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THE UNIVERSITY OF SYDNEY
Department of Public Health

Professor G. Berry
Professor in Epidemiology and Biostatistics
Head of Department

Department of Public Health (A27)
University of Sydney
NSW 2006 Australia
Telephone (61-2) 692 4367
Fax (61-2) 692 4179

GB:mmm

The Hon. Ben Humphreys,
Minister for Veterans' Affairs,
Parliament House,
CANBERRA, ACT 2600.

Dear Minister,

I have pleasure in submitting the report of the study, *Dapsone Exposure, Vietnam Service and Cancer Incidence*. This study was carried out by the Australian Institute of Health and Welfare with review from the Scientific Advisory Committee.

Yours sincerely,

Professor G. Berry
Chairperson of Scientific Advisory Committee
for the Study of Carcinogenicity of Dapsone

AUSTRALIAN INSTITUTE OF
HEALTH & WELFARE
Bennett House,Hospital Point, Acton, ACT
GPO Box 570, Canberra, ACT 2601, Austrlia
Telephone International +61 6 243 5000 National (06) 243 5000
Fax International +61 6 257 1470 National (06) 257 1470

The Hon B. C. Humphreys MP
Minister for Veterans' Affairs
Commonwealth Parliament Offices
295 Ann Street
BRISBANE QLD 4000

Dear Minister

I am pleased to transmit herewith the final report of the investigation of the carcinogenicity of Dapsone in Vietnam veterans which was conducted by this Institute.

Yours sincerely

L R Smith

Dr L R Smith
Director
21 December 1992

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Executive summary

Background

Perceived ill-health of Vietnam veterans and their families has been a public issue since 1978. Initially, the major concern was possible effects of exposure of Vietnam veterans to some herbicides (notably Agent Orange) used during the Vietnam conflict.

Two studies, of mortality among Vietnam veterans and of birth defects in their children, were commissioned by the Commonwealth Government in the early 1980s but did not find any effects attributable to the use of chemicals in Vietnam. The Royal Commission into the Use and Effects of Chemical Agents on Australian Personnel in Vietnam was established in 1983.

Dapsone was one of the chemicals reviewed by the Royal Commission. During the Vietnam conflict Australian forces had used this drug, initially for the treatment of falciparum malaria and later also for its prevention. The Royal Commission recommended studies into the carcinogenicity of dapsone. The recommendation was supported by the Hogg report, which was commissioned by the Commonwealth to coordinate its response to the findings of the Royal Commission.

The Department of Veterans' Affairs asked the Australian Institute of Health and Welfare (AIHW—then called the Australian Institute of Health) to conduct a study of cancer incidence in relation to dapsone use. A protocol, completed in November 1990, defined the study aims and design, dealing with data collection and analysis, limitations of the study, reporting, and privacy. This protocol was accepted by the Scientific Advisory Committee formed to advise the Minister for Veterans' Affairs on the study, the State and Territory cancer registries, and the AIHW Ethics Committee.

Dapsone

Dapsone (4,4'-diaminodiphenyl-sulphone) is a sulphonamide-like drug that probably acts by inhibiting folate synthesis. Folate synthesis is an essential metabolic step in those unicellular organisms that, unlike humans, cannot use preformed folates. Dapsone is used for short- and long-term treatment of leprosy and for the prevention and treatment of malaria. Adverse reactions to its use include haemolytic anaemia, methaemoglobinaemia, peripheral neuropathy, gastrointestinal symptoms, fever, pruritus and various rashes.

Despite dapsone's widespread clinical use for many years, there is little evidence that it is associated with an increased risk of cancer. There are case reports of cancers among persons who have taken dapsone, but no specific or unusual site of cancer consistently appears in these reports. None of the reports gives a biological argument for an association of specific cancers with dapsone use. Moreover, most of the patients described in these reports had leprosy and had taken dapsone at higher doses and for much longer than was the case with dapsone used prophylactically against or as treatment for malaria by Australian servicemen.

Chronic carcinogenicity studies undertaken in both rats and mice show limited evidence of carcinogenicity. Mutagenicity studies have also been equivocal.

In the absence of further data, the International Agency for Research on Cancer has been unable to determine whether dapsone should be regarded as a carcinogen of humans.

Sites of cancer of a priori interest

For dapsone exposure, the sites of cancer that have been noted in previous studies are non-Hodgkin's lymphoma, Hodgkin's disease, oral cancer, kidney cancer, bladder cancer and leukemia. Because of the earlier interest in herbicides, this study also examines cancer incidence for sites of cancer that have been hypothesised as being related to herbicide exposure: non-Hodgkin's lymphoma, Hodgkin's disease, soft tissue and other sarcoma, nasal cancer, nasopharyngeal cancer, thyroid cancer, testis cancer and primary liver cancer.

Design of this study

The aim of this study was to assess and quantify any association between cancer incidence and exposure to dapsone and to Vietnam service among Australian Army servicemen who served in Vietnam during the Vietnam conflict.

The study cohort ('servicemen') consisted of all 115,407 males who served in the Australian Army for at least one year between 1 January 1965 and 1 March 1972. Identification of servicemen, those who had been exposed to dapsone, and those treated for malaria was done through Army records. Cancer incidence was determined by reference to State and Territory cancer registry records for the period 1972 to 1989, although not all registries had complete coverage for all of this period. Cancer incidence was examined for all cancers, and for 28 sites of cancer that included the cancers of a priori interest as well as groupings with more than 30 incident cases.

Cancer incidence rates, controlling for age and calendar year, were compared for several subgroups of servicemen:

- dapsone-exposed Vietnam veterans compared with non-exposed Vietnam veterans;
- for dapsone-exposed Vietnam veterans, those with the higher exposures compared with those with the lower exposures;
- Vietnam veterans with malaria compared with other Vietnam veterans;
- Vietnam veterans compared with non-veterans;
- dapsone-exposed Vietnam veterans compared with non-veterans;
- servicemen compared with other males in the Australian population.

