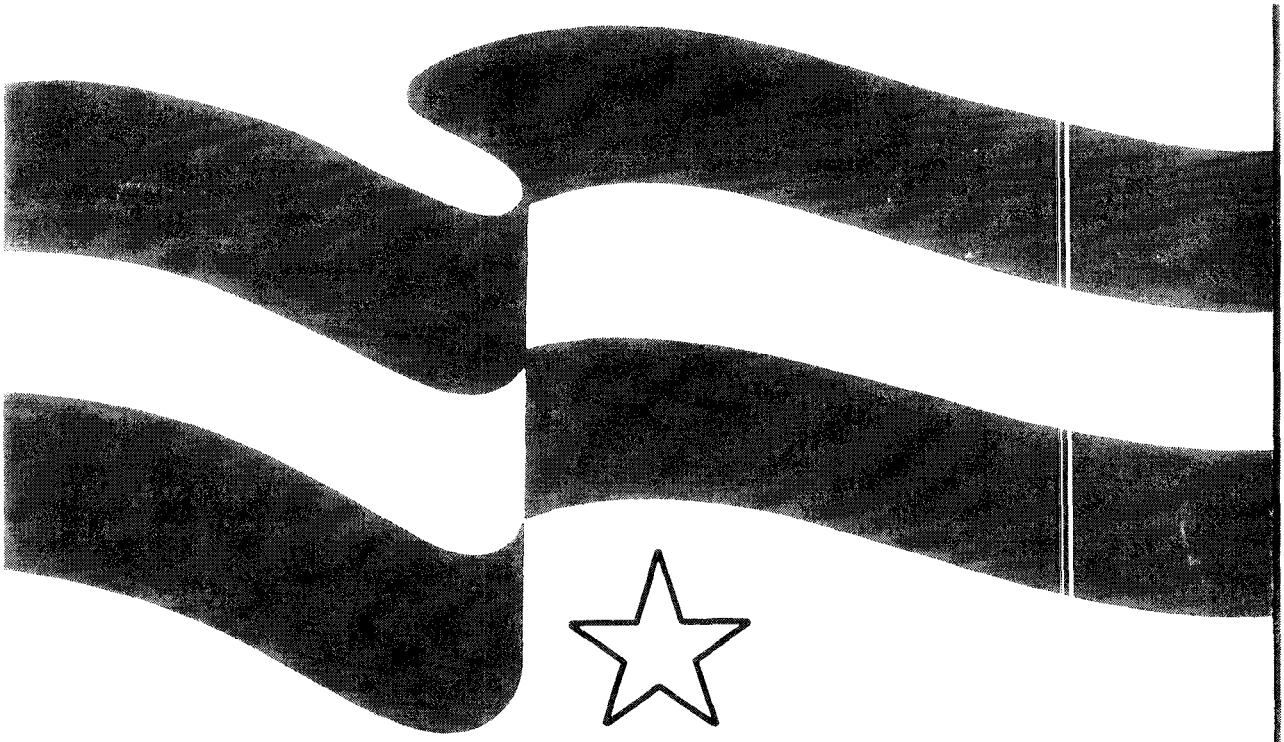

The Association of Selected Cancers with Service in the U.S. Military in Vietnam

Final Report

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
Centers for Disease Control

CDC
CENTERS FOR DISEASE CONTROL

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Final Report

The Selected Cancers Cooperative Study Group
September 1990

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
Centers for Disease Control
Center for Environmental Health and Injury Control
Agent Orange Projects
Atlanta, Georgia 30333

Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the U.S. Department of Health and Human Services.

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SUMMARY

The Selected Cancers Study (SCS) is one of several studies undertaken to assess the effects of military service in Vietnam and exposure to herbicides on the subsequent health of American veterans of that conflict. In this population-based, case-control study, we examined the risk of (1) non-Hodgkin's lymphoma, (2) soft tissue and other sarcomas, (3) Hodgkin's disease, and (4) nasal, (5) nasopharyngeal, and (6) primary liver cancer among Vietnam veterans. We chose these malignancies because the published results of other studies suggested that they were associated with exposure to phenoxyherbicides. Agent Orange, which was used extensively in Vietnam, is a combination of two phenoxyherbicides. Because of the difficulty in estimating the amount of exposure to Agent Orange for individual veterans, we evaluated the exposure indirectly. We focused our analysis on the association of Vietnam service and cancer. Other studies on the risk of these cancers in association with military service in Vietnam or with exposure to phenoxyherbicides in nonmilitary settings have produced inconsistent results.

In this study, we restricted the case group to men who were between the ages of 15 and 39 in 1968, near the peak of U.S. troop strength in Vietnam. All men who were diagnosed in a 4-year period (late 1984-late 1988) as having any of the six cancers and who lived in the geographic areas covered by eight tumor registries were eligible for this study. These areas, encompassing three states (Connecticut, Kansas, and Iowa) and five large metropolitan areas (Miami, Detroit, San Francisco, Seattle, and Atlanta), included about 10% of the U.S. population. The comparison group of controls was scientifically drawn from households with telephones and included men of the same age who did not have any of the six cancers.

Information on military service in Vietnam, along with relevant medical and occupational history was collected from both case and control subjects via a telephone interview based on a standardized questionnaire. Interview participation rates were high both for men with cancer (87%) and for controls who completed the selection process (83%). A panel, made up of pathologists who are experts in each of the six cancers, confirmed the cancer diagnoses. The U.S. Army and Joint Services Environmental Support Group, of the Department of Defense, attempted to verify reported military service in Vietnam. The group was unaware of the case or control status of the subject whose record was being reviewed.

For several of the six cancers, the SCS is larger than any other study of men in this relatively young age range that has included confirmation of the diagnosis by a review pathologist panel and the extensive collection of data through a standardized interview.

The strength of the association between military service in Vietnam and each of the sites and types of cancer was assessed by the odds ratio (OR), an estimate of the relative risk that indicates whether cancer is more likely to develop in men who served in Vietnam than in men who did not. An OR of 1.0 would indicate that the risk of cancer among Vietnam veterans is the same as that among other men.

Results

We found an increased risk of 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 men had a roughly 50% increased risk for NHL (OR = 1.47). This is a statistically significant increase ($p = 0.01$), with the 95% confidence interval ranging from 1.09 to 1.97. When we restricted the comparison population to men who had served in the military, but not in Vietnam, or further restricted it to those who had served during the time of the Vietnam conflict, we found little change in the estimate of a 50%

increased risk. Thus, the increased risk appears to be specific to Vietnam veterans, rather than being associated with military service in general.

The data suggested a higher relative risk for veterans who had served a longer time in Vietnam, although the result was not statistically significant ($p = 0.10$). An examination of several characteristics of Vietnam military service, however, 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.

We found no evidence that the increased risk of NHL might be related to exposure to Agent Orange in Vietnam. The pattern of risk among subgroups of Vietnam veterans seemed to be the opposite of the pattern of use for Agent Orange in Vietnam: Navy veterans who served on ocean-going vessels tended to be at higher risk (OR = 2.17) than Vietnam veterans who were based on land (OR = 1.30), and Vietnam veterans who served in III Corps, the region of heaviest Agent Orange use, tended to be at somewhat lower risk than Vietnam veterans who served in other regions. Only 1 of the 99 Vietnam veterans with NHL reported that he had handled equipment or containers used with Agent Orange, and none reported having sprayed defoliants. These data, along with evidence from other studies on the likelihood of Vietnam veterans' exposure to Agent Orange, make it quite unlikely that the increased risk of NHL among Vietnam veterans results from exposure to herbicides. In our study, none of the other factors we examined appeared to be responsible for that risk. We examined most known or suspected risk factors for NHL, including immunodeficiency, the use of drugs to prevent malaria, and the use of intravenous drugs, for example, but none explained the increase in risk for Vietnam veterans. We were unable to determine why these men are at higher risk for NHL.

The risk estimate identified in our study is not high. It is, however, of the order of size the study was designed to be able to detect. The possibility that our finding is entirely explained by chance can never be completely ruled out, but that explanation is highly unlikely. If the result for NHL is viewed by itself, there is only a 1 in 100 likelihood that it is due to chance. We designed our study to examine the associations between military service and six malignancies, but the question of whether to adjust for multiple comparisons is controversial. The probability, however, of observing one or more (out of six) associations as extreme as that observed for NHL (when in fact no associations exist) is, at most, 7 in 100.

A risk of this magnitude may be due to unrecognized bias or uncontrolled confounding, but an examination of several recognized potential sources of bias or confounding produced little evidence that these factors had an appreciable effect on our results. For example, the lack of an association between Vietnam service and any of the other malignancies limits the likelihood that the observed association with NHL is due to underascertainment of Vietnam veterans in the control group. Since we studied all cancers simultaneously, using the same design and an identical group of control subjects, several biases concerning selection and information quality should have similarly affected the risk estimates for each of the six cancers.

The risk estimates for the other five cancers were 1.14 (95% confidence interval (CI) 0.71-1.83) for Hodgkin's disease, 1.00 (95% CI 0.63-1.58) for soft tissue and other sarcomas, 0.66 (95% CI 0.15-2.91) for nasal carcinoma, 0.53 (95% CI 0.16-1.77) 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 indicating 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. When we restricted the cancer group to soft tissue sarcoma, the relative risk was 0.94. We found no indication that 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.

In summary, our findings suggest that:

1. Vietnam veterans have a roughly 50% increased risk of developing non-Hodgkin's lymphoma 15 to 25 years after military service in Vietnam.
2. Veterans who served in locations other than Vietnam do not have a similar increased risk of non-Hodgkin's lymphoma.
3. The increased risk of non-Hodgkin's lymphoma among Vietnam veterans is not explained by exposure to Agent Orange. Because most of the Vietnam veterans in this study were probably not (or only minimally) exposed to Agent Orange, the results do not constitute an adequate test of the hypothesis that exposure to Agent Orange or dioxin is associated with the development of NHL. A sufficient test would require the study of persons with, and others without, known exposure.
4. Vietnam veterans are not at increased risk for soft tissue or other sarcomas, Hodgkin's disease, nasal cancer, nasopharyngeal cancer, or primary liver cancer.

1. INTRODUCTION

1.1 BACKGROUND

Between 1962 and 1971, an estimated 19 million gallons of herbicide were sprayed in Vietnam to defoliate herbaceous cover and destroy crops, with Agent Orange accounting for about 60% of the total volume (Craig, 1975; Westing, 1984). This defoliant was a 1:1 mixture of two phenoxyherbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), the latter containing 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as a contaminant. Other herbicides, some including 2,4-D or 2,4,5-T, were also used in Vietnam, but on a smaller scale.

In the United States, 2,4-D and 2,4,5-T had been widely used as herbicides in the 1950s and 1960s, but concern over their use in Vietnam was heightened by results of a study suggesting that 2,4,5-T caused reproductive malformations in rodents (Courtney et al., 1970). According to the results, 113 milligrams per kilogram (mg/kg) body weight of 2,4,5-T administered to female mice on days 6 o 15 of pregnancy resulted in malformations in their offspring, and 2,4,5-T administered to rats on days 10-15 of pregnancy increased the incidence of kidney anomalies. In June 1969, reports in some Vietnamese newspapers suggested that Agent Orange had produced birth defects in humans (EPA, 1971). In 1970 the use of Agent Orange in Vietnam was suspended.

In 1976, the use of Agent Orange in Vietnam received more attention after an explosion at a chemical factory in Seveso, Italy that released 2,4,5-trichlorophenol and TCDD. In 1978 the issue of Agent Orange and its potential health effects was presented in a television documentary titled "Agent Orange: Vietnam's Deadly Fog." Results of later studies indicated that TCDD is carcinogenic in rodents, increasing the incidence of hepatocellular carcinomas and neoplasms in the rat's lung, hard palate, nasal turbinate, and thyroid; in addition, TCDD has produced hepatocellular tumors, thyroid tumors, and fibrosarcoma of integumentary tissue in mice (reviewed in IARC, 1977; Hay, 1982).

Results of case-control studies conducted in Sweden in the late 1970s and early 1980s suggested that phenoxyherbicides (or their contaminant, TCDD) might also be carcinogenic in humans. Hardell and Sandström (1979) found a statistically significant 5.3-fold increase in malignant mesenchymal tumors among men who were classified as having been occupationally exposed to phenoxyherbicides. Later, Eriksson and coworkers (1981) reported a statistically significant 6.8-fold increase in soft tissue sarcoma among men exposed to phenoxyherbicides. In another case-control study, the same group of investigators (Hardell et al., 1981) found a sixfold increase in lymphomas (non-Hodgkin's lymphoma and Hodgkin's disease) among Swedish men exposed to phenoxyherbicides; the investigators found an increased risk for both non-Hodgkin's lymphoma and Hodgkin's disease. In 1982, Hardel and coworkers reported that exposure to phenoxyherbicides also tended to be associated with nasal and nasopharyngeal cancer. They observed a 2.1-fold increase, but the association was not statistically significant.

In numerous later epidemiologic studies, investigators have examined the association between exposure to phenoxyherbicides and cancer (Cantor, 1982; Riihimäki et al., 1982; Balarajan and Acheson, 1984; Gallagher and Threlfall, 1984; Smith et al., 1984; Lynge, 1985; Coggon et al., 1986; Hoar et al., 1986; Pearce et al., 1986; Vineis et al., 1986; Wiklund and Holm, 1986; Woods et al., 1987; Persson et al., 1989; Reif et al., 1989; Wiklund et al., 1989). These studies have used a variety of methods to classify exposure, and the results of these

studies have not been consistent. They have been the subject of several reviews (IARC, 1986; Sterling and Arundel, 1986; Bond et al., 1989; Lilienfeld and Gallo, 1989; Johnson, 1990).

