnam or off the Coast of Vietnam: No %[b]	No (N)	Yes %[b]	Yes (N)
Cholangiocarcinoma (Total)	81603	13.9	(17)	—	(0)
Definite		9.0	(11)	—	(0)
Probable		4.9	(6)	—	(0)
Hepatocellular carcinoma (Total)	81703	82.0	(100)	87.5	(7)
Definite		61.5	(75)	50.0	(4)
Probable		20.5	(25)	37.5	(3)
Clear cell carcinoma	83223	0.8	(1)	—	(0)
Definite					
Primary sclerosing adenocarcinoma (Total)	83503	3.3	(4)	12.5	(1)
Definite		1.6	(2)	—	(0)
Probable		1.6	(2)	12.5	(1)
All primary liver cancer cases (Total)		100.0	(122)	100.0	(8)

[a] International Classification of Diseases for Oncology, 1976
[b] Percentage of cases in each Vietnam service category with the indicated histology

Table 8.6. Association Between Military Service in Vietnam and Primary Liver Cancer Among Selected Groups of Men

	Controls	Liver Cancer Cases	Table 8.3, Model 3 Odds Ratio (95% Confidence Interval)
Men in main analyses	1775	124	1.16 (0.5[illegible]-2.68)
Sensitivity Analyses[a]			
Additions to analyses:			
Men with AIDS or an AIDS-related condition	1776	124	1.16 (0.5[illegible]-2.68)
Men who were in Vietnam or off its coast, but not stationed there (include as exposed)	1802	126	1.25 (0.5[illegible]-2.66)
Case subjects whose diagnosis was not confirmed because a specimen was not obtained or was deemed inadequate for review	1775	147	1.12 (0.5[illegible]-2.46)
Deceased case-control subject pairs[b]	1837	124	1.25 (0.5[illegible]-2.97)
Exclusions from analyses:			
Men without a telephone in the household	1757	113	1.17 (0.4[illegible]-2.84)
Men interviewed in person	1751	117	1.31 (0.5[illegible]-3.06)
Men whose interview was not rated as good or excellent	1745	114	1.22 (0.5[illegible]-2.99)
Men who were 30 or older in 1968	1012	45	1.34 (0.4[illegible]-3.68)
Case subjects with a proxy interview	1775	45	0.67 (0.[illegible]-3.18)[c]
Men whose Vietnam service could not be confirmed[d]	1768	123	1.04 (0.4[illegible]-2.51)
Case subjects with other than definite liver cancer	1775	89	0.63 (0.2[illegible]-1.96)[e]
Case subjects with other than hepatocellular carcinoma	1775	102	1.26 (0.5[illegible]-3.10)
Case subjects with other than hepatocellular or sclerosing carcinoma	1775	107	1.36 (0.5[illegible]-2.66)

[a] Sensitivity analyses show the effect of adding (or removing) men to (or from) the main analysis. Each addition (or exclusion) is applied separately. Numbers of controls and cases are numbers remaining in analyses after additions or exclusions
[b] All case subjects were included in the analysis, regardless of vital status. If a deceased control subject did not meet the inclusion criteria listed in Table 2.1, he was not included. The model adjusts only for registry and age group in 1968 (Table 8.3, Model 3)
[c] Excludes 4 of 8 Vietnam veteran case subjects and 2 of 133 Vietnam veteran control subjects
[d] Men who gave permission for military records review, whose records were located, and whose Vietnam service could not be confirmed were excluded
[e] Excludes four of eight Vietnam veteran case subjects and no Vietnam veteran control subjects

in the OR to 0.67, although the CI still overlapped that with all cases included. Furthermore, the results were not found to be particularly sensitive to (1) restricting the age group to the younger men; (2) changing the cell type of liver cancer analyzed; or (3) including deceased controls in the analysis.

8.4 SUMMARY

Our results provide no evidence of a statistically significant higher risk of primary liver cancer among Vietnam veterans. Compared with (1) men who did not serve in Vietnam; (2) men who served in the military, but not in Vietnam; and (3) men who did not serve in the military, Vietnam veterans did not have a higher risk for malignancy at this site.

We discuss our results further in Chapter 9.

9. DISCUSSION

9.1 MAJOR FINDINGS

We found an increased risk for non-Hodgkin's lymphoma (NHL) among Vietnam veterans relative to men who did not serve in Vietnam but no increased risk for the other five cancers. After accounting for other factors that might influence the development of NHL among Vietnam veterans, we found that these veterans have a roughly 50% increased risk for NHL (OR = 1.47). This is a statistically significant increase (p = 0.01), with the 95% confidence interval (CI) ranging from 1.09 to 1.97. When we restricted the comparison population to men who had served at any time in the military but not in Vietnam or further restricted it to men who had served during the Vietnam conflict but not in Vietnam, we found little change in the estimate of a 50% increased risk. Therefore, the increased risk appears to be associated specifically with Vietnam veterans rather than with military service in general.

An examination of several characteristics of Vietnam military service showed only slight differences between groups of Vietnam veterans, and these did not prove to be statistically significant. In particular, the risk differed only slightly by dates of service, age at entry on duty in Vietnam, rank, or type of unit the veteran served in (combat, combat support, or support). Differences in risk by branch of service (with risk higher for the Navy and Marines than for the Army or Air Force) lacked statistical significance. The estimated relative risk was somewhat higher for men who had served a longer time in Vietnam, although the risk difference was not statistically significant. We found no evidence that the increased risk of NHL might be related to exposure to Agent Orange in Vietnam.

The estimated relative risks for the other five cancers were 1.00 (95% CI 0.63-1.58) for soft tissue and other sarcomas, 1.14 (95% CI 0.71-1.83) for Hodgkin's disease, 0.66 (95% CI 0.15-2.91) for nasal carcinoma, 0.52 (95% CI 0.15-1.75) for nasopharyngeal carcinoma, and 1.16 (95% CI 0.50-2.68) for primary liver cancer. None of the estimates were significantly different from 1.0, the value that would indicate that the risk among Vietnam veterans is identical to that among men who did not serve in Vietnam. Of particular interest is our finding of no increased risk for sarcoma, a group of cancers that has been of great concern among Vietnam veterans. Restricting the cancer group to men with soft tissue sarcoma yielded an estimated relative risk of 0.94.

We found no indication that the risk for any particular subclass of sarcoma was increased after Vietnam service or that any subgroup of Vietnam veterans was at increased risk of sarcoma. As with NHL, we found no indication that the pattern of distribution of sarcoma among the 26 Vietnam veterans with sarcoma was related to the pattern of Agent Orange use in Vietnam.

This chapter begins with a discussion of issues applicable to all six cancer investigations, including exposure to Agent Orange and the potential for bias. Later each cancer is discussed in detail.

9.2 AGENT ORANGE

Because of previous reports indicating a possible association between phenoxyherbicides and several of the cancers under investigation (Hardell and Sandström, 1979; Eriksson et al., 1981; Hardell et al., 1981; Hardell et al., 1982; Hardell and Bengtsson, 1983; Hoar et al., 1986), much public attention has focused on the possible effects of exposure to Agent Orange. Advances in the methods for measuring TCDD in serum, along with the recognition of its approximate 7-year half-life (Pirkle et al., 1989), have contributed to our understanding