Where possible, these comparisons were made separately for National Service (conscript) and Australian Regular Army (volunteer) servicemen.

Cancer mortality was not directly assessed.

Cancer incidence and dapsone exposure

Total cancer incidence

A total of 509 cancers were identified among Vietnam veterans. The relative cancer incidence rate at all sites combined for dapsone-exposed servicemen compared with other Vietnam veterans was 0.88. The 95 per cent confidence interval (95% CI) for the relative rate is 0.74 to 1.05, which includes equal incidence rates in both groups. The upper limit shows that the data from this study are inconsistent with a markedly higher total cancer incidence among dapsone-exposed servicemen compared with other Vietnam veterans; that is, there is no evidence from this study of an excess of overall cancer occurrence in those Vietnam veterans who had taken dapsone.

Relative cancer incidence rates among dapsone-exposed Vietnam veterans compared with other Vietnam veterans: all sites

Number of cancer cases among Vietnam veterans			
Exposed to dapsone	Not exposed to dapsone	Relative incidence rate	95% CI
247	262	0.88	(0.74, 1.05)

Most servicemen who took dapsone took a total (cumulative) dose of less than 5 grams. Dapsone-exposed servicemen whose total dose of dapsone differed by 5 grams were estimated to have a 1.1-fold difference in their overall cancer incidence rate. The 95 per cent confidence interval, 0.8 to 1.5, is consistent with no difference in cancer incidence for servicemen exposed to different doses of dapsone. The upper limit of this confidence interval shows that the data from the study are inconsistent with large differences in total cancer incidence for servicemen exposed to different total doses of dapsone; that is, Vietnam veterans who took more dapsone did not appear to be much more likely to develop cancer than those who took less dapsone.

Different sites of cancer

For none of the 28 sites of cancer examined was the cancer incidence among the dapsone-exposed servicemen statistically significantly greater than that among other Vietnam veterans. For no site of cancer examined was there a statistically significant dose–response relationship between the total amount of dapsone received and cancer incidence.

For one cancer, that of the testis, the rate of occurrence was much less than expected. On biological and statistical grounds, this apparent protective effect of dapsone probably reflects chance alone.

Specific sites of cancer

Six sites of cancer—non-Hodgkin's lymphoma, kidney, Hodgkin's disease, bladder, oral and leukemia—were of particular interest because previous research,

independent of this study, had suggested that they might be associated with dapsone exposure. None of these sites had, however, shown particularly marked relationships with dapsone exposure in these other data sets. This was also the case in this study.

Relative cancer incidence rates among dapsone-exposed Vietnam veterans compared with other Vietnam veterans: specific sites

Cancer site	Number of cancer cases among Vietnam veterans: Exposed to dapsone	Not exposed to dapsone	Relative incidence rate	95% C
Non-Hodgkin's lymphoma (ICD 200, 202)	19	9	1.8	(0.8, 3.9)
Kidney (ICD 189)	6	6	1.3	(0.4, 4.1)
Hodgkin's disease (ICD 201)	7	4	1.2	(0.3, 5.5)
Bladder (ICD 188)	13	14	1.0	(0.5, 2.1)
Oral (ICD 140–146, 149)	16	27	0.6	(0.3, 1.1)
Leukemia (ICD 204–208)	7	13	0.5	(0.2, 1.2)

Dose response among dapsone-exposed Vietnam veterans: specific sites

Cancer site	Relative incidence rate for doses differing by 5 grams	95% CI
Non-Hodgkin's lymphoma (ICD 200, 202)	0.5	(0.2, 1.4)
Kidney (ICD 189)	0.5	(0.1, 3.1)
Hodgkin's disease (ICD 201)	1.2	(0.2, 6.6)
Bladder (ICD 188)	2.1	(0.6, 7.3)
Oral (ICD 140–146, 149)	0.9	(0.3, 2.7)
Leukemia (ICD 204–208)	1.8	(0.3, 9.9)

For none of these six sites was the cancer incidence particularly high among dapsone-exposed servicemen compared with other Vietnam veterans. None of the relative incidence rates was statistically significantly different from equal cancer incidence rates in the two groups of servicemen. The dose–response relationships were also unremarkable.

The observed relative rates are similar to those for total cancer incidence and for other sites of cancer. If dapsone exposure were causing some cancers, increased cancer incidence should be apparent among some or all of these six specific sites of cancer, even if the elevation in rates was not statistically significant. Cancer incidence

for these six sites, individually and collectively, cannot be taken as definite evidence that dapsone exposure has led to an increased number of cancers.

The wide confidence intervals for some comparisons show, however, that this study has low power to detect differences in cancer incidence for some sites of cancer. The maximum latency period between dapsone exposure and registration of a cancer is 24 years, so an increase in cancer incidence 20 or more years after exposure to dapsone may not be detected by this study.

Cancer incidence and Vietnam service

Total cancer incidence

The study identified a total of 1,638 cancers among the servicemen. The overall relative cancer incidence rate for Vietnam veterans compared with non-veterans (those servicemen who had not been posted to Vietnam) was 0.99. The 95 per cent confidence interval for the relative rate is 0.89 to 1.10, which includes equal incidence rates in both groups. The upper limit shows that the data from this study are inconsistent with a markedly higher total cancer incidence among Vietnam veterans compared with non-veterans.

Relative cancer incidence rates among Vietnam veterans compared with non-veterans: all sites

Number of cancer cases among servicemen			
Served in Vietnam	Did not serve in Vietnam	Relative incidence rate	95% CI
509	1,129	0.99	(0.89, 1.10)

Different sites of cancer

For none of the 28 sites of cancer examined was the cancer incidence among Vietnam veterans statistically significantly greater than that among non-veterans. This was also true for servicemen who had served as volunteers in the Australian Regular Army. Among National Servicemen three sites of cancer—pancreas, lung and brain—showed statistically significantly higher incidence among Vietnam veterans compared with non-veterans.