1.2 STUDY DEVELOPMENT

In December 1979, the Veterans Health Programs Extension and Improvement Act of 1979 was signed into law. It called for the Veterans Administration (VA) to "conduct an epidemiological study of persons who, while serving in the Armed Forces of the United States during the period of the Vietnam conflict, were exposed to any of the class of chemicals known as 'the dioxins' produced during the manufacture of the various phenoxyherbicides (including the herbicide known as 'Agent Orange') to determine if there may be long-term adverse health effects in such persons from such exposure" (Public Law 96-151, 38 U.S.C. 219). In November 1981, another law expanded the scope of that study to include "an evaluation of any long-term adverse health effects in humans of such military service, including exposure to other herbicides, chemicals, medications, or environmental hazards or conditions" (Public Law 97-72, 38 U.S.C. 219).

In January 1983, responsibility for implementing the Congressional mandate was transferred from the VA to the Centers for Disease Control (CDC). A team of CDC scientists prepared a "protocol outline," which set down the rudiments of CDC's study plans and served as the basis for a formal interagency agreement with the VA. In response to the legislative directives, CDC proposed three separate studies. One, the Agent Orange Study, was to address exposure to dioxin-containing herbicides, and another, the Vietnam Experience Study, was to evaluate health effects resulting from all factors related to service in Vietnam (CDC VES, 1988a-c). Since, in these studies, malignancies would not be identified in sufficient numbers to adequately examine possible increases in rare tumors, CDC proposed a third study, the Selected Cancers Study (SCS), to investigate certain uncommon forms of cancer that have been linked in some studies to occupational exposure to phenoxyherbicides or chlorophenols.

The SCS, a population-based case-control study, was considered to be a critical part of CDC's efforts because of concern about the risk of cancer among Vietnam veterans. The original protocol called for a study of soft tissue sarcomas and lymphomas, but, as recommended by external reviewers, the protocol was expanded to include the other malignancies. A case-control study was necessary because of the rarity of the cancers of interest among men in the age group that served in Vietnam. If a cohort study had been conducted, it would have had to be massive, and this requirement would have unnecessarily delayed CDC's ability to provide information on the risks of these cancers among Vietnam veterans compared with men who did not serve in the U.S. military in Vietnam.

The term population-based implies that all cases (or a random sample) of the selected cancers in defined population groups will be ascertained and that an attempt will be made to include them in the study. Compared with the more typical hospital-based case-control study, this type of design avoids selection biases arising from the use of cases and controls from a particular hospital.

In designing the SCS, CDC initially assumed that a large proportion (25%) of Vietnam veterans would prove to have been exposed to Agent Orange. The results of studies (CDC VHS, 1988; CDC VHS, 1989) published since 1985 make this premise unlikely; however, these results did not make it necessary for us to change the design of our study. We, like others, focus on the risk of cancer after Vietnam service in general. We only indirectly examine any possible association with exposure to herbicides by investigating characteristics of service, such as military branch, region of service in Vietnam, time period of that service,

and duties involving the handling of herbicides. The results of the SCS have been accepted for publication in the Archives of Internal Medicine (SCS, 1990a-c).

2. METHODS

2.1 IDENTIFICATION AND ENROLLMENT OF SUBJECTS

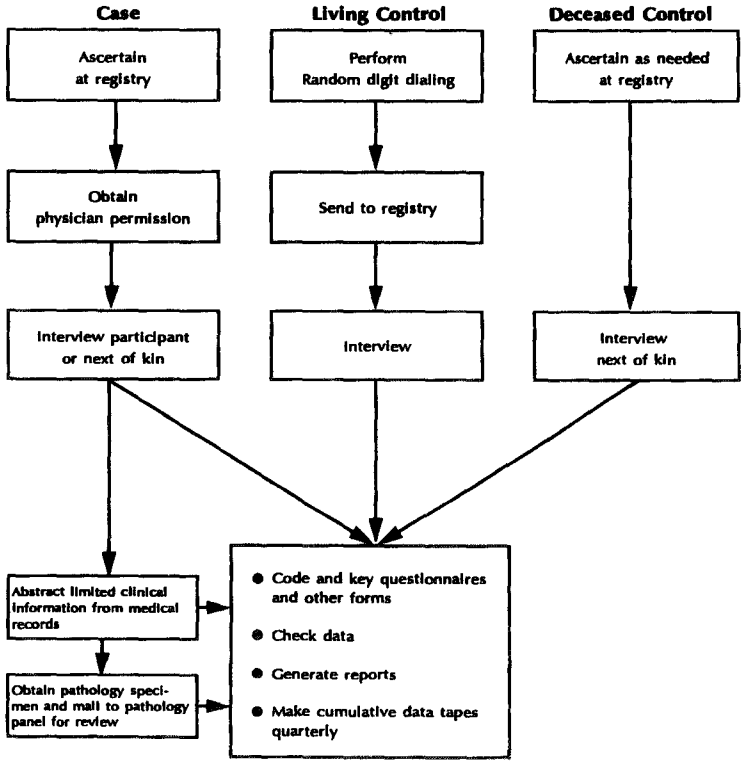
Figure 2.1 gives an overview of the data collection methods. We used similar procedures to enroll men with each of the six cancers of interest and selected living control subjects through random digit dialing. In the following sections, we describe the various steps in the identification of subjects and in the collection of data.

2.1.1 Cases

All males with a cancer of interest (1) whose disease was diagnosed between December 1, 1984, and November 30, 1988, and (2) who lived in an area covered by one of eight collaborating cancer registries were eligible for inclusion in the study. Appendix A shows the International Classification of Diseases for Oncology (ICD-O) codes considered for inclusion (WHO, 1976). Eligible "cases" were further restricted to men who were born between 1929 and 1953, thus defining a group that was of military service age (15-39 years in 1968) during the Vietnam conflict. To simplify our presentation, we frequently refer to a veteran's "age in 1968" rather than to his "date of birth."

The participating cancer registries were chosen on the basis of competitive bids made in response to CDC's request for proposals. Initially, six tumor registries submitted acceptable proposals. Because of concerns about the possibility of inadequate statistical power of the study, however, and a reluctance to extend the study further in time, a second round of competitive bidding was conducted. As a result, two more registries were added. These registries included eligible cases diagnosed between October 1, 1985, and November 30,

Figure 2.1. Components of Data Collection for Case, Living Control, and Deceased Control Subjects in the Selected Cancers Study



1988. The eight collaborating registries represented a diverse cross section of the U.S. population, in five metropolitan areas (Atlanta, Detroit, San Francisco, Seattle, and Miami) and three states (Connecticut, Iowa, and Kansas).

To maximize the number of interviews with living cases, we asked each registry to develop a "rapid ascertainment" method for identifying cases as soon as possible after they were diagnosed. This system differed among registries (and often among the more than 500 hospitals that were screened for eligible cases), but, typically, it included a twice monthly review of records of patients who had had tissue examined by the surgical pathology department. Additional components included reviews of (1) logs in the cytology and hematology departments, (2) discharge summaries and diagnostic indices, (3) reports from independent pathology laboratories, (4) tumor service records, and (5) death certificates. With only one exception, all registries reviewed reports arriving after the rapid ascertainment had been completed to determine whether any eligible cases had been overlooked; if so, the eligible cases were added to the study.

All registries either notified or sought the permission of a physician involved in the case subject's care regarding participation in the study. Registry personnel then notified eligible case subjects, by mail, that their participation in a scientific study was requested. If a case subject died before participating, registry personnel attempted to identify a next-of-kin or other suitable proxy respondent.

2.1.2 Controls

Households containing a potential (living) control were identified through random digit dialing (RDD) (Waksberg, 1978), and a screening questionnaire (shown in Appendix B) was administered by Westat, Inc., to establish the presence of at least one eligible control in each household. The same control series was used for each cancer under investigation.

Random Digit Dialing

RDD allowed the rapid enumeration of a sample of population-based controls. In 1986, about 93% of U.S households had a telephone (Thornberry and Massey, 1988). There are differences between telephone and nontelephone households with respect to demographics, economics, and health characteristics (Mohadjer and Morganstein, 1990), but results from previous studies indicate that RDD controls are reasonably representative of the general population (Hartge et al., 1984; Wingo et al., 1988).

The sampling unit (cluster) in RDD is defined as a group of 100 telephone numbers beginning with the same eight digits (e.g., 404-677-89xx). Before the study began, the number of clusters needed per registry was chosen so that the mean number of selected control subjects per cluster would be three or fewer, and the organization responsible for control selection (Westat, Inc.) randomly selected clusters from the geographic area covered by each registry. (A mean of 1.7 control subjects per cluster were actually interviewed.) Compared with a larger number of controls per cluster, a smaller number would result in reduced variances of the estimates (Levy and Lemeshow, 1980). For more information on the sampling distributions of estimates derived from RDD, see the section titled "Sample Characteristics for Random Digit Dialing."

Clusters were included in the final sample only if the first answered phone number was that of a residence. A random sample of the phone numbers within each cluster was then generated to provide an equal number of households per cluster within each registry. The sample sizes of clusters and number of households per cluster were determined by the expected numbers of controls per cluster. Interviewers adhered to specific rules concerning the number and timing of calls placed to each number, with at least three calls made in the evening, two in the daytime, and two during weekends over a 2-week period. If an answer was not obtained, the telephone number was checked through the local phone company.

To determine if an eligible control subject lived in the household, the person answering the phone was asked to participate in a brief interview. The study was introduced as a general study of men's health, and, to avoid biasing participation, the interviewer did not mention Vietnam or herbicides. Interviewers obtained the name and address of each potential control so that a letter, explaining the purpose of the study, could be sent to the subject before the actual interview was conducted. Westat, Inc., sent the names, addresses, and phone numbers of selected controls to the tumor registries for final interviewing.

As shown in Table 2.1, about 53% (15,768) of the 29,590 phone numbers that were called were residential, and of these households, 91% (14,328) provided information on eligibility. Of the 4,822 households with at least one eligible male, 91% (4,381) provided his name and address. As determined through the local phone company, 493 numbers were classified as "no answer (residential)," 991 as "no answer (nonresidential)," 172 as "no answer (working)," and 179 as "no answer (no information)." Residences with answering machines at which no resident was directly contacted are included in the "no answer (residential)" category.

Sample Characteristics For Random Digit Dialing

As described above, RDD samples are cluster samples in which households are selected in two stages: (1) selection of a cluster of 100 telephone numbers and (2) selection of phone numbers within the cluster. In practice, cluster samples tend to have larger sampling errors for statistics than simple random samples of the same size because most natural groupings contain persons who tend to resemble one another (Groves, 1989).

The sampling error of the population mean estimated by a cluster sample (e.g., $\bar{y}$) is inflated by two factors: (1) the population intracluster correlation, ρ, which is a measure of the covariation of pairs of persons in the same cluster, and (2) the number of households chosen from a cluster, b:

$$\text{Var}(\bar{y}) = (S^2/n)[1 + \rho(b - 1)],$$

where S^2 is the population element variance. If persons in the same cluster are similar on the

Table 2.1. Household Screening for Potential Control Subjects, by Random Digit Dialing Interview Outcome

Random Digit Dialing Interview Outcome	N	%
Total households	15768	53.3
Eligible		
Fully complete	4381	14.8
Partially complete[a]	441	1.5
Ineligible	9506	32.1
Refusal or break off	749	2.5
Language problem	177	0.6
Other nonresponse	21	0.1
No answer (residential)	493	1.7
Total nonhouseholds	13471	45.5
Out of area[b]	180	0.6
Nonresidential	3749	12.7
Nonworking	8551	28.9
No answer (nonresidential)	991	3.3
Total unknown	351	1.2
No answer (working)	172	0.6
No answer (no information)[c]	179	0.6
Total telephone numbers called[d]	29590	100.0

[a] Name or address was not provided
[b] Residents did not live in one of the specified counties
[c] Information could not be obtained from the telephone business office
[d] All totals combined

characteristic, then ρ will be positive, and the sampling error of the estimated mean will be greater than that from a simple random sample. The relationship between these two sampling designs is summarized by the design effect, the ratio of the sampling variance reflecting the complexities of the design (e.g., $Var(\bar{y})$) to the sampling variance expected from a simple random sample of the same size, estimated by s^2/n:

$$\text{Design effect} = 1 + \rho(b - 1),$$

where b is the mean cluster size. Cluster sampling generally results in design effect values that are greater than 1.0 (Groves, 1989).

Table 2.2 shows the number of clusters, mean cluster size, intracluster correlation, and design effect for several characteristics of interviewed men. The mean number of interviewed control subjects per cluster ranged from 1.3 (Seattle) to 2.3 (San Francisco). For each characteristic, the intracluster correlations varied somewhat by registry, but, in general their low values resulted in design effects close to 1.0. Although some intracluster correlation coefficients were slightly elevated, even the largest intracluster correlation (for racial/ethnic group in Detroit, $\hat{\rho} = 0.24$), however, yielded a design effect of only 1.14.