Relative cancer incidence rates among Vietnam veterans compared with non-veterans: selected sites

	National Service				Australian Regular Army			
	No. of cases		Relative Incidence		No. of cases		Relative Incidence	
Cancer site	VV	NV	rate	95% CI	VV	NV	rate	95% CI
Pancreas (ICD 157)	7	1	11.0	(1.4, >10)	6	24	0.9	(0.4, 2.1)
Lung (ICD 162)	13	6	3.9	(1.5, 10.0)	46	158	0.8	(0.5, 1.1)
Brain (ICD 191)	8	7	3.0	(1.1, 8.2)	9	14	1.0	(0.4, 2.3)

Note: 'VV' denotes Vietnam veteran; 'NV' denotes non-veteran.

There was nothing in the medical literature to link these three sites of cancer with Vietnam service. Curiously, any increased risk is apparently confined to National Servicemen because the estimated risks for these sites of cancer among members of the Australian Regular Army are not greater than unity. This could, however, occur if there were some relevant aspect of Vietnam service that differed substantially between these two groups of servicemen.

One statistical consideration is that these three nominally statistically significant results have occurred when testing for differences at 29 sites in the two service groups. With so many tests, it is to be expected that, even if there were no real underlying difference, chance would result in a few being nominally statistically significant. For 58 tests, the expected number of nominally statistically significant raised estimates is 1.4, and observing three such results is not unusual.

Specific sites of cancer

Eight sites of cancer—nasopharyngeal, primary liver, non-Hodgkin's lymphoma, Hodgkin's disease, soft tissue, thyroid, testis and nasal—were of particular interest because previous research, independent of this study, had nominated them as possibly being associated with herbicide exposure. The following table shows relative cancer incidence rates for these sites.

Relative cancer incidence rates among Vietnam veterans compared with non-veterans: specific sites

Cancer site	Number of cases		Relative incidence rate	95% CI
	Vietnam veterans	Non-veterans		
Nasopharyngeal (ICD 147)	4	1	5.8	(0.6, >10)
Primary liver (ICD 155)	3	2	3.0	(0.3, >10)
Non-Hodgkin's lymphoma (ICD 200, 202)	28	47	1.1	(0.7, 1.8)
Hodgkin's disease (ICD 201)	11	22	1.1	(0.5, 2.2)
Soft tissue and other sarcoma (ICD 170–171)	10	19	1.0	(0.4, 2.1)
Thyroid (ICD 193)	3	8	0.9	(0.1, 3.5)
Testis (ICD 186)	26	57	0.8	(0.5, 1.2)
Nasal (ICD 160)	1	3	0.4	(0.0, 5.3)

If herbicide exposure were causing some cancers and if Vietnam veterans were exposed to herbicides, increased cancer incidence should be apparent among some or all of the specific sites of cancer, even if the elevation in rates was not statistically significant. For no site is cancer incidence among Vietnam veterans statistically significantly different from that among non-veterans. The two highest and the lowest estimated relative rates are based on five or fewer cancer cases, and the confidence intervals are correspondingly wide. The other five estimated rates, based on more than 10 cancer cases, are close to unity. Cancer incidence for these five sites of cancer, individually and collectively, cannot be taken as definite evidence that posting to Vietnam has led to an increased number of cancers.

Conclusion

The study revealed no definite evidence that dapsone exposure was associated with an increase in total cancer incidence. Cancer incidence was assessed at six sites that had been suggested in previous publications as those for which an effect of dapsone was most likely. The study does not provide definite evidence of increased cancer incidence at these sites. Similar conclusions apply to the other 22 sites that were examined.

The study revealed no definite evidence that Vietnam service was associated with an increase in total cancer incidence. Cancer incidence was assessed at eight sites that had been suggested in previous publications as those for which an effect of exposure to herbicides was most likely. The study does not provide definite evidence of increased cancer incidence at these sites. Similar conclusions apply to the other 20 sites that were examined.

For those sites of cancer with few cases the confidence intervals were wide. The study results cannot therefore rule out an increased incidence at one or more of these sites.

The most recent cancer registration used in this study was for 1989, 24 years after first exposure to dapsone or service in Vietnam. Accordingly, this study cannot detect cancers that may arise at greater latencies after exposure to dapsone or Vietnam service.

1 Introduction

1.1 Background

Concerns about the health of Vietnam veterans

Perceived ill-health of Vietnam veterans and their families became a public issue from about 1978. Of particular concern were possible effects of exposure of Vietnam veterans to some herbicides (notably Agent Orange) used during the Vietnam conflict.

The Commonwealth Government responded in the early 1980s by commissioning two studies, to examine mortality in Vietnam veterans and to examine birth defects in their children. Neither of the studies identified harm arising from use of chemicals in Vietnam.

The Evatt Royal Commission

Concerns persisted. The Royal Commission into the Use and Effects of Chemical Agents on Australian Personnel in Vietnam (the Evatt Royal Commission) was established in 1983 (Evatt 1985).

Dapsone was one of the chemicals reviewed by the Royal Commission. During the Vietnam conflict Australian forces had used this drug, initially for the treatment of falciparum malaria and later also for its prevention.

In its review of expert opinion on the potential carcinogenicity of dapsone, the Royal Commission gave particular weight to the evidence of Dr Philippe Shubik, part of whose written submission stated, 'On present data I am unable to say whether dapsone is actually carcinogenic in humans' (Evatt 1985, p. VIII-381). However, when referring to the chemicals being considered by the Royal Commission, Dr Shubik nominated dapsone as 'the most likely compound to pose a potential carcinogenic hazard' (p. VIII-381).

In his oral evidence, Dr Shubik stated, 'Insofar as dapsone is concerned, compounds that do produce leukopenia with white cell problems, are, of course, suspect of being carcinogenic' (p. VIII-383). He also recommended that an epidemiological study be performed if possible.

While acknowledging that there was no evidence that dapsone was carcinogenic in man (Evatt 1985, p. VIII-382), the Royal Commission recommended as follows in relation to dapsone:

1. THAT Government finance through the NHMRC [National Health and Medical Research Council] studies of the carcinogenicity of dapsone.
2. THAT any Vietnam veteran suffering from cancer who may have taken dapsone should have his claim treated on the basis that a reasonable hypothesis exists connecting his disease with war service. (p. XV-46)

The Hogg report

In 1987 Mr Bob Hogg, consultant to the Minister for Veterans' Affairs and responsible for coordinating the Commonwealth Government's response to the report of the Royal Commission, recommended 'that the Government immediately establish an epidemiological study into the possible health effects arising from the use of dapsone' (Hogg 1987, p. 46). The Commonwealth Government decided to accept this recommendation only as it related to cancer.

Subsequent action

Following this decision the Department of Veterans' Affairs wrote to the NHMRC about the proposed study. The NHMRC passed the request to the Australian Institute of Health and Welfare (AIHW—then called the Australian Institute of Health).

The Institute advised the Department not to proceed immediately with an epidemiological study. Instead, it wished first to determine whether the number of cancers likely to have occurred among Vietnam veterans would justify a study at that time or whether the study should be deferred until sufficient cancers had accumulated. The Department agreed and commissioned the Institute to advise on these options. The Institute later reported that a study commencing in 1989–90 would be worthwhile.

Preparation of a study protocol

A protocol for the proposed study was completed in November 1990. This protocol defined the study aims and design, dealing with data collection and analysis, limitations of the study, reporting, and privacy and confidentiality considerations relating to the work to be performed.

The protocol was accepted by the Scientific Advisory Committee formed to advise the Minister for Veterans' Affairs on the study, the State and Territory cancer registries, and the AIHW Ethics Committee. The protocol is reproduced at Appendix A.

1.2 Dapsone

Dapsone, a drug first synthesised in 1945, is used for the prophylaxis of malaria and the treatment of malaria and leprosy. During the Vietnam conflict the falciparum variety of malaria was prevalent and posed a serious threat to Australian troops. Dapsone was found to be highly effective in preventing and treating falciparum malaria.

The drug was first used in Vietnam for the treatment of soldiers affected by malaria in September 1967. In November 1968 it was introduced as a preventive measure. All Army and land-based Navy members took 25 milligrams of dapsone and 200 milligrams of proguanil daily. This regimen continued until February 1970 when, following the occurrence of several cases of damage to white blood cells, the

drug was restricted to those serving in high risk areas. Use of the drug ceased in December 1972.

The chemical structure of dapsone (4,4'-diaminodiphenyl-sulphone) is similar to that of the sulphonamides. It probably acts by inhibiting folate synthesis. Folate synthesis is an essential metabolic step in those unicellular organisms that, unlike humans, cannot use preformed folates.

The drug is well absorbed and eliminated from the human body by being acetylated in the liver. The half-life of elimination averages approximately one to two days. In principle, it would be expected that slow acetylators, who comprise about 30 per cent of the Australian population, would eliminate the drug more slowly, although this has not been convincingly demonstrated. The usual dosage of the drug ranges from 25 milligrams per week to 400–600 milligrams per week.

Adverse reactions to dapsone do occur. Haemolytic anaemia is common, particularly among individuals with hereditary glucose-6-phosphate deficiency. Methaemoglobinaemia, peripheral neuropathy, gastrointestinal symptoms, fever, pruritus and various rashes have also been reported.

Carcinogenicity of dapsone

Human populations

Despite widespread clinical use for many years, there is little evidence that dapsone is associated with an increased risk of cancer. There are case reports of cancers among persons who have taken dapsone, but no specific or unusual site of cancer is apparent from these reports. Moreover, most of the patients described in these reports had leprosy and had taken dapsone at higher doses and for much longer than was the case with dapsone used prophylactically against and in the treatment of malaria by Australian servicemen.

Four epidemiological studies (Table 1.1) have assessed cancer mortality in large cohorts of leprosy patients, many of whom had received large doses of dapsone for extended periods. The main focus of these studies was that cancer incidence, especially for lymphomas, is generally high among immunosuppressed patients, but this is not seen among leprosy patients. The studies were only secondarily interested in dapsone exposure and cancer incidence.

Table 1.1 *Cohort studies of cancer mortality among leprosy patients*

Study	Number of patients	Number of cancers	
		Observed	Expected
Oleinick (1969)	848	21	19.7[a]
Kolonel & Hirohata (1977)	1,123	33	30.56
Tokudome et al. (1981)	2,383	84	80.85
Brinton et al. (1984)	1,678	77	58.54
Combined	6,032	215	189.7[a]

[a] Limited precision available from study.

The expected numbers of cancers in Table 1.1 were calculated using age- and gender-specific rates in comparable general populations. Overall, the estimated relative risk of cancer mortality is 1.13 times higher among patients with leprosy compared with the general population. The 95 per cent confidence interval is 0.99 to 1.30, so the relative risk among leprosy patients is not statistically significantly different from that in the general population. The estimated risks are not statistically significantly different between the four studies (homogeneity chi-square test statistic of 2.4 for 3 degrees of freedom, $p > 0.05$). Therefore, despite the nominally statistically significant relative risk reported by one of the studies (Brinton et al. 1984), it appears that leprosy patients are not at a greatly elevated risk of death from cancer compared with the general population.

The fact that most of these leprosy patients had taken high doses of dapsone for extended periods suggests that dapsone use is not associated with an increased risk of cancer. Kolonel and Hirohata (1977) found no large or statistically significant difference in relative cancer incidence rates between two periods, one before the introduction of dapsone and the other after. Similarly, Brinton et al. (1984) approached this issue by examining variation in relative cancer mortality rates with time between initial hospital admission and death and with period of sulphone use. There was no large or statistically significant variation in cancer death rates with these two factors.

Oleinick (1969), Kolonel and Hirohata (1977) and Tokudome et al. (1981) did not identify any sites of cancer for which leprosy patients were at particular risk. Brinton et al. (1984) observed statistically significantly higher risks for oral, bladder and kidney cancers and, for males only, lymphoma. But none of these cancers showed a consistent pattern with time since first hospital admission or with period of sulphone use. The oral cancers were heterogeneous. Brinton et al. thought that these increased risks 'probably related to various confounding factors in this population' (1984, p. 113).