These results suggest that conventional statistical methods for analyzing data from the SCS which do not account for the cluster sampling, such as the Mantel-Haenszel procedure and logistic regression (Breslow and Day, 1980; Kleinbaum et al., 1982), will not affect the validity of the results.

Frequency Matching

The age distribution for Vietnam veterans with the cancers of interest is distinct. Therefore, to make our estimates more precise, in selecting controls, we used frequency matching (on date of birth and registry) (Rothman, 1986). Although matching (by itself) does not control for confounding in case-control studies, it leads to the enrollment of roughly equal numbers of case and control subjects in various strata. Stratification or multivariable techniques must be used to control confounding, regardless of whether matching is used in the design.

We divided dates of birth of the eligible cases into 5-year categories (1929-33, 1934-38, 1939-43, 1944-48, and 1949-53), and for each of the 40 registry and date-of-birth strata (8 registries times 5 date-of-birth strata), estimated the number of lymphoma (Hodgkin's disease and non-Hodgkin's lymphoma combined) cases that were likely to occur. The number of cases of non-Hodgkin's lymphoma was much greater than we originally anticipated; this increase was, in part, due to the Acquired Immunodeficiency Syndrome (AIDS) epidemic.

Table 2.2. Sampling Characteristics for Living Control Subjects Chosen by Random Digit Dialing and Interviewed, by Registry

			Characteristics[a]									
	Clusters		Age at Interview		Racial/ Ethnic Group		Education		Smoking History		Stationed in Vietnam	
Registry	N	Mean Size	ICC[b]	Deff[c]	ICC	Deff	ICC	Deff	ICC	Deff	ICC	Deff
Atlanta	74	2.0	-0.02	0.98	0.18	1.18	0.21	1.21	-0.06	0.94	-0.03	0.97
Connecticut	185	1.6	0.02	1.01	0.07	1.04	0.04	1.03	-0.09	0.95	-0.02	0.99
Iowa	166	1.5	0.16	1.08	0	1.00	0.08	1.04	0.09	1.04	0.16	1.08
Kansas	97	1.7	0.18	1.13	0.05	1.03	0.02	1.01	-0.01	0.99	-0.02	0.99
Miami	84	1.6	-0.06	0.96	0.11	1.07	0.13	1.08	0	1.00	-0.02	0.99
San Francisco	216	2.3	0.09	1.11	0.14	1.18	0.08	1.10	0	1.00	-0.01	0.99
Detroit	160	1.6	0.10	1.06	0.24	1.14	0.02	1.01	0.07	1.04	-0.01	1.00
Seattle	124	1.3	-0.01	1.00	0.01	1.00	0.03	1.01	-0.02	0.99	0.10	1.03
All registries	1106	1.7	0.07	1.05	0.17	1.12	0.09	1.06	0	1.00	0.03	1.02

[a] Race is coded as 1 = white, 0 = other; education is coded as 1-4 (see section 2.5.2); smoking history is coded as 1 = ever, 0 = never; stationed in Vietnam is coded as 1 = yes, 0 = no

[b] Intracluster correlation coefficient

[c] Design effect

Accordingly, in the fourth year of control selection, we modified the selection criterion so that controls were matched to men with non-Hodgkin's lymphoma, rather than to men with any lymphoma.

Deceased Controls

The selection of deceased control subjects may increase the comparability of information obtained from (proxy) cases and controls, but the suitability of deceased controls as a comparison group is controversial. Certain exposures (e.g., cigarette smoking and drinking) are overrepresented among premature deaths (Gordis, 1982; McLaughlin et al. 1985), possibly producing biased results. The SCS included at least one living control subject per case subject (whether the case subject was living or deceased), but a deceased control series was also included for possible use as a comparison group for deceased case subjects.

We pair-matched deceased controls, selected from death certificate files, to deceased cases on registry, date of birth, race (Asian versus other), and the time interval (within 60 days) between the death of the identified case and the interview of his proxy. We included race in the matching criteria because of the high incidence of nasal, nasopharyngeal, and liver cancer among persons of Asian heritage (Falk, 1982; Redmond et al., 1982; Shanmugaratnam, 1982), and we included the time between death and the interviews of the proxy to maximize the comparability of the information.

A death certificate for each deceased control was collected from the source registry. Using standard rules for determining the underlying cause of death, a nosologist coded the cause of death as defined in the 9th revision of the International Classification of Diseases (WHO, 1977). Men were not included in the deceased control series if they died from any of the cancers under investigation or from homicide or suicide.

Unless stated otherwise, controls selected through RDD were used in all analyses as the comparison group. Deceased controls are included in analyses that examine the sensitivity of our results to various inclusion or exclusion criteria (see section 2.5.4). The proportion of case subjects who had died before the interview varied from 2% for Hodgkin's disease to 64% for primary liver cancer.

2.2 PARTICIPATION OF SUBJECTS

2.2.1 Interview and Pathology Confirmation

Table 2.3 shows the nonparticipation rates for the (RDD) controls and the comparable rates for the identified cases. Of the 2,299 selected controls, 389 (17%) did not participate; of the 3,496 cases (all malignancies combined), 444 (13%) did not participate. For both case and control subjects, the main reason for nonparticipation was a refusal to be interviewed. After the controls had been selected, personnel in the participating tumor registries administered the study interviews. The median number of days between receipt of control information by the registry and interview was 46; the median number of days between the date of case diagnosis and interview was 103.

We tried to confirm the pathologic diagnosis of all cases, and unless otherwise specified, we restricted all analyses to confirmed cases. The pathology department in which the case was originally diagnosed was asked to lend microscope slides of tissue or tissue blocks, showing representative areas of the tumor, for review. In requesting specimens, we emphasized that the purpose of the review was to obtain a uniform decision on morphologic type, not to assess the accuracy of the original diagnosis. Certain tumor registries and hospitals would not release the tissue slides or blocks unless they had received the signed permission of the case subjects (or their proxies).

Table 2.3. Number of Men Who Were Not Interviewed, by Cancer Group

	Living Control Subjects	Case Subjects[a]				
		Lymphoma	Sarcoma	Nasal Cancer	Nasopharyngeal Cancer	Liver Cancer
Control subjects selected for interview, or case subjects identified	2299	2354	612	89	131	310
Not interviewed	389	281	91	9	16	47
Reason for nonparticipation						
Physician refusal	—	59	23	3	1	4
Subject refusal	287	142	48	4	9	22
Inability to locate	76	44	14	0	2	10
Language problem	6	9	1	0	2	5
Other	20	27	5	2	2	6

[a] Includes living and deceased case subjects

Specimens were mailed to the appropriate panel: (1) lymphoma (including non-Hodgkin's lymphoma and Hodgkin's disease), (2) sarcoma, (3) nasal and nasopharyngeal cancer, or (4) primary liver cancer. Each of the three pathologists on a panel independently reviewed the material and made a diagnosis; they then compared their diagnoses and reached a consensus diagnosis. In making the consensus diagnosis, the panel sometimes required additional material from the source registry. Appendices C through F show the pathology report forms that each panel used.

The numbers of specimens obtained and confirmed for interviewed case subjects are shown in Table 2.4. Further aspects of case definitions and participation rates are discussed below.

2.2.2 Cases

Lymphoma: Non-Hodgkin's Lymphoma and Hodgkin's Disease

Men with an initial diagnosis of NHL, Hodgkin's disease, or "lymphoma, not otherwise specified" were considered eligible for inclusion, with the final classification determined after the pathology specimens were reviewed. Of the 2,354 men who were identified as "lymphoma cases," 88% (2,073) were interviewed. Microscope slides of tissue or tissue blocks were obtained for 97% (2,004) of the interviewed men, and a lymphoma diagnosis was confirmed for 93% (1,511 as NHL and 343 as Hodgkin's disease). Pathology specimens from 14 men could not be further classified as NHL or Hodgkin's disease, and these men were not included in the analyses. The panel reported that the specimens for 129 of the 136 nonconfirmed diagnoses (2,004 - 1,511 - 343 - 14 = 136) were not adequate for review. Men with NHL were classified according to the Working Formulation (NCI, 1982), and cases of Hodgkin's disease according to the 1976 revision of the ICD-O codes (WHO, 1976).

Sarcoma

We considered all men with a definitive or tentative diagnosis of sarcoma (whether soft tissue or other) to be potentially eligible for inclusion, regardless of whether the suspected malignancy was derived from connective tissue, viscera, or the skeletal system. Eligibility was based on a list (see Appendix A) of more than 60 ICD-O morphology codes and subclassifications (WHO, 1976) that included those diagnoses used by other researchers in studies of sarcoma and phenoxyherbicides. Because a classification by tumor site may miss many cases that are morphologically classifiable as soft tissue sarcoma (Young et al., 1981; Berg, 1982; Lynge et al., 1987), we based our inclusion criteria on morphology. Men with a diagnosis of Kaposi's sarcoma or mesothelioma were not included.

Table 2.4. Number of Men Identified, Interviewed, and Included in Most Analyses

	Living Control Subjects	Case Subjects					
		Lymphoma[a]		Sarcoma	Nasal Cancer	Nasopharyngeal Cancer	Liver Cancer
Control subjects selected for interview, or case subjects identified[b]	2299	2354		612	89	131	310
Interviewed	1910	2073		521	80	115	263
Specimen obtained	N/A	2004		511	78	113	233
		Non-Hodgkin's Lymphoma	Hodgkin's Disease				
Diagnosis confirmed[c]	N/A	1511	343	386	70	113	168
Excluded from analysis							
Military or Vietnam service status unknown	(7)	(5)	(0)	(4)	(0)	(1)	(2)
In or off the coast of Vietnam, but not stationed there	(27)	(13)	(1)	(8)	(1)	(1)	(2)
AIDS or AIDS-related condition	(1)	(290)	(17)	(3)	(3)	(1)	(0)
Not a resident of the U.S. before 1969	(99)	(56)	(15)	(23)	(4)	(21)	(34)
History of Von Recklinghausen's neurofibromatosis or postirradiation osteosarcoma[d]	(0)	(—)	(—)	(6)	(—)	(—)	(—)
Total excluded[e]	(134)	(354)	(33)	(44)	(8)	(24)	(38)
Total available for analysis[f]	1776	1157	310	342	62	89	130

[a] Case subjects were considered eligible after an initial diagnosis of non-Hodgkin's lymphoma, Hodgkin's disease, or "lymphoma not otherwise specified." Final lymphoma classification was determined after pathology specimen review

[b] A total of 15,768 households and calls to 190 phone numbers (which were not answered and assumed residential) were included in the sample; 14,328 households provided information on eligibility. Of the 4,822 households with an eligible subject identified, 4,381 provided a name and address. Of these, 2,299 were selected for interview

[c] Fourteen men with a confirmed lymphoma diagnosis could not be further classified as having non-Hodgkin's lymphoma or Hodgkin's disease

[d] Applicable only to analysis of men with sarcoma

[e] Because men can be in more than one exclusion category, the total exclusions may be less than sum of the individual exclusions

[f] Proxy interviews were conducted for 117 men with non-Hodgkin's lymphoma, 5 with Hodgkin's disease, 30 with sarcoma, 8 with nasal cancer, 6 with nasopharyngeal cancer, and 83 with liver cancer who were deceased at the time of interview. After eligibility criteria were applied to the deceased control subjects to match deceased case subjects, 93 matched pairs (non-Hodgkin's lymphoma), 22 matched pairs (sarcoma), and 62 matched pairs (primary liver cancer) remained

Of the 612 identified men with a diagnosis of sarcoma, 88% (521) were interviewed. We obtained microscope slides or tissue blocks for 98% (511) of these cases, and the pathology panel confirmed the diagnosis for 76% (386). The review pathologists reported that, for many of the diagnoses that were not confirmed, the quality and representativeness of the specimens were marginal. As with NHL and Hodgkin's disease, only confirmed sarcoma cases were included in the analyses.

Nasal Cancer

Nasal cancer was defined to include malignancies of the sinus or nasal cavity. Of the 89 identified men with a diagnosis of nasal cancer, 80 (90%) were interviewed; specimens were obtained for 78, and a diagnosis of nasal cancer was confirmed for 70. A diagnosis of "probable" nasal cancer was assigned to one man who had a metastatic tumor that was judged to be consistent with a nasal primary tumor. Most nasal malignancies were carcinomas, and unless otherwise specified, the case group was restricted to the 52 men with either "definite" or "probable" nasal carcinoma.

Nasopharyngeal Cancer

Of the 131 identified men with a diagnosis of nasopharyngeal cancer, 115 (88%) were interviewed, and the diagnosis was confirmed for all 113 men from whom specimens were obtained. Ninety-seven (86%) men were classified as having "definite" nasopharyngeal cancer, and 16 as having "probable" nasopharyngeal cancer. A "probable" diagnosis was based on data from the medical history along with the histology of tissue in the cervical lymph nodes that were consistent with primary nasopharyngeal cancer. Most nasopharyngeal malignancies were carcinomas, and unless otherwise specified, the case group was restricted to the 102 men with a "definite" or "probable" nasopharyngeal carcinoma.

Primary Liver Cancer

Of the 310 identified men with a diagnosis of liver cancer, we interviewed 263 (85%) and obtained specimens for 233. Of these 233 men, the panel confirmed the diagnosis of primary liver cancer for 168 (72%). For most of the unconfirmed tumors, the review panel reported that the cancer had metastasized and was not primary to the liver.