None of these studies presented any biological argument for an association of specific cancers with dapsone use. Their particular interest in lymphomas was that leprosy is an immunosuppressive disease, rather than that these patients used dapsone.

Animal studies

Chronic carcinogenicity studies have been undertaken in both rats and mice (see IARC 1980). Two studies found no statistically significant increased risk of cancer among mice exposed to dapsone. In three studies, high doses of dapsone induced mesenchymal tumours of the spleen in male rats (and of the peritoneum in two studies). A possible increase in thyroid tumours in rats was reported in two studies.

There is no biological argument why dapsone exposure should lead to these cancers. Overall, there is limited evidence of carcinogenicity in mice or in female rats.

Mutagenicity tests

The results of mutagenicity studies have also been equivocal. Neither dapsone nor its *N*-acetyl or *NN*-diacetyl metabolites have shown mutagenic activity in *Salmonella typhimurium* strains, although some abnormalities have occurred in human lymphocytes exposed to high concentrations of the drug (see IARC 1980, 1987).

Summary

There have been few scientific studies of the carcinogenicity of dapsone. In the absence of further data, the International Agency for Research on Cancer is unable to determine whether dapsone should be regarded as a carcinogen of humans (IARC 1987).

There is limited evidence of carcinogenicity in animals and mutagenicity tests have been generally negative. There is little evidence for carcinogenicity in human populations. These studies do not discuss any biological rationale for relating dapsone to specific sites of cancer.

1.3 Sites of cancer of a priori interest

The study protocol (Appendix A) discusses the sites of cancer of particular interest for this study: non-Hodgkin's lymphoma, Hodgkin's disease, oral cancer, kidney cancer, bladder cancer and leukemia.

Because of the earlier interest in herbicides, this study also considers cancers that may be associated with herbicide exposure: non-Hodgkin's lymphoma, Hodgkin's disease, soft tissue and other sarcoma, nasal cancer, nasopharyngeal cancer, thyroid cancer, testicular cancer and primary liver cancer. This list includes those cancers identified by the Selected Cancers Cooperative Study Group (1990a, 1990b, 1990c).

Two other studies have appeared since the protocol was written. Saracci et al. (1991) have identified apparent increases in risk for cancers of the thyroid, testis and other endocrine glands among chemical workers involved in the manufacture of herbicides. Fingerhut et al. (1991) have suggested that chemical workers involved in the manufacture of herbicides are at a slightly increased risk of connective and other soft tissue cancer (ICD 171), rather than of the combined grouping of ICD 170 and 171.

1.4 Report structure

The background to this study and to the uses and pharmacology of dapsone are described in this chapter. Chapter 2 describes the aims of the study. Chapter 3 documents the data collection, collation and analysis.

Chapter 4 compares cancer incidence rates for different subgroups. The characteristics of the study population are summarised in Section 4.1. Cancer incidence rates for dapsone-exposed Vietnam veterans are compared with those for other Vietnam veterans in Section 4.2; Section 4.3 assesses whether higher total doses of dapsone are associated with different cancer incidence rates when compared with lower total doses of dapsone. Section 4.4 looks at whether servicemen who contracted malaria in Vietnam have cancer incidence rates that differ from those of other Vietnam veterans. Cancer incidence rates among Vietnam veterans compared with those among non-veterans are the subject of Section 4.5; Section 4.6 combines elements of Sections 4.2 and 4.5, comparing cancer incidence among dapsone-exposed Vietnam veterans and non-veterans. Cancer incidence in 1982 to 1984 in the study population and in the rest of the Australian male population is examined in Section 4.7.

Chapter 5 discusses the relative cancer incidence rates in Chapter 4 for each site of cancer.

There are five appendices. The study protocol is reproduced at Appendix A. Appendix B describes the algorithms used for matching service and cancer registration records. It also shows the effect on the analysis of using different criteria for matching the study cohort with the cancer incidence records.

Appendix C presents technical statistical material. Section C.1 details the algorithm used to calculate the expected number of cancers, while Section C.2 assesses the robustness of the analyses to different assumptions when calculating these expected numbers. Section C.3 discusses how the data were organised for analysis. Other statistical issues are canvassed in Section C.4.

Members of the Scientific Advisory Committee to the Minister for Veterans' Affairs and project staff are listed in Appendices D and E respectively.

2 Aim of the study

The aim of this study is to assess and quantify any association between cancer incidence and exposure to dapsone and to Vietnam service among Australian Army servicemen who served in Vietnam during the Vietnam conflict.

The study cohort ('servicemen') consisted of all 115,407 males who served in the Australian Army for at least one year between 1 January 1965 and 1 March 1972. Identification of servicemen, those who had been exposed to dapsone, and those treated for malaria was done through Army records. Cancer incidence was determined by reference to State and Territory cancer registry records for the period 1972 to 1989, although not all registries had complete coverage for all of this period. Cancer incidence was examined for all cancers, and for 28 sites of cancer that included the cancers of a priori interest as well as groupings with more than 30 incident cases.

Cancer incidence rates, controlling for age and calendar year, were compared for several subgroups of the study cohort:

- dapsone-exposed Vietnam veterans compared with non-exposed Vietnam veterans (Section 4.2);
- for dapsone-exposed Vietnam veterans, those with the higher exposures compared with those with the lower exposures (Section 4.3);
- Vietnam veterans with malaria compared with other Vietnam veterans (Section 4.4);
- Vietnam veterans compared with non-veterans (Section 4.5);
- dapsone-exposed Vietnam veterans compared with non-veterans (Section 4.6);
- servicemen compared with other males in the Australian population (Section 4.7).

Where possible, these comparisons were made separately for National Service (conscript) and Australian Regular Army (volunteer) servicemen. Associations between malaria and cancer incidence were assessed because such associations could induce an apparent association between dapsone exposure and cancer incidence.

Cancer mortality was not directly assessed.