In contrast to the other malignancies that we were investigating, specimens from men with liver cancer were often obtained by needle biopsy, and, frequently, the material that had to be reviewed was only marginally adequate. We tried to obtain material after autopsies, but, usually, specimens were not available. Therefore, the pathology panel could not always make a definitive diagnosis, and we assigned 45 subjects to a category of "probable carcinoma primary to the liver." Unless otherwise specified, the 168 confirmed cases of primary liver cancer used in the analyses include these 45 "probable" cases and the 123 "definite" primary liver cancer cases.

2.2.3 Case and Control Subjects Excluded from the Analyses

Interviewed control and case subjects with confirmed malignancies were excluded from the analyses if one or more of the following four criteria applied:

1. Their military service in Vietnam was unknown.
2. They were in Vietnam or off the coast of Vietnam, but were not stationed there.
3. They had AIDS (or an AIDS-related illness), a condition strongly increasing the risk for NHL, as determined from the questionnaire or reported by the registry.
4. They were not residents of the United States before 1969.

We assessed the sensitivity of our results to criteria 2 and 3 in supplemental analyses (see section 2.5.4).

Table 2.4 shows the number of men excluded from the SCS for the aforementioned reasons, and for all categories of cases and controls, the largest number of exclusions (n = 315) resulted from the determination of AIDS or an AIDS-related condition. About 80% of the NHL exclusions fell into this category, as did the majority of exclusions among men with Hodgkin's disease. In contrast, the number of men with AIDS or an AIDS-related condition varied between 0 (liver cancer) and 3 (sarcoma and nasal cancer) for the other cancers. Only one RDD control subject was identified as having AIDS or an AIDS-related condition.

Also excluded were 252 men who were not residents of the United States before 1969 and were therefore not likely to have served in the U.S. military in Vietnam. (An examination of the responses of these men indicated that none was a Vietnam veteran.) Relatively few men were excluded for other reasons. Military service in Vietnam was unknown for only 19 (0.5% of all men included in the SCS). Many of these men were deceased, and the interviewed proxy could not supply the necessary information.

In addition, we excluded five men with sarcoma who had histories of Von Recklinghausen's neurofibromatosis and one man with a probable postirradiation osteosarcoma. Both characteristics predispose a person to sarcoma.

2.2.4 Sample Size and Power

Table 2.5 provides estimates of the power of this study to detect various odds ratios (ORs) on the basis of the expected and actual number of cases of each malignancy. We calculated these values (Schlesselman, 1982), using a two-tailed test and a Type I error rate of 0.05 and assuming that 7.5% of the control subjects served in Vietnam. For lymphoma (NHL and Hodgkin's disease combined), it was estimated that the SCS would have a greater than 99% probability of detecting a twofold increase in the risk for Vietnam veterans (CDC, 1983). For the other cancers, the power to detect an OR of 2.0 was estimated to be 0.98 (sarcoma), 0.82 (nasal and nasopharyngeal cancer combined), and 0.82 (liver).

The enrollment of men differed somewhat from that expected, with a larger number of men with NHL or Hodgkin's disease (and therefore a larger number of controls) and slightly fewer men with nasal, nasopharyngeal, and primary liver cancer. With the actual number of cases in the SCS, we had excellent power to detect a twofold increased risk among Vietnam veterans for NHL, Hodgkin's disease, and sarcoma. The power was lower (75%) for detecting a twofold increased risk for primary liver cancer. We were less likely to detect an OR of 2.0 for either nasal or nasopharyngeal carcinoma, but our power to detect a threefold increased risk was 0.87 and 0.97, respectively.

Table 2.5. Power[a] of the Selected Cancers Study to Detect Various Relative Risks, by Malignancy

Malignancy		N	Odds Ratios 1.5	2.0	3.0	4.0
Lymphoma[b]	Expected[c]	1324	0.84	>0.99	>0.99	>0.99
Non-Hodgkin's lymphoma	Actual	1157	0.88[d]	>0.99	>0.99	>0.99
Hodgkin's disease	Actual	310	0.52	0.96	>0.99	>0.99
Sarcoma	Expected	425	0.58	0.98	>0.99	>0.99
	Actual	342	0.55	0.97	>0.99	>0.99
Nasal and nasopharyngeal[e]	Expected	170	0.33	0.82	>0.99	>0.99
Nasal[f]	Actual	48	0.14	0.38	0.87	0.99
Nasopharyngeal[f]	Actual	80	0.20	0.56	0.97	>0.99
Liver	Expected	170	0.33	0.82	>0.99	>0.99
	Actual	130	0.28	0.75	>0.99	>0.99

[a] Power calculations are based on a two-tailed test with $\alpha = 0.05$. There were 1,300 expected control subjects; 1,776 control subjects were actually enrolled. The prevalence of military service in Vietnam among the control subjects was 7.5%

[b] Number of men with either non-Hodgkin's lymphoma or Hodgkin's disease; these two malignancies were combined in the protocol

[c] Expected number of men given in the protocol; actual number refers to men who were included in the main analyses

[d] The actual control:case ratio (1,776:1,157) was higher than expected (1,300:1,324); therefore, power was higher for the actual numbers

[e] Number of men with either nasal or nasopharyngeal cancer; these two malignancies were combined in the protocol

[f] Includes only carcinomas

2.3 TELEPHONE INTERVIEW

2.3.1 Background

The primary source of exposure data for the SCS was a telephone interview. Each registry was responsible for interviewing both case and control men in its area, and the same questionnaire (see Appendix G) was used for all. No reference was made to the subject's present cancer.

Before interviewing the subjects, interviewers were required to attend a 3-day training session. We could not blind the interviewers to the case or control status of the subjects, but training personnel emphasized that the questionnaire should be administered identically to both case and control subjects. To avoid introducing biases into the study, we randomly assigned interviewers to cases and controls and instructed them to carefully follow the standardized questionnaire. Except for confirming military service in Vietnam, we made no attempt to confirm information obtained during the interview. However, the registry supervisor called back 10% of the study subjects, and asked them a subset of items from the questionnaire.

The questionnaire required an average of 50 minutes to complete. Interviewers administered the questionnaire in English, Spanish and Cantonese Chinese, using professionally made translations. No attempt was made, however, to interview subjects who did not speak one of these three languages.

Of the completed interviews, 99% of the control subjects and 96% of the case subjects were interviewed by telephone, with in-person interviews conducted if participation could be obtained only in this manner (Table 2.6). The numbers of men added to or excluded from other supplemental analyses are also shown in Table 2.6; these criteria will be discussed in the appropriate sections.

Because the identification of living controls depended upon their having a telephone, all subjects were asked if they had a telephone in their household 4 months before the interview. (For proxy interviews, the question referred to either the month of diagnosis (cases) or the month of death (controls).) Table 2.6 shows that 1% of the controls and 4% of the cases (all malignancies combined) did not have a phone 4 months before the interview. Sensitivity analyses were conducted to assess whether the exclusion of men with in-person interviews or in households without telephones would alter our results (see section 2.5.4).

2.3.2 Variables Used in the Analyses

Military Service in Vietnam

Subjects who reported serving on active duty in the U.S. military were asked if they had been "stationed in Vietnam or off the coast of Vietnam." (As used throughout this report, the category "stationed in Vietnam" consists of men who reported being stationed in Vietnam or off the coast of Vietnam; we use this phrase interchangeably with "Vietnam veterans" and "men who served in Vietnam.") In addition, 53 men (about 1%) reported that they were in Vietnam or off its coast, but had not been stationed there. The responses of these men indicated that most were in Vietnam only briefly, and they are included (in the exposed group) only in analyses that tested the sensitivity of our results to the exposure definition. Table 2.7 shows the distribution of men according to military service in Vietnam; of the 1,776 controls included in the analyses, 7.5% (n = 133) reported having served in the military in Vietnam.

We obtained information from men reporting military service in Vietnam concerning tour dates, branch(es) of service, rank(s), unit, location(s) in Vietnam, job duties, and self-perceived exposure to herbicides. Except for men in the blue water Navy, we classified location in Vietnam according to military regions: I, II, III, and IV Corps (Figure 2.2). Vietnam

Table 2.6. Number of Men Added To (or Excluded From) Main Analyses According to Various Criteria

		Case Subjects					
	Living Control Subjects	Non-Hodgkin's Lymphoma	Sarcoma	Hodgkin's Disease	Nasal Carcinoma	Nasopharyngeal Carcinoma	Liver Cancer
Men in main analyses[a]	1775	1156	340	310	48	80	124
Additions to analyses:							
Men with AIDS or an AIDS-related condition	1[b]	280	3	17	1	0	0
Men who were in Vietnam or off its coast, but not stationed there (include as exposed)	26	12	8	1	1	1	2
Case subjects whose diagnosis was not confirmed because a specimen was not obtained or was deemed inadequate for review	—	—[c]	11	—[c]	1	2	23
Exclusions from analyses:							
Men without a telephone in the household	(18)	(27)	(19)	(10)	(3)	(3)	(21)
Men interviewed in person	(24)	(44)	(21)	(6)	(1)	(6)	(7)
Men whose interview was not rated as good or excellent	(30)	(26)	(7)	(2)	(4)	(4)	(10)
Men who were 30 or older in 1968	(743)	(628)	(144)	(94)	(32)	(42)	(79)
Case subjects with a proxy interview	—	(119)	(30)	(5)	(6)	(5)	(79)
Men whose Vietnam service could not be confirmed[d]	(7)	(9)	(6)	(1)	(0)	(0)	(1)

[a] Men with unknown education level were excluded from the total available for analysis (Table 2.4). For Hodgkin's disease, two additional controls with an unknown number of siblings were excluded, resulting in 1,773 controls

[b] Values represent men added to (or excluded from) various analyses

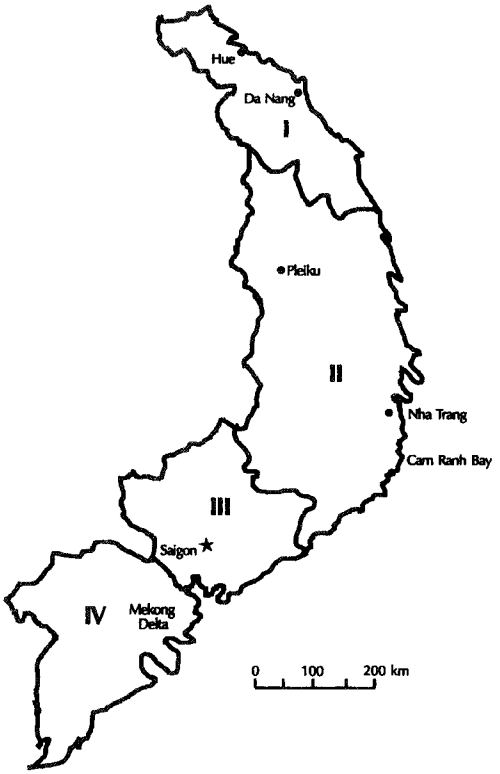
[c] Lymphoma case subjects whose diagnoses could not be confirmed were not categorized into those with non-Hodgkin's lymphoma or Hodgkin's disease

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

Table 2.7. Classification of Military Service, by Cancer Type

	Living Control Subjects (N=1776)	Case Subjects					
		Non-Hodgkin's Lymphoma (N=1157)	Sarcoma (N=342)	Hodgkin's Disease (N=310)	Nasal Carcinoma (N=48)	Nasopharyngeal Carcinoma (N=80)	Liver Cancer (N=130)
Military service in Vietnam	133	99	26	28	2	3	8
Military service, but not in Vietnam	682	454	121	107	28	28	60
Military service from 1964 to 1972, but not in Vietnam	203	94	41	35	8	8	18
No military service	961	604	195	175	18	49	62

Figure 2.2.Military Regions in South Vietnam



veterans who were in the Navy were subdivided according to blue water (ocean-going vessels), brown water (smaller vessels patrolling near shore or along rivers), and shore.

We assessed the agreement between self-reported and record-based information for military service in Vietnam. Men who indicated that they had served in Vietnam while in the military were asked to sign and return a form giving us permission to review their military records. (We did not attempt to corroborate that men not reporting having served in Vietnam were not Vietnam veterans.) The U.S. Army and Joint Services Environmental Support Group (ESG), an organization created within the Department of Defense to conduct military records' research on all branches of service in relation to various issues, reviewed the records without knowledge of a subject's case or control status. (The form used in the abstracting of military information is shown in Appendix H.) Results for several steps in the verification process are shown in Table 2.8.

Of the 301 Vietnam veterans included in the analyses, 87% (146/168) of the cases and 74% (98/133) of the controls gave permission for record review. Of these men, records were located for 89% (130) of the cases and for 87% (85) of the controls. Military service in Vietnam could be corroborated by information in the records of 87% (113) of the cases and 92% (78) of the controls for whom records were located. Unless otherwise specified, we classified military service in Vietnam according to interview responses; men whose service could not be corroborated by record review were, however, excluded in supplemental analyses (see section 2.5.4).

On the basis of responses to the study questionnaire concerning branch, unit, and job duties in Vietnam, ESG also classified the veterans' units into three categories: (1) support

Table 2.8. Number of Vietnam Veterans Giving Permission for Review of Military Records and Confirmation Rates, by Cancer Type

	Living Control Subjects		Case Subjects											
			Non-Hodgkin's Lymphoma		Sarcoma		Hodgkin's Disease		Nasal Cancer		Naso-pharyngeal Cancer		Liver Cancer	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Vietnam veterans[a]	133		99		26		28		3		4		8	
Permission given for record review	98	(73.7)[b]	87	(87.9)	23	(88.5)	24	(85.7)	3	(100)	3	(75.0)	6	(75.0)
Records located	85	(86.7)	74	(85.1)	23	(100)	22	(91.7)	3	(100)	2	(66.7)	6	(100)
Confirmation of military service in Vietnam	78	(91.8)	65	(87.8)	17	(73.9)	21	(95.5)	3	(100)	2	(100)	5	(83.3)

[a] Subject reported that he was "stationed in Vietnam or off the coast of Vietnam" while serving on active duty in the U.S. military

[b] Value in parentheses is percentage of the number immediately above

(relatively distant from the enemy), (2) combat support (support in an area that could be fired upon or support that could be assigned to work with combat units), or (3) combat (front-line duties and assignments).

The ESG, of necessity, based this classification on a subjective evaluation of available information, and in using these categories, it may have misclassified the intensity of combat for some men. ESG was not asked to relate any of the provided responses to the study questionnaire to possible exposure to herbicides in Vietnam.

Occupational Exposure to Phenoxyherbicides and Chlorophenols Other Than in Vietnam

We considered exposure to phenoxyherbicides and chlorophenols outside of Vietnam to be a potential confounder of the association between the various malignancies and military service in Vietnam. Subjects were therefore asked (see section C of the questionnaire in Appendix G) to name the specific herbicides that they used on farms, in landscaping, in right-of-way maintenance, and in forestry work. A toxicologist reviewed the responses, as well as those concerning exposure to insecticides, and classified the responses into categories based on the chemical structure of each pesticide. Of the men included in the analyses, the following were considered to have been exposed to phenoxyherbicides outside of Vietnam: 105 controls, 59 men with NHL, 15 men with sarcoma, 16 men with Hodgkin's disease, 1 man with nasopharyngeal carcinoma, 3 men with nasal carcinoma, and 0 men with primary liver cancer.

Exposure to chlorophenols, which are chemically related to phenoxyherbicides and which can also be contaminated with TCDD, has been suggested as a risk factor for many of the cancers that have been associated with exposure to phenoxyherbicides (IARC, 1987). We assessed possible contact with chlorophenols or dioxin by examining each subject's description of his responsibilities in jobs at incinerators, leather tanning plants, saw mills, and meat packing plants and in jobs involving contact with electrical transformers, cutting oils, and hexachlorophene. If the subject reported working with wood preservatives, he was asked for their names and uses. Of the men included in the analyses, 200 control subjects, 140 men with NHL, 53 men with sarcoma, 39 men with Hodgkin's disease, 5 men with nasal carcinoma, 14 men with nasopharyngeal carcinoma, and 8 men with primary liver cancer were classified as having been exposed to chlorophenols other than in Vietnam.

The prevalences of exposure to phenoxyherbicides and chlorophenols, among cases and controls, are shown in Chapters 3 through 8. We assessed these exposures without knowledge of the subject's case or control status.

Additional Characteristics

Information was collected for many additional characteristics thought to be potential confounders. The questionnaire covered seven major areas: (1) demographic information, (2) medical history, (3) family history of cancer, (4) occupational history (including military service in Vietnam and elsewhere), (5) hobbies, (6) smoking and drinking history, and (7) use of various prescribed and illicit drugs.

A determination of AIDS (or an AIDS-related condition) was based on self-reported and supplemental information supplied by the registries. During the interview, subjects were asked, "Did a doctor ever tell you that you had an immunodeficiency problem or a defect in your immune system?" and if they answered "yes," they were asked to name the problem or defect (see section B of the questionnaire, Appendix G). Then, to identify men with AIDS or an AIDS-related illness, a physician, without knowledge of the subject's case or control status, reviewed the responses. In addition, registries were asked to identify men with lymphoma who had (or possibly had) AIDS.

2.4 DATA MANAGEMENT

2.4.1 Quality Control

We monitored work at the eight registries every 2 weeks and entered data on the progress of each study subject through the system (e.g., identification, physician permission, interview, and pathology retrieval) into a computerized data base (Figure 2.1). Delinquency reports, indicating that a subject's progress through the system was delayed, were generated and reviewed monthly with supervisors at the tumor registries. Every 6 months, either the CDC principal investigator or project manager met with the collaborating groups.

At a central location, a trained staff coded and entered all information from the questionnaires into a data set; questions regarding coding were referred to senior project staff. A computerized editing system, with more than 1,500 range edits and more than 1,300 logic checks, insured the accuracy of keypunching. Data failing any edit check were manually compared to information on the questionnaire. A similar system was used to monitor the accuracy of data gathered for pathology information.

2.4.2 Treatment of Missing Values

For almost every question in the interview, some subjects (or their proxies) gave a response of "don't know" or failed to give an answer. In addition, we did not ask proxy respondents certain questions (e.g., about the study subject's sexual orientation or contact with chemicals in Vietnam) because of the sensitivity of the topic or concerns over the validity of the responses. Subjects with missing values for dichotomous variables ("yes/no") were generally included with the "no" responses in the analysis. This is equivalent to limiting the exposed men to those who responded "yes" and considering all other men (including those with missing data) to have responded in some other manner.

We had two exceptions to this general treatment of missing values for dichotomous variables, and both pertained to data on military service in Vietnam. The first exception was that, to avoid misclassifying the exposure variable of greatest interest, military service in Vietnam, we excluded from the analysis men with missing data for this question. Twelve of the 2,090 cases (all malignancies combined) and 7 of the 1,776 controls were deleted for this reason (Table 2.4). The second exception concerned information on possible exposure to

Agent Orange (and other defoliants), location of service, and type of unit in Vietnam. Subjects with proxy interviews were deleted from analyses concerning these questions, as were subjects for whom data were missing for other reasons.

For variables with more than two categories, subjects with missing data were either (1) deleted from the analyses or (2) an additional indicator variable was used to represent unknown values. This latter approach had the effect of adding another category to the coding of the responses (i.e., a category representing the unavailability of information). Miettinen (1985) has discussed the advantages and limitations of each approach, and in our analyses the two methods yielded identical results.

2.5 ANALYTIC METHODS

2.5.1 Overview of Analytic Strategy

Our objective was to determine whether men who served in the U.S. military in Vietnam are at higher risk for developing (1) NHL, (2) Hodgkin's disease, (3) soft tissue and other sarcomas, (4) nasal cancer, (5) nasopharyngeal cancer, or (6) primary liver cancer than are other men in the United States. We assessed the strength of each association using the odds ratio (OR), an estimate of the relative risk, and we calculated 95% confidence intervals (CIs) around these ORs to indicate the precision of the estimates. For instance, an OR of 1.32 (95% CI 0.87-1.82) for the association between military service in Vietnam and a particular cancer can be interpreted as indicating that the risk of the particular cancer is 1.32-fold (or 32%) higher among Vietnam veterans than among men who are not Vietnam veterans. Furthermore, a simple interpretation of the range of the CI indicates that one can be 95% certain (confident) that the true population (as opposed to the observed) OR is no less than 0.87 and is no greater than 1.82. If a 95% CI excludes 1.0, the OR can be considered to be statistically significant (i.e., a two-sided p-value <0.05). However, CIs provide more information on the estimated OR because all values within the 95% CI are not equally compatible with the data (Poole, 1987). For example, although the value 0.91 is included in the 95% CI given, it would not be within the 80% CI. Therefore, one could be 80% certain that 0.91 is not the true OR.

Although the goal of the study is to determine whether Vietnam veterans are at increased risk for the selected cancers, there are several possible choices for the nonexposed (referent) group. On the basis of responses to questions in the military and occupational history sections of the questionnaire, we considered four possibilities:

1. All men who were not in the military in Vietnam regardless of other military service.
2. Men who were in the military but did not serve in Vietnam.
3. Men who were in the military between 1964 and 1972 but who did not serve in Vietnam.
4. Men who never served in the military.

Groups 2 and 4 make up group 1, and group 3 is a subset of group 2.

The use of group 4, men who never served in the military, as the referent (nonexposed) group might be expected to introduce a selection bias analogous to the "healthy worker effect" (Checkoway et al., 1989). For example, the selection of healthy men into the U.S. military in Vietnam could potentially lead to a lower incidence of cancer 20 years after induction, obscuring what might otherwise be observed as an increase in cancer incidence relative to an appropriate referent group. Veterans who served in Vietnam, however, might also substantially differ from veterans who served in other locations, and thus the results of the analysis using either group 2 or 3 as the nonexposed group might be difficult to interpret. We chose to use all men other than Vietnam veterans (group 1) as the nonexposed group in most analyses, but we considered the effects of using group 2 or 3 as the nonexposed group

in additional analyses (shown in the relevant chapters). The use of alternative referent groups also addresses the issue of whether an observed effect is specific to military service in Vietnam or whether it applies to military service in general.

2.5.2 Confounding and Interaction

Background

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) that differed between Vietnam veterans and other men. For example, potentially, Vietnam veterans could differ from other men in some way (e.g., a higher prevalence of cigarette smoking) that could increase their risk for one of the malignancies of interest, regardless of their military service in Vietnam. Alternatively, because of the relation of another extraneous characteristic to both military service in Vietnam and cancer, Vietnam veterans might be (incorrectly) observed to be at a decreased risk. This "mixing of effects" is referred to as confounding.

We therefore collected information on a wide range of demographic characteristics and on civilian exposure to pesticides, occupations, hobbies, and behaviors that have been previously reported to be associated with the cancers of interest. We based our selection of these characteristics on reviews of the epidemiologic literature (Falk, 1982; Greene, 1982; Redmond et al., 1982; Shanmugaratnam, 1982; Tucker and Fraumeni, 1982; Cook-Mozaffari and Van Rensburg, 1984; Grufferman and Delzell, 1984; Acheson, 1986). To assess and control for, the possible confounding effects of these covariates, we used stratified and multivariable analyses. Furthermore, because we selected controls through frequency matching, we needed to control for the design variables (date of birth and registry) in order to obtain valid estimates (Breslow and Day, 1980; Rothman, 1986).

We also examined whether any characteristic modified the association between military service in Vietnam and the cancer of interest (i.e., we asked, Is there an interaction?) We used a relatively stringent statistical criterion of ($p<0.01$) to assess interactions between military service in Vietnam and the covariates for three reasons:

1. Our goal was to determine whether Vietnam veterans in general are at increased risk for any of the examined malignancies.
2. We did not have strong prior hypotheses concerning potential effect-modifiers.
3. Numerous characteristics were considered as potential effect modifiers.

We also examined the risk of cancer among subgroups of Vietnam veterans, defined by characteristics such as location and calendar years of military service in Vietnam.

Covariates Included in All Analyses

Unless otherwise specified, we treated all characteristics as categorical variables in the analyses. We assessed seven variables as possible confounders for all malignancies:

1. Registry: eight categories.
2. Date of birth: 1929 to 33, 1934 to 38, 1939 to 43, 1944 to 48, and 1949 to 53 (in most analyses this variable was expressed as "age in 1968").
3. Racial or ethnic group: white, non-Hispanic; black, non-Hispanic; Asian; Hispanic; other.
4. Highest level of educational achievement: less than high school, high school, 1 to 3 years of college, 4 or more years of college.
5. A history of spraying or mixing any herbicides other than in Vietnam: yes/no.
6. Any reported exposure to phenoxyherbicides other than in Vietnam: yes/no.
7. Possible exposure to chlorophenols or dioxin in various occupations: yes/no.

The numbers of control and case subjects within each category of these variables are shown in Chapters 3 through 8.

Covariates Specific to Each Malignancy

The characteristics we considered as potential confounders were those with substantial evidence for an association with the malignancy of interest. These characteristics, therefore, differed among the six cancers. In addition, because of the strong association of age with both military service in Vietnam and the incidence of NHL, indicator variables representing 1-year age increments within the date-of-birth categories were included in the models for NHL. Unless otherwise noted, all of the following characteristics are coded as dichotomous variables.

Non-Hodgkin's lymphoma	Medical irradiation, raised in the Jewish religion, marital status, 1-year age increment within each 5-year date-of-birth interval (five categories), pack years of cigarette smoking (five categories), reported immunodeficiency disease other than AIDS, rheumatoid arthritis, systemic lupus erythematosus, use of immunosuppressive drugs, and use of phenytoin or related compounds.
Hodgkin's disease	Medical irradiation, infectious mononucleosis, chemotherapy, appendectomy, tonsillectomy, cigarette smoking, marital status, raised in the Jewish religion, number of siblings raised with (four categories), raised in an urban setting.
Soft tissue and other sarcomas	Cigarette smoking, worked in a meat-packing or processing plant.
Nasal carcinoma	Cigarette smoking, occupational exposure to wood dust.
Nasopharyngeal carcinoma	Infectious mononucleosis, cigarette smoking.
Primary liver cancer	Use of androgenic steroids, hepatitis, cirrhosis, liver disease other than cirrhosis or hepatitis, cigarette smoking, alcohol consumption, worked in a dry cleaning business, worked with or around chemical solvents

2.5.3 Statistical Analyses

Vietnam Veterans Vs Other Men

Our analysis of the association between each cancer and military service in Vietnam began with a comparison of the proportion of control and case subjects who reported having served in the military in Vietnam. We also assessed the distributions of other characteristics between case and control subjects in this manner, but the matched design of the study complicated our interpretation of the results. Failure to account for the matched design generally results in an underestimation of the strength of the association (Rothman, 1986).