3 Data collection, collation and analysis

3.1 Identification of the study cohort

The primary records used for the study were four computer files obtained from the Soldier Career Management Agency. These files listed servicemen who served in the Australian Army at any time during the Vietnam conflict era. The first file showed Army number, service type (National Service or Australian Regular Army), full name and date of birth. For some servicemen, initials rather than forenames were available. For others, only the month and year of birth were available, rather than the full date of birth. These data deficiencies affected the development of the methodology for this study.

The other files, each indexed by Army number, covered aspects of service in Vietnam. For each Vietnam veteran, the postings file listed dates of service in Vietnam and the units in which service was undertaken.

3.2 Identification of servicemen who took dapsone or had malaria

The Army supplied data on when and where dapsone was used in Vietnam for prevention of malaria. These data were generally available day by day at the sub-unit organisational level. The dose of dapsone taken prophylactically by each Vietnam veteran was inferred from these data and from information from the postings file.

Records of servicemen treated for malaria in both Australian and some United States medical units were obtained from the Royal Australian Army Medical Corps and the Australian War Memorial. From knowledge of the dosage regimens used for treatment of malaria at various times, it was possible to infer total dosage of dapsone taken by servicemen with malaria.

A total dosage of dapsone was thus imputed for each serviceman. See Appendix A for details.

3.3 Identification of servicemen with cancer

The State cancer registries provided details of their cancer registrations for as much as possible of the period 1972 to 1989. Registrations for the Australian Capital Territory are included with the New South Wales data; those for the Northern Territory were not available for this study. With few exceptions, the cancer registrations showed full name and date of birth together with date of diagnosis and the cancer site coded according to the ninth revision of the International Classification of Diseases (ICD-9).

Where possible, records for servicemen and for cancer registrations were matched on full name and date of birth. Partial matches were also sought and assessed (Appendix B). The matching score and ICD-9 code for each serviceman identified as having a cancer was recorded.

3.4 Determination of the population at risk

As noted, the study cohort ('servicemen') consisted of all males who had served in the Australian Army for at least one year between 1 January 1965 and 1 March 1972. For each year between 1970 and 1989 the number of servicemen, classified by five factors, was tabulated. The factors were as follows:

- five-year age group (20–24, 25–29, 30–34, and so on);
- service type (National Service, Australian Regular Army);
- Vietnam service (Vietnam veteran, non-veteran);
- total cumulative dapsone dose (none, less than 2,000 milligrams, 2,000–3,999 milligrams, 4,000–5,999 milligrams, greater than 5,999 milligrams);
- treatment for malaria (malaria, no malaria).

This tabulation gives the denominator ('person-years at risk') for calculation of cancer incidence rates.

3.5 Potential risk factors

The study aims to assess whether potential risk factors, such as dapsone exposure, correlate with differential cancer incidence rates. But, to do this convincingly, it is important to take account of other factors already known to be associated with differential cancer incidence rates. If these other factors are differentially distributed in the groups being compared they will distort the estimated risk associated with the potential risk factors.

For example, cancer incidence rates are known to vary with age and calendar year. The age variation is well known from medical research. Giles et al. (1987) document age-specific variation in cancer incidence rates within the general Australian population. In most studies, the variation with calendar year occurs because people born in different years happen to have different age-specific cancer incidence rates. In this study, however, a more important consideration is that the data from each cancer registry were available for only some years. Besides, these data do not necessarily cover all cancers occurring within the nominal geographical region in each year.

Age and calendar year could be differentially distributed in the two groups being compared. Accordingly, all analyses in this report take account of these two variables. Appendix C shows that the conclusions of the analyses are robust to the coarseness of classification of these two variables.

The method of calculation of the expected numbers of cancers in different subgroups is unaffected by mortality in the cohort, provided the mortality is either small or depends only on age or year of birth, or both. The study cohort consists

predominantly of young adult men: 88 per cent of the cohort was younger than 45 years old in 1989. Moreover, mortality, at least of National Servicemen, is known to be less than that in the rest of the Australian male population (Adena et al. 1985).

3.6 Analysis of cancer incidence

The protocol identifies various sites of cancers that previous research suggests may be differentially distributed in various subgroups of servicemen. Table 3.1 lists the 29 categories of cancers for which separate analyses were conducted.

Most analyses in this report compare cancer incidence in two subgroups; for example, Section 4.2 compares cancer incidence among Vietnam veterans exposed to dapsone with that among Vietnam veterans not exposed to dapsone. The analyses are usually repeated for 29 sites of cancer, each of which is summarised on a single line in a table. In Section 4.2 the analyses are repeated for four different study populations: all Vietnam veterans (Table 4.6); Vietnam veterans aged less than 26 (Table 4.7); National Service Vietnam veterans (Table 4.8); and Australian Regular Army Vietnam veterans (Table 4.9).

Cancer incidence rates have not been compared directly. Instead, the observed number of incident cancer cases in each subgroup has been compared with the expected number of cases assuming equal incidence rates in the subgroups. The ratio of the two observed numbers of cancers divided by the ratio of the expected numbers of cancers is the relative cancer incidence rate.

A relative rate of 1 means that the cancer incidence rates are equal in the two groups. A relative rate of, say, 0.88 means that the cancer incidence rate in the first subgroup is 0.88 times that in the second subgroup.

A standard statistical assumption is that the observed number of cases has a Poisson distribution the mean of which is the expected number of cancer cases (Breslow & Day 1987). The Poisson assumption allows the closeness of the observed and expected numbers of cases to be assessed statistically. Breslow and Day describe in detail various aspects of Poisson regression modelling.

When there are two subgroups, Poisson regression modelling allows a 95 per cent confidence interval to be calculated for the relative cancer incidence rate. It also produces a test statistic for assessing whether the cancer incidence rates are equal in the two subgroups. If there is no difference in incidence, the test statistic has an asymptotic chi-square distribution with 1 degree of freedom. High values suggest a statistically significant difference.