We accounted for frequency-matched design by using either (1) the Mantel-Haenszel summary OR (Kleinbaum et al., 1982), (2) unconditional logistic regression, with date of birth and registry included as covariates (represented by 39 indicator variables), or (3) conditional logistic regression (Rothman, 1986). Whenever possible, we used these techniques in conjunction with each other, and, in all instances, we obtained very similar results.

We assessed the homogeneity of the association between Vietnam service and the selected cancer across strata (defined by age group, registry, or other covariates), using the test statistic described by Breslow and Day (1980), logistic regression models (Kleinbaum et al., 1982), or, in instances in which the stratum-specific numbers were small, exact tests (SERC, 1990). None of the examined characteristics significantly ($p<0.01$) modified the association between military service in Vietnam and any of the cancers. If any cell in a 2 x 2 table of interest contained less than five study subjects, we calculated exact confidence limits for the association between Vietnam service and cancer (Ipsen, 1984).

All the p-values we used in the SCS were two-sided, and we calculated the CIs by various procedures. Unless otherwise specified, we used large-sample estimates (derived from the standard errors associated with coefficients in logistic regression models) to calculate the CIs. Whenever sample sizes were small, in calculating CIs, we also used Cornfield's approximation and exact, mid-p values (SERC, 1990).

Because unconditional logistic regression can produce biased estimates when the number of subjects per stratum (i.e., the 40 registry and date-of-birth cells) is small (Breslow and Day, 1980; Rothman, 1986), the most appropriate multivariable analysis is conditional logistic regression. For three reasons, however, several of the multivariable analyses presented in this report are based on unconditional logistic regression, with the design factors included as covariates. The reasons are (1) similarity of the parameter estimates for unconditional and conditional logistic regression, (2) the ease of use of available software, and (3) the smaller amount of computational time required. Whenever possible, we recalculated the final estimates by using conditional logistic regression.

Examples of the similarity of the various analytic approaches are shown in Tables 2.9 and 2.10, for the malignancies with the largest (NHL) and smallest (nasal carcinoma) number of cases. For each cancer, we had to adjust the results for the design variables, and, in particular, for the 5-year date-of-birth intervals. Adjustment for these variables, however, with

Table 2.9. Risk of Non-Hodgkin's Lymphoma Among Vietnam Veterans Relative To the Risk Among Men Who Did Not Serve in Vietnam, as Estimated by Various Techniques[a]

Method and Covariates	Odds Ratio (95% Confidence Interval)	P-value
I. Unadjusted 2 x 2 table	1.16 (0.88-1.52)	0.29
II. Mantel-Haenszel summary odds ratio[b]		
Adjust for age group in 1968	1.40 (1.05-1.85)	0.02
Adjust for registry	1.18 (0.90-1.55)	0.24
Adjust for age group in 1968 and registry	1.42 (1.07-1.89)	0.02
III. Unconditional logistic regression[c]		
Adjust for age group in 1968 and registry	1.43 (1.07-1.91)	0.02
+ 1-year age interval	1.45 (1.08-1.93)	0.01
+ racial/ethnic group, education	1.46 (1.09-1.96)	0.01
IV. Conditional logistic regression[d]		
Match on age group in 1968 and registry	1.42 (1.07-1.89)	0.02
+ adjust for 1-year age interval	1.44 (1.08-1.92)	0.01
+ adjust for racial/ethnic group, education	1.45 (1.09-1.94)	0.01

[a] Two subjects (1 case, 1 control) with missing data for education were deleted from all analyses, leaving 2,93[illegible] men
[b] Calculated by using SAS PROC FREQ (Version 5.18) (SAS Institute Inc., 1985); Breslow-Day test for homogeneity of the odds ratio across the five age groups: $p=0.53$
[c] Calculated by using BMDPLR (Version 1988) (Dixon et al., 1988)
[d] Calculated by using EGRET (Version 0.23.25) (SERC, 1990)

Table 2.10. Risk of Nasal Carcinoma Among Vietnam Veterans Relative To the Risk Among Men Who Did Not Serve In Vietnam, as Estimated by Various Techniques[a]

Method and Covariates	Odds Ratio (95% Confidence Interval)	P-value
I. Unadjusted 2 x 2 table	0.54 (0.13-2.24)[b]	0.38
II. Mantel-Haenszel summary odds ratio[c]		
Adjust for age group in 1968	0.77 (0.17-3.46)	0.74
Adjust for registry	0.55 (0.13-2.25)	0.40
Adjust for age group in 1968 and registry	0.70 (0.16-3.04)	0.64
III. Unconditional logistic regression[d]		
Adjust for age group in 1968 and registry	0.70 (0.16-3.07)	0.62
+ racial/ethnic group, education	0.67 (0.15-3.00)	0.58
IV. Conditional logistic regression[e]		
Match on age group in 1968 and registry	0.70 (0.16-3.05)	0.64
+ adjust for racial/ethnic group, education	0.68 (0.15-2.98)	0.68

[a] One control subject with missing data for education was deleted from all analyses, leaving 1,823 men
[b] The exact mid-p value 95% confidence interval ranges from 0.09 to 1.89
[c] Calculated by using SAS PROC FREQ (Version 5.18) (SAS Institute Inc., 1985); exact test for homogeneity of the odds ratio across age group strata as calculated by EGRET (Version 0.23.25) (SERC, 1990) is p=0.83
[d] Calculated by using BMDPLR (Version 1988) (Dixon et al., 1988)
[e] Calculated by using EGRET (Version 0.23.25) (SERC, 1990)

either Mantel-Haenszel summary ORs, unconditional logistic regression, or conditional logistic regression, yielded very similar results.

Analyses Specific to Vietnam Veterans

To assess the association between selected cancers and certain subgroups that served in Vietnam, we examined the association between various characteristics of military service in Vietnam and NHL, Hodgkin's disease, and soft tissue and other sarcomas. (We had too few exposed cases to perform comparable analyses for primary liver cancer, nasal cancer, and nasopharyngeal cancer.) These Vietnam-specific characteristics included:

1. Branch of service: Army, Air Force, Marines, Navy, or Coast Guard.
2. Duration of service in Vietnam: less than 1 year, 1 to 1.4 years, 1.5 to 1.9 years, or 2 or more years.
3. Calendar years of military service in Vietnam: only before 1966, 1966 to 1969, or only after 1969 (these categories were mutually exclusive).
4. Age at beginning of first tour in Vietnam: less than 21 years, 21 to 25 years, or 26 or more years.
5. Rank at end of last tour: E1 to E3, E4 to E9 (and warrant officer), or officer.
6. Type of unit in Vietnam: support, combat support, or combat.
7. Military region in Vietnam: I, II, III, IV Corps, or blue-water Navy.
8. Number of years since start of first tour in Vietnam: less than 17 years, 17 to 18 years, 19 to 21 years, or 22 or more years.

In the Army, E1 to E3 indicate various levels of private, E4 corresponds to corporal, and E5 to E9 represent various ranks of sergeant. Several of the characteristics listed above would be expected to be associated with the probability of exposure to Agent Orange and other defoliants. For example, Military Region III accounted for more than 50% of all defoliants used in South Vietnam (Westing, 1984), with particularly heavy spraying from 1966 to 1969.

Classifying exposure to Agent Orange on the basis of self-reported information is likely to result in a great deal of misclassification (CDC VHS, 1988; CDC VHS, 1989); nevertheless, we also examined the association between various self-reported assessments of Agent Orange exposure and NHL, Hodgkin's disease, and sarcomas. The five self-reported characteristics were (1) passed through a defoliated area, (2) present when others were spraying Agent Orange, (3) got Agent Orange on skin or clothes, (4) handled equipment or containers that had been used with Agent Orange, and (5) sprayed Agent Orange.

A few Vietnam veterans, in addition to reporting possible exposure to Agent Orange, also reported exposure to "defoliants" or "dioxin."

2.5.4 Sensitivity Analyses

As previously noted, we assessed, in additional analyses, the sensitivity of our results to various assumptions about the inclusion of subjects in the SCS. In these supplemental analyses, we examined the association between military service in Vietnam and each cancer after either including or excluding men according to different eligibility requirements (Table 2.6). We then compared the results of these supplemental analyses with those from the main analyses. The following groups were included with or excluded from the supplemental analyses:

Men included in supplemental analyses

1. Men who were "in Vietnam or off the coast of Vietnam," but who were not stationed there.
2. Men with AIDS or an AIDS-related condition.
3. Deceased control subjects.

Men excluded from supplemental analyses

1. Men without a telephone in the household 4 months before the interview.
2. Men whose interview was not rated as "good" or "excellent."
3. Men who were interviewed in person.
4. Men who had proxy interviews.
5. Men who in 1968 were 30 years of age or older.
6. Men whose self-reported military service in Vietnam could not be corroborated by information in military records.

We conducted some other supplemental analyses that applied only to certain cancers: for example, a supplemental analysis for primary liver cancer that excluded case subjects with a "probable" diagnosis. The results of all sensitivity analyses are shown in chapters specific to each malignancy.

3. NON-HODGKIN'S LYMPHOMA

3.1 BACKGROUND

Non-Hodgkin's lymphoma (NHL), a heterogenous group of malignancies of the lymphoreticular system, refers to all lymphomas other than Hodgkin's disease. Among 30- to 59-year-old men in the United States, the annual incidence of NHL (unrelated to AIDS) is about 10 per 100,000 (Young et al., 1981).

Results of animal studies conducted in the early 1970s suggested that exposing rodents to 2,4,5-T during pregnancy could result in malformations in their offspring (Courtney et al., 1970). There is also evidence that 2,3,7,8-tetrachlorodibenzo-p-dioxin (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 NHL was increased in 1979 by a report from Sweden of a cluster of patients with histiocytic lymphoma and previous exposure to phenoxyherbicides or chlorophenols (Hardell, 1979). Results of a later case-control study (Hardell et al., 1981), which included 60 cases of Hodgkin's disease and 105 cases of NHL, showed that occupational exposure to phenoxyherbicides was associated with a fivefold increased risk for malignant lymphoma (95% CI 2.9-8.1). The investigators did not present the results of separate analyses for NHL and Hodgkin's disease, but they stated that their relative risks were similar.

In other case-control studies, investigators have also reported that occupational groups with potential exposure to phenoxyherbicides are at increased risk for NHL, but the strengths of the associations have been less striking. For example, Hoar and coworkers (1986) found a twofold increased risk (95% CI 1.2-4.1) for NHL among farmers who reported ever using phenoxyherbicides, and other investigators have reported increased risks of 1.4 (95% CI 1.04-1.85) (Brownson et al., 1989) and 1.2 (95% CI 0.99-1.56) (Reif et al., 1989) among farmers. In a recent mortality study of Saskatchewan farmers, Wigle and coworkers (1990) documented a dose-response relationship between number of acres sprayed with herbicides and NHL. Results of other case-control studies have also suggested an increased risk for NHL among persons potentially exposed to phenoxyherbicides (Schumacher, 1985; Woods et al., 1987), but some results have been negative (Pearce et al., 1986). Persson and coworkers (1989) reported a significantly increased risk of NHL (OR = 4.9) among persons who reported using herbicides but a decreased risk of NHL among farmers (OR = 0.5, 95% CI 0.1-0.7).

Historical cohort studies of men thought to have been exposed to phenoxyherbicides, either during their use or manufacture, are limited by the relatively low incidence of NHL. For example, Riihimäki and coworkers (1982), in a study of 1,926 men who used 2,4-D and 2,4,5-T for brush control, observed 26 cancer deaths versus 36.5 expected, and in the fairly short follow-up period, they observed no cases of lymphoma. In a study of 20,245 Swedish pesticide appliers with a mean follow-up of 12 years, 21 cases of NHL were observed versus 20.8 expected (Wiklund et al., 1987). Lynge (1985) reported no increase in the number of lymphoma cases (7 observed versus 5.4 expected) among 4,563 persons involved in the manufacture of phenoxyherbicides. Cook and coworkers (1986), however, observed a nonsignificant twofold increase in the number of NHL cases among persons who were potentially exposed to chlorophenols and 2,4,5-T. Several reviews of the relevant epidemiologic and laboratory studies have been published (IARC, 1986; Bond et al., 1989; Lilienfeld and Gallo, 1989; Johnson, 1990).

Of the other factors that have been reported to increase the risk for NHL, the association with altered immune function is the most striking. Compared with the general population, persons with immunodeficiency disorders may be 10,000 times more likely to develop cancer

of the lymphoreticular system, and the risk of certain lymphomas is increased 350-fold among patients receiving immunosuppressive therapy (Greene, 1982). Furthermore, the risk and severity of NHL among patients with AIDS is greatly increased (Kaplan, 1989). Other investigators have reported that the risk of NHL is increased after exposure to ionizing radiation, the use of hydantoin drugs, and cigarette smoking and among persons with rheumatoid disorders, but the results are not entirely consistent (Greene, 1980; Greene, 1982).

Because of the difficulty in measuring previous exposure to Agent Orange, its possible effect on the risk of cancer among Vietnam veterans has been studied only indirectly by comparing the occurrence of cancer among Vietnam veterans with that in other groups. Most investigators have reported that Vietnam veterans do not show an increased mortality from NHL (Lawrence et al., 1985; Anderson et al., 1986; Bailey et al., 1986), but Breslin et al. (1988) reported a twofold (95% CI 1.17-3.79) increase among Marines who served in Vietnam. They also reported, however, that mortality from NHL tended to be lower than expected among Army veterans who served in Vietnam.

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

3.2 METHODS

3.2.1 Subjects and Sources of Data

Details of the design and conduct of the Selected Cancers Study (SCS) are given in Chapter 2. All males who (1) were born between 1929 and 1953, (2) were diagnosed as having NHL, "lymphoma, not otherwise specified," or Hodgkin's disease between December 1, 1984, and November 30, 1988, and (3) lived in an area covered by one of eight collaborating tumor registries were eligible for inclusion in the NHL case group. Experts in lymphoma pathology, who reviewed the specimens, made the final classification of the diagnosis. The primary source of exposure data was a standardized questionnaire administered by telephone.

As Table 2.4 shows, of the 2,354 identified cases of lymphoma (NHL and Hodgkin's disease combined), 2,073 (80%) of the subjects were interviewed, and microscope slides or blocks were obtained for 2,004. A lymphoma diagnosis was confirmed for 93% of these men, and 1,511 were classified as having NHL. Population-based controls were selected through RDD (Waksberg, 1978) and were frequency-matched (by registry and 5-year date-of-birth interval) to all lymphoma cases. As Table 2.4 shows, 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 the coast of Vietnam, but were not stationed there, (3) they had AIDS (or an AIDS-related illness), a condition strongly increasing the risk for NHL, or (4) they were not residents of the U.S.A. before 1969. These restrictions resulted in 1,157 men with NHL and 1,776 controls. One case and one control were deleted from analyses involving education as a covariate because of missing data.

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, 88% (87/99) of men with NHL and 74% (98/133) of the controls gave permission for record review. Of these men, records were located for 85% of the cases and 87% of the controls. Among those whose records could be found, military

service in Vietnam could be corroborated by information in the records of 88% of the cases and 92% of the controls. Unless otherwise specified, we classified military service in Vietnam according to interview response. The sensitivity of our results to this decision and to several inclusion and exclusion criteria was evaluated in supplemental analyses.

3.2.2 Statistical Analyses

We assessed whether men who served in the U.S. military in Vietnam are at higher risk for developing NHL compared with other men. Details on our analytic methods are in Chapter 2. We had several choices for the nonexposed (referent) group, but unless we specify otherwise, 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 NHL (Greene, 1980; Greene, 1982). 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, and possible exposure to chlorophenols or dioxin in various occupations. (Other characteristics controlled for in the analyses of NHL are described in Section 3.3 (Model 3 of Table 3.3).)

Unconditional logistic regression with 39 indicator variables (representing the 40 date-of-birth and registry strata) was used in multivariable analyses. As Table 2.9 shows, this method yields results that are almost identical to those obtained by using the Mantel-Haenszel summary OR and conditional logistic regression. The homogeneity of the association between Vietnam service and NHL across strata of age, registry, and other characteristics was assessed by using the test statistic described by Breslow and Day (1980) and by using likelihood ratio tests in logistic regression models. The influence of potential confounders on the association between military service in Vietnam and NHL was assessed in logistic regression models that controlled for several covariates simultaneously. As Table 2.5 shows, we had an 88% power to detect a 1.5-fold increased risk among Vietnam veterans and a greater than 99% power to detect a twofold increase. All reported p-values are two-sided; 95% confidence intervals (CIs) are also provided.

We also examined whether the risk for NHL 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 the start of the first tour in Vietnam. We were aware that the potential for misclassification was great (CDC VHS, 1988; CDC VHS, 1989); nevertheless, we also evaluated the association between several self-reported assessments of exposure to Agent Orange and NHL.

3.3 RESULTS

3.3.1 Descriptive Characteristics

The distribution of cases and controls across the 40 cells defined by the frequency-matched design is shown in Table 3.1, and various characteristics of cases and controls are summarized in Table 3.2. Despite the frequency matching on age, men with NHL were somewhat older than the control subjects (mean ages of 29 and 27 years in 1968, respectively), primarily because we excluded from the case group many young men with AIDS. Although the racial or ethnic composition of the case and control subjects was similar, cases had less formal education, were less likely to have ever been married, tended to have smoked more cigarettes, and tended to have been raised in the Jewish religion. Men with NHL

Table 3.1. Distribution of Men With Non-Hodgkin's Lymphoma 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	9: 20[a]	17: 34	15: 35	16: 24	25: 29	82: 142
2	22: 37	32: 56	27: 49	44: 69	62: 74	187: 285
3	19: 39	20: 30	39: 58	47: 51	59: 69	184: 247
4	14: 31	17: 25	26: 36	32: 29	41: 45	130: 166
5	3: 17	8: 24	10: 14	13: 25	19: 22	53: 102
6	32: 89	38:102	38: 89	45: 80	51: 73	204: 433
7	23: 42	30: 46	39: 46	44: 41	68: 70	204: 245
8	13: 27	17: 37	20: 30	28: 30	35: 32	113: 156
Total	135:302	179:354	214:357	269:349	360:414	1157:1776

[a] N cases:N controls

also more frequently reported a history of medical irradiation, rheumatoid arthritis, systemic lupus erythematosus, an immunodeficiency problem other than AIDS, and use of immunosuppressive drugs. Case and control subjects differed only slightly, however, in their reporting of occupational exposure to herbicides or chlorophenols. Fewer case than control subjects had malaria or had taken drugs to treat or prevent malaria; more case than control subjects reported having used intravenous drugs.

Table 3.2. Distribution of Selected Covariates[a] Among Men With Non-Hodgkin's Lymphoma and Among Control Subjects

	Controls (N = 1776)[b]		Non-Hodgkin's Lymphoma Cases (N= 1157)[b]	
	%[c]	(N)	%[c]	(N)
Design Characteristics				
Registry				
1	8.0	(142)	7.1	(82)
2	16.0	(285)	16.2	(187)
3	13.9	(247)	15.9	(184)
4	9.3	(166)	11.2	(130)
5	5.7	(102)	4.6	(53)
6	24.4	(433)	17.6	(204)
7	13.8	(245)	17.6	(204)
8	8.8	(156)	9.8	(113)
Age in 1968 (years)				
15 to 19	17.0	(302)	11.7	(135)
20 to 24	19.9	(354)	15.5	(179)
25 to 29	20.1	(357)	18.5	(214)
30 to 34	19.7	(349)	23.2	(269)
35 to 39	23.3	(414)	31.1	(360)
Stationed in Vietnam or off the coast of Vietnam	7.5	(133)	8.6	(99)
Other reported characteristics				
Racial/ethnic group				
White non-Hispanic	84.3	(1497)	87.7	(1015)
Black non-Hispanic	8.1	(143)	7.3	(85)
Hispanic	5.6	(99)	3.1	(36)
Asian	1.7	(31)	1.2	(14)
Other/unknown	0.3	(6)	0.6	(7)
Highest level of education completed				
Less than high school	11.3	(200)	15.1	(174)
High school, technical school	29.5	(523)	33.3	(385)
1 to 3 years of college	20.6	(366)	20.1	(232)
4 or more years of college	38.6	(686)	31.6	(365)

Table 3.2. Distribution of Selected Covariates[a] Among Men With Non-Hodgkin's Lymphoma and Among Control Subjects — Continued

	Controls (N = 1776)[b]		Non-Hodgkin's Lymphoma Cases (N= 1157)[b]	
	%[c]	(N)	%[c]	(N)
Smoked cigarettes regularly	66.8	(1186)	70.5	(816)
Number of pack-years[d]				
0 (Never smoked)	33.3	(590)	29.9	(341)
0.1 to <15	22.0	(390)	16.8	(192)
15 to <30	20.1	(356)	19.3	(220)
30 to <45	13.0	(230)	15.1	(172)
45 or more	11.6	(206)	19.0	(217)
Drank alcohol regularly	71.1	(1262)	70.3	(813)
Raised in the Jewish religion	3.0	(53)	3.6	(42)
Never married	7.3	(129)	8.5	(98)
Lived or worked on a farm or ranch	44.8	(796)	45.3	(524)
Sprayed or mixed any herbicide on a farm or ranch	9.6	(170)	9.3	(108)
Contact with herbicides on a farm or ranch, 21 or more days per year, 5 or more years before the date of diagnosis[e]	2.4	(43)	2.1	(24)
Sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work	7.3	(129)	6.4	(74)
Occupational exposure to phenoxyherbicides	5.9	(105)	5.1	(59)
Occupational exposure to chlorophenols	11.3	(200)	12.1	(140)
Occupational exposure to 2,4,5-T	0.9	(16)	1.0	(12)
Occupational exposure to 2,4-D	5.8	(103)	4.8	(56)
Worked with or around asbestos	18.2	(324)	17.3	(200)
Worked in a leather tanning plant	0.5	(8)	0.6	(7)
Worked in a pulp, saw, or planing mill	5.7	(101)	6.7	(78)
Worked in a meat packing or processing plant	5.9	(104)	7.1	(82)
Worked with or around wood preservatives	11.8	(209)	12.1	(140)
Worked with or around cutting oils	20.5	(364)	20.3	(235)
Exposure to medical radiation 5 or more years before the date of diagnosis[e]	2.6	(47)	3.4	(39)
Had systemic lupus erythematosus	0.1	(2)	0.5	(6)
Diagnosed with rheumatoid arthritis	3.6	(64)	5.0	(58)
Had mononucleosis	6.5	(115)	6.7	(77)
Had an immune disease other than AIDS 3 or more years before the date of diagnosis[f]	0.1	(2)	0.2	(2)
Had malaria	1.4	(25)	1.1	(13)
Had an appendectomy	16.0	(285)	18.1	(209)
Had a tonsillectomy	47.5	(843)	51.6	(597)
Took phenytoin or related compounds for epilepsy or seizures	1.0	(17)	1.5	(17)
Took immunosuppressive drugs following an organ transplant	0.1	(1)	0.5	(6)
Took intravenous drug not prescribed by a physician	1.9	(33)	2.4	(25)
Took medication to treat or prevent malaria	11.4	(202)	9.9	(114)

[a] The covariates are described in the text

[b] Information on education for one non-Vietnam veteran control and one non-Vietnam veteran case was missing. Missing also was information on the number of pack-years for 4 controls and 15 cases (2 Vietnam veterans). Information on illicit intravenous drug use was not asked of proxy respondents for 120 cases (8 Vietnam veterans)

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

[d] Average number of packs of cigarettes smoked daily times the number of years subject smoked. One pack-year equals 7,305 cigarettes smoked

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

[f] For controls, 3 or more years before the date the registry was notified of selection

3.3.2 Overall Association

A slightly larger proportion of men with NHL than control subjects (8.6% vs. 7.5%) reported military service in Vietnam. After the design factors had been controlled for (Table 3.3, Model 1), the risk of NHL among Vietnam veterans relative to that among other men was 1.45 (95% CI 1.08-1.93). This differs from the unadjusted estimate (OR = 1.16) mostly because of confounding by age. Further adjustment for ethnicity, education, and several covariates (Model 3) produced little change in the effect of military service in Vietnam (OR = 1.47, 95% CI 1.09-1.97). To assure control of confounding, in subsequent analyses, we controlled for all covariates listed in Model 3.

Inclusion in the model of a history of having had malaria, of having taken medicine to treat or prevent malaria, or of having used intravenous drugs did not explain the increased risk for Vietnam veterans. Results of additional analyses indicated that the association between Vietnam service and NHL did not differ across categories of age, registry, ethnicity, educational achievement, or any of the characteristics included in Model 3. We also examined the association of Vietnam service with NHL, using the three alternative referent groups shown in Table 3.4. Differences in the choice of referent group had little effect on the estimate of risk. Relative to other Vietnam-era veterans who served between 1964 and 1972, the estimate of risk for Vietnam veterans was 1.52.