Table 3.1 *ICD-9 codes and labels for sites of cancers analysed in this report*

ICD-9 code	Cancer site
140–208	All
140–146, 149	Oral
140	Lip
147	Nasopharyngeal
151	Stomach
153	Colon
154	Rectum
155	Primary liver
157	Pancreas
160	Nasal
161	Larynx
162	Lung
170–171	Soft tissue and other sarcomas
170	Bone
171	Connective tissue
172	Skin melanoma
185	Prostate
186	Testis
188	Bladder
189	Kidney
191	Brain
193	Thyroid
200, 202	Non-Hodgkin's lymphoma
200	Lympho- and reticulo-sarcoma
202	Other lymphoid and histocytic
201	Hodgkin's disease
204–208	Leukemia
205	Myelocytic leukemia
195–199	Site not specified

Note: The portion of the label used as a shortened label in later tables is shown in bold. Sites that are part of another site are indented; for example, lip cancers (ICD 140) are a subset of oral cancers (ICD 140–146, 149), which are a subset of all cancers (ICD 140–208).

Source: WHO (1978).

Box 3.1 An example of a typical analysis

As an example of a typical analysis, the first few (and the last) lines of Table 4.6 are as follows:

Site of cancer	Dapsone		No dapsone		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	247	263.5	262	245.5	0.88	(0.74, 1.05)	2.1
Oral	16	21.3	27	21.7	0.6	(0.3 , 1.1)	2.7

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$).

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

The analysis for 'All cancers' is summarised in a single line. The two subgroups are defined by exposure to dapsone.

Observed and expected cancer cases and the relative rate

Among Vietnam veterans (the study population indicated by the first line following the table), there were 509 (= 247 + 262) cancer cases. Of these, 247 were observed in dapsone-exposed Vietnam veterans and the other 262 were in unexposed Vietnam veterans. Assuming that these two subgroups had equal incidence rates, the algorithm in Section C.1 gives the expected number of cancers as 263.5 and 245.5 respectively in these two groups.

The relative cancer incidence rate is the ratio of the observed number of cancers divided by the ratio of the expected number of cancers. For 'All cancers' it is 0.88:

$$\frac{(247/262)}{(263.5/245.5)}$$

Calculation of a 95 per cent confidence interval for the relative rate

The maximum likelihood estimate of the standard error of the natural logarithm of the relative rate is 0.089:

$$\left(\frac{1}{247} + \frac{1}{262}\right)^{\frac{1}{2}}$$

An asymptotic 95 per cent confidence interval for the logarithm of the relative rate is (log (0.88) - 1.96 x 0.089) to (log (0.88) + 1.96 x 0.089); that is, -0.31 to 0.05. (The factor of 1.96 is the Normal multiplier for the standard error when producing 95 per cent confidence intervals.)

Therefore an asymptotic 95 per cent confidence interval for the relative rate is 0.74 to 1.05. This means that we are 95 per cent sure that the true relative rate is between 0.74 and 1.05: there is only a 5 per cent (1 in 20) chance that it will be less than 0.74 or greater than 1.05. This confidence interval means that the observed numbers of cancers are not inconsistent with equal cancer incidence rates in the two subgroups.

The asymptotic confidence intervals are inappropriate when there are too few cancer cases in one or both categories for which cancer incidence rates are being compared. Accordingly, exact binomial confidence intervals have been calculated when there are four or fewer cancers in one or both categories. If there are no cancers in a given category, the 95 per cent confidence interval is asymmetric but still has 95 per cent coverage.

Infinite estimates or upper confidence intervals are shown as '∞'. Where an upper confidence interval is finite but greater than 10, it is shown as '>10'.

Statistical test of equal incidence rates

The maximum likelihood test statistic is 2.1:

$$2 \times \left(247 \log\left(\frac{247}{263.5}\right) + 262 \log\left(\frac{262}{245.5}\right)\right)$$

This is less than 3.84, the 5 per cent value for a chi-square distribution with 1 degree of freedom, so the test is 'not statistically significant at the 5 per cent level'. This is often written in statistical shorthand as '$p > 0.05$'. The standard conclusion is that the observed and expected numbers of cancers are insufficiently discrepant to conclude that the cancer incidence rates differ between dapsone-exposed Vietnam veterans and those not exposed to dapsone.

Similar calculations can be done for 'Oral cancers', and this analysis is also summarised on a single line of the table. Table 4.6 has 29 lines corresponding to analyses for 29 different sites of cancer.

Dose–response analysis

For analysing the possible ordered relationship between cancer incidence and dapsone dose (Section 4.3), there are five subgroups: no dapsone exposure; total dapsone exposure of less than 2 grams; total exposure from 2 to 4 grams; total exposure from 4 to 6 grams; and total exposure over 6 grams. The general principles of a Poisson regression analysis are the same as for only two subgroups, although the calculations are more complex.

The estimated trends for cancer incidence with total dapsone dose are derived from a Poisson regression model. Given the observed and expected number of cases for the four dapsone-exposed subgroups, the regression model for the logarithm of the observed number is

logarithm of the expected number of cases
$+ \alpha$
$+ \beta \times$ total dapsone dose

where α and β are regression parameters that are to be estimated and the total dapsone dose is taken to be either 1, 3, 5 or 7 grams (for the four exposed subgroups). The dose–response estimates (see Table 4.11, for example) are given by $\exp(\beta)$. Asymptotic 95 per cent confidence intervals can be calculated from the estimated standard error of β, and a test statistic (which is asymptotically chi-square distributed with 1 degree of freedom) is also available.

This regression model excludes the subgroup of Vietnam veterans not exposed to dapsone, although the data from this group were used in the calculation of the expected number of cancers. This is a standard issue in bioassay, where the response (here, cancer incidence) may differ for unexposed persons compared with the extrapolation to zero dose among exposed persons. In these circumstances, it is appropriate and standard practice to estimate dose response among the exposed persons only.

4 Cancer incidence in different groups

4.1 Characteristics of the study population

A total of 115,407 men served in the Australian Army for at least one year during the Vietnam conflict era (1 January 1965 to 1 March 1972). Table 4.1 shows these servicemen classified by type of service—National Service (NS) or Australian Regular Army (ARA)—and year of birth. It also shows the same classification for Vietnam veterans and for dapsone-exposed Vietnam veterans. Table 4.2 shows these servicemen classified by type of service, service in Vietnam, total dapsone dose, and treatment for malaria.

For the 20 years of follow-up (1970 to 1989), the 'person-years at risk' for the servicemen can be calculated; for example, they can be estimated for the numbers of servicemen in Table 4.2 by multiplying the numbers by twenty.

Table 4.3 shows the number of cancer registrations for males, classified by State and calendar year of registration (1972 to 1989). For some years no registrations were available for some States; for other years not all cancers were registered or available (Figure 4.1). All cancer registrations were available for all States for only 1982, 1983 and 1984. The data for 1982 are the basis for the Australian cancer incidence rates published in Giles et al. (1987). Data for the Australian Capital Territory are included in the New South Wales data; data for the Northern Territory were unavailable.

Figure 4.1 follows overleaf

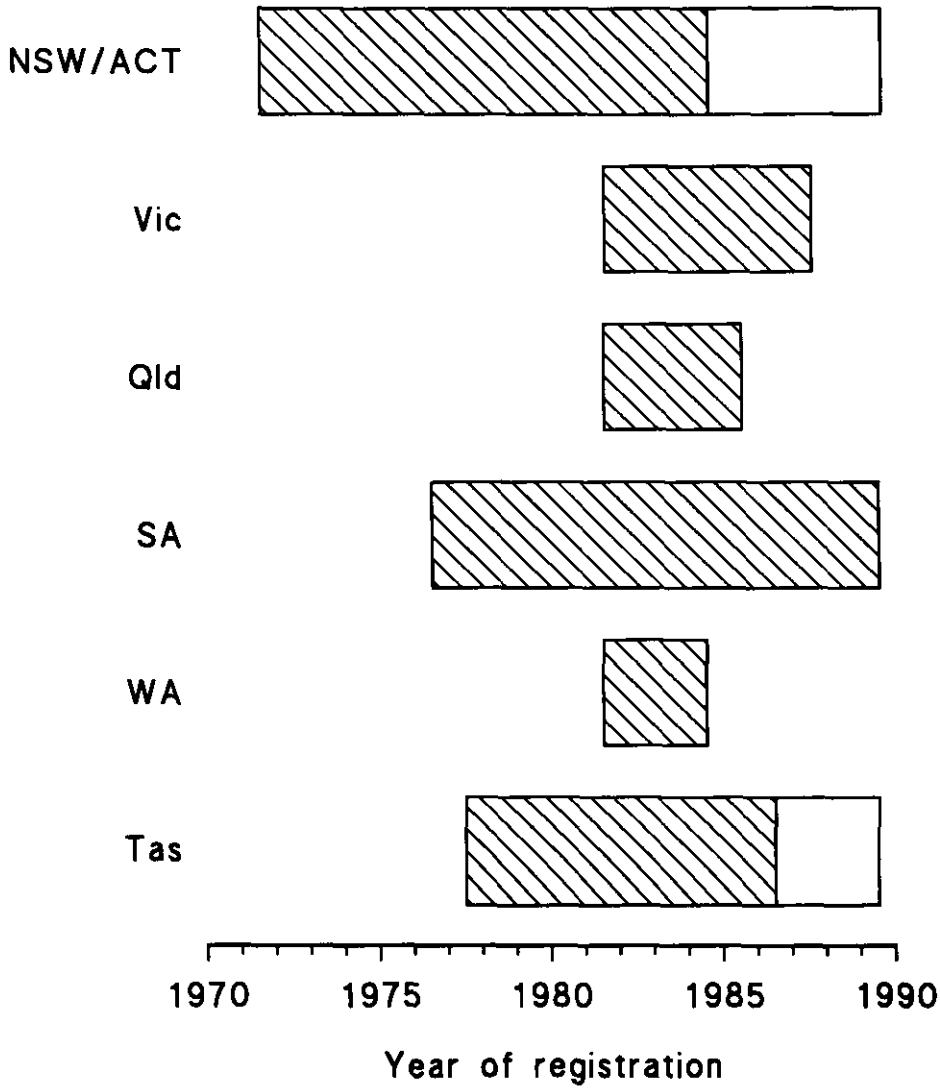

Figure 4.1 *Cancer registration data used by the study*

Note: Registration years with complete coverage are shown shaded; those with incomplete coverage are unshaded (see Table 4.3).

A total of 1,638 exact or partial matches between the records for servicemen and the cancer registration records were identified (see Appendix B for details). These cancer registrations were classified according to the three-digit code level of the ninth revision of the International Classification of Diseases (see WHO 1978). The 16 most frequently incident cancers are listed in Table 4.4.

Table 4.5 shows the person-years at risk and the number of servicemen identified as having cancer, classified by five-year age group (at the time that the cancer was registered) and service in Vietnam.

Table 4.1 reports five National Servicemen as born before 1910. These dates are presumably errors in the file of service particulars. The method of analysis ignores age groups for which there are no cancers, however, and no cancers were identified for any servicemen born before 1910. Correction of the dates of birth for these five servicemen would result in only small changes in the numbers of servicemen in younger age groups, and so would not affect the conclusions from the analysis.

4.2 Dapsone-exposed Vietnam veterans compared with other Vietnam veterans

All Vietnam veterans

Initially, all Vietnam veterans were considered as the study population. The subgroups of interest within the Vietnam veteran study population were those exposed to dapsone and those not exposed. The exposure group in these analyses is dapsone-exposed Vietnam veterans; the comparison group is Vietnam veterans not exposed to dapsone. Relative cancer incidence rates are expressed as the rate in dapsone-exposed Vietnam veterans compared with other Vietnam veterans.

No non-veteran was recorded as exposed to dapsone. The exposure group therefore comprises all Army personnel known to have taken dapsone.

It is arguable that the comparison group could include non-veterans. It is, however, plausible that selection for Vietnam service could have led to different cancer