Table 3.3. Association Between Military Service in Vietnam and Non-Hodgkin's Lymphoma

Model[a]	Odds Ratio[b] (95% Confidence Interval)
1. Adjusted for registry and age group in 1968	1.45 (1.08-1.93)[c]
2. Adjusted for registry, age group in 1968, racial/ethnic group, and education	1.46 (1.09-1.96)
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	
—immunodeficiency problem other than AIDS[d]	
—immunosuppressive drugs following an organ transplant	
—systemic lupus erythematosus	
—rheumatoid arthritis	
—phenytoin or related compounds for epilepsy or seizures	
—medical radiation[e]	
reported demographic and lifestyle characteristics	
—number of pack-years[f]	
—marital status	
—raised in the Jewish religion	1.47 (1.09-1.97)

[a] One control and one case 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. Models also control for 1-year increments within 5-year age groups

[c] By using conditional logistic regression, the odds ratio (95% confidence interval) for Model 1 is 1.44 (1.08-1.92)

[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

[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

[f] Average number of packs of cigarettes smoked daily times the number of years subject smoked. One pack-year equals 7,305 cigarettes smoked

Table 3.4. Risk of Non-Hodgkin's Lymphoma Among Vietnam Veterans Relative To the Risk Among Four Referent Groups

Risk Group	Controls (N = 1776) %[a]	Controls (N = 1776) (N)	Non-Hodgkin's Lymphoma Cases (N = 1157) %[a]	Non-Hodgkin's Lymphoma Cases (N = 1157) (N)	Odds Ratio[b] (95% Confidence Interval)
Exposed group					
Men who served in Vietnam	7.5	(133)	8.6	(99)	
Referent groups					
Men who did not serve in Vietnam	92.5	(1643)	91.4	(1058)	1.47 (1.09-1.97)
Men who served in the military at any time but not in Vietnam	38.4	(682)	39.2	(454)	1.63 (1.14-2.33)
Men who served at any time from 1964 to 1972 in the military but not in Vietnam[c]	11.4	(203)	8.1	(94)	1.52 (1.00-2.32)
Men who never served in the military	54.1	(961)	52.2	(604)	1.41 (1.03-1.93)

[a] The percentage of controls or cases in the indicated exposed or referent group
[b] Odds ratios estimate the risk of non-Hodgkin's lymphoma 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 3.3 (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 96 cases)

As Table 3.5 shows, no histologic cell type appears to be overrepresented among Vietnam veterans. Similar proportions of Vietnam veterans and other men were diagnosed as having

Table 3.5. Histologic Classification of Malignancies Among Men With Non-Hodgkin's Lymphoma, by Military Service in Vietnam

Working Formulation Classification	ICD-O Code[a]	Stationed in Vietnam or off the Coast of Vietnam: No %[b]	No (N)	Yes %[b]	Yes (N)
Low grade (Total)		35.6	(377)	34.3	(34)
Small lymphocytic with plasmacytoid features	96113	0.4	(4)	—	(0)
Small lymphocytic	96203	11.7	(124)	9.1	(9)
Intermediate cell[c]	96213	1.2	(13)	2.0	(2)
Follicular, mixed small and large	96913	5.0	(53)	5.1	(5)
Mantle zone[c]	96943	0.2	(2)	—	(0)
Follicular, small cleaved	96963	17.1	(181)	18.2	(18)
Intermediate grade (Total)		46.1	(488)	50.5	(50)
Diffuse, small and large	96133	9.6	(102)	8.1	(8)
Diffuse, small cleaved	96223	5.4	(57)	6.1	(6)
Diffuse, large cleaved	96243	0.9	(9)	1.0	(1)
Diffuse, large noncleaved	96343	8.7	(92)	7.1	(7)
Diffuse, large	96403	18.6	(197)	23.2	(23)
Follicular, large	96423	2.9	(31)	5.1	(5)
High grade (Total)		17.2	(182)	15.2	(15)
Small, noncleaved	96003	3.2	(34)	2.0	(2)
Lymphoblastic	96023	0.8	(8)	—	(0)
Immunoblastic	96123	13.0	(138)	12.1	(12)
Burkitt's	97503	0.2	(2)	1.0	(1)
Unclassified non-Hodgkin's lymphoma	95913	1.0	(11)	—	(0)
All non-Hodgkin's lymphoma cases (Total)		100.0	(1058)	100.0	(99)

[a] International Classification of Diseases for Oncology, 1976
[b] Percentage of cases in each Vietnam service category with the indicated histology
[c] Generally considered low grade. Not graded by the Working Formulation

low- (34% vs. 36%), intermediate- (51% vs. 46%), and high-grade (15% vs. 17%) NHL; $p = 0.73$ as assessed by a χ^2 test with two degrees of freedom.

3.3.3 Characteristics of Military Service in Vietnam

Table 3.6 shows the estimated risk of NHL by branch of service for both Vietnam veterans and veterans who served elsewhere, relative to men who never served on active duty in the U.S. military. Relative risks tend to be highest for Vietnam veterans who served in the Marines and Navy, but the ORs did not significantly differ across branches ($p = 0.29$). The relative risk estimate for Navy men who served in Vietnam, viewed singly, however, was statistically significant. In contrast to the Vietnam veterans, other veterans tended to have decreased estimates of risk for NHL (except the 10 men in the Coast Guard), with estimates ranging from 0.77 to 0.91 by branch.

Most additional attributes of military service in Vietnam, shown in Table 3.7, were not strongly associated with differences in risk. For example, trends in the estimated risk of NHL according to calendar year of service, age at first tour in Vietnam, or rank at end of first tour were not consistent. The risk of NHL did tend to rise with increasing years of service in Vietnam ($p = 0.10$, test for trend); among men who were stationed in Vietnam for 1.5 to 1.9 years, the risk increased threefold, but among men who were in Vietnam for 2 or more years, the risk decreased (OR = 1.54). Small differences in risk by type of unit were not statistically significant. The estimated risk of NHL tended to be lower among men who had ever served in III Corps (the area surrounding Saigon, OR = 0.96) than among those who had not been in III Corps (OR = 1.70) ($p = 0.06$ for testing the difference between the two estimated risks). Interestingly, of the 32 men with NHL who served in the Navy, 28 served in blue water on ocean-going vessels. None of the Navy veterans with NHL reported serving in brown water (on small vessels engaged in patrolling near shore or on rivers). As a group, land-based men (including men who served in the brown-water and shore Navy) tended to have a lower risk than did men who were stationed at sea.

Table 3.6. Association Between Branch of Military Service and Non-Hodgkin's Lymphoma by Vietnam Veteran Status

	Non-Vietnam Veterans					Vietnam Veterans					
Branch of Service	Controls (N = 682)[b] %[a]	(N)	Non-Hodgkin's Lymphoma Cases (N = 454)[b] %[a]	(N)	Odds Ratio[c] (95% Confidence Interval)	Controls (N = 133) %[a]	(N)	Non-Hodgkin's Lymphoma Cases (N = 99) %[a]	(N)	Odds Ratio[c] (95% Confidence Interval)	P-value
Army	52.5	(358)	52.6	(239)	0.82 (0.66-1.02)	52.6	(70)	45.5	(45)	1.19 (0.79-1.80)	
Air Force	18.2	(124)	19.4	(88)	0.91 (0.67-1.25)	13.5	(18)	12.1	(12)	1.02 (0.47-2.24)	0.29[d]
Marines	5.7	(39)	5.3	(24)	0.77 (0.45-1.32)	9.8	(13)	10.1	(10)	1.84 (0.78-4.34)	
Navy	17.0	(116)	15.6	(71)	0.79 (0.57-1.11)	23.3	(31)	32.3	(32)	1.89 (1.11-3.24)	
Coast Guard	0.7	(5)	1.1	(5)	1.45 (0.39-5.38)	0.8	(1)	—	(0)	—[e]	

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

[b] The sum of the subjects in all branches is less than N because information about branch of service was missing for 67 men

[c] Odds ratios estimate the risk of non-Hodgkin's lymphoma for a given category of men relative to the risk among men with no military service (961 controls and 604 cases); 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

[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 3.7. Association Between Selected Characteristics of Military Service in Vietnam and Non-Hodgkin's Lymphoma

Characteristic	Controls (N = 1776) %[a] (N)	Non-Hodgkin's Lymphoma Cases (N = 1157) %[a] (N)	Odds Ratio[b] (95% Confidence Interval)	P-value[c]
No military service in Vietnam	— (1643)	— (1058)	Referent	
Military service in Vietnam	— (133)	— (99)	1.47 (1.09-1.97)	
Duration of service in Vietnam (years)				
<1	59.8 (79)	43.8 (42)	1.05 (0.70-1.57)	
1 to 1.4	13.6 (18)	18.8 (18)	1.98 (1.00-3.94)	0.06
1.5 to 1.9	9.8 (13)	18.8 (18)	2.99 (1.41-6.31)	
≥2	16.7 (22)	18.8 (18)	1.54 (0.79-3.01)	
Unknown	— (1)	— (3)		
Calendar years stationed in Vietnam				
Before 1966	7.5 (10)	9.3 (9)	1.38 (0.54-3.55)	
1966 to 1969	78.2 (104)	76.3 (74)	1.41 (1.01-1.98)	0.93
After 1969	14.3 (19)	14.4 (14)	1.64 (0.79-3.39)	
Unknown	— (0)	— (2)		
Age at beginning of first tour in Vietnam (years)				
<21	42.9 (57)	42.9 (42)	1.73 (1.11-2.70)	
21 to 25	37.6 (50)	31.6 (31)	1.20 (0.74-1.94)	0.52
≥26	19.6 (26)	25.5 (25)	1.45 (0.81-2.60)	
Unknown	— (0)	— (1)		
Rank at end of last tour in Vietnam[d]				
E1 to E3	16.2 (21)	12.5 (12)	1.29 (0.61-2.72)	
E4 to E9	73.1 (95)	75.0 (72)	1.44 (1.02-2.03)	0.84
Officer	10.8 (14)	12.5 (12)	1.78 (0.80-3.96)	
Unknown	— (3)	— (3)		
Type of unit in Vietnam				
Support	53.5 (69)	62.9 (56)	1.50 (1.02-2.21)	
Combat Support	26.4 (34)	20.2 (18)	1.18 (0.65-2.15)	0.76
Combat	20.2 (26)	16.9 (15)	1.25 (0.63-2.45)	
Unknown	— (4)	— (10)		
Corps in Vietnam				
I	18.9 (23)	25.3 (23)	2.25 (1.21-4.18)	
II	24.6 (30)	20.9 (19)	1.22 (0.66-2.26)	0.11
III	32.8 (40)	20.9 (19)	0.89 (0.50-1.58)	
IV	3.3 (4)	2.2 (2)	0.90 (0.15-5.41)	
Blue water Navy[e]	20.5 (25)	30.8 (28)	2.17 (1.22-3.86)	
Unknown	— (11)	— (8)		
Ever in III Corps in Vietnam				
No	36.8 (46)	40.9 (38)	1.70 (1.07-2.71)	
Yes	43.2 (54)	29.0 (27)	0.96 (0.59-1.57)	0.06
Blue water Navy[e]	20.0 (25)	30.1 (28)	2.18 (1.23-3.88)	
Unknown	— (8)	— (6)		
Land vs. sea duty in Vietnam				
All land-based Men	81.2 (108)	71.7 (71)	1.30 (0.93-1.82)	
All branches other than Navy	76.7 (102)	67.7 (67)	1.29 (0.92-1.82)	
Navy—shore	3.0 (4)	4.0 (4)	2.26 (0.52-9.78)	0.11[f]
Navy—brown water	1.5 (2)	— (0)	—[g]	
Sea-based blue water Navy	18.8 (25)	28.3 (28)	2.18 (1.23-3.87)	

[a] Percentage of case or control subjects who served in Vietnam with the specified characteristic (unknowns excluded)

[b] Odds ratios estimate the risk of non-Hodgkin's lymphoma 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 3.3 (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

We also examined the association between self-perceived contact with Agent Orange and NHL among Vietnam veterans (Table 3.8), but found no characteristic to be associated with an increased risk of NHL. For example, the 73 men (about a third of all Vietnam veterans) who reported that they had passed through a defoliated area in Vietnam were at no higher risk (OR = 0.82, 95% CI 0.45-1.49) of NHL than other Vietnam veterans. All other ORs for self-perceived contacts were less than or near 1.0, and none were statistically significant. Very few men reported handling equipment or containers that had been used with Agent Orange (three controls, one case) or spraying Agent Orange (two controls, no cases).

The association between time since first service in Vietnam and date of diagnosis of NHL was also examined (Table 3.9). Because of the relatively limited time spans of both the current study and the intensive American involvement in Vietnam, the distribution of time periods since military service in Vietnam was narrow. Within the confines of this study (time periods of <17 years to ≥22 years), however, there is little evidence that the risk of NHL varies with time.

3.3.4 Subgroups of Vietnam Veterans

To further assess the possibility that subgroups of Vietnam veterans might be at increased risk for NHL, we cross-classified location of service (representing the four military regions in Vietnam and men who served in the blue-water Navy) with other characteristics of military service in Vietnam (Table 3.10). The Mantel-Haenszel summary OR, adjusted for location, as

Table 3.8. Association Between Self-Reported Possible Contact With Agent Orange[a] and Non-Hodgkin's Lymphoma Among Men Who Served in the Military in Vietnam

		Controls (N = 133)		Non-Hodgkin's Lymphoma Cases (N = 99)		Odds Ratio[c] (95% Confidence Interval)
Characteristic	Category	%[b]	(N)	%[b]	(N)	
Reported passing through a defoliated area	No	65.4	(87)	70.3	(64)	
	Yes	34.6	(46)	29.7	(27)	0.82 (0.45-1.49)
	Unknown	—	(0)	—	(8)	
Reported any possible contact with Agent Orange[d]	No	74.4	(99)	71.4	(65)	
	Yes	25.6	(34)	28.6	(26)	1.08 (0.58-2.02)
	Unknown	—	(0)	—	(8)	
Reported being present when others were spraying Agent Orange	No	89.5	(119)	90.1	(82)	
	Yes	10.5	(14)	9.9	(9)	0.98 (0.39-2.48)
	Unknown	—	(0)	—	(8)	
Reported getting Agent Orange on skin or clothes	No	92.5	(123)	91.2	(83)	
	Yes	7.5	(10)	8.8	(8)	1.08 (0.40-2.96)
	Unknown	—	(0)	—	(8)	
Reported handling equipment or containers that had been used with Agent Orange	No	97.7	(130)	98.9	(90)	
	Yes	2.3	(3)	1.1	(1)	0.41 (0.04-4.07)
	Unknown	—	(0)	—	(8)	
Reported spraying Agent Orange	No	98.5	(131)	100	(91)	
	Yes	1.5	(2)		(0)	—[e]
	Unknown	—	(0)	—	(8)	

[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 eight deceased men

[c] Odds ratios estimate the risk of non-Hodgkin's lymphoma 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 3.3 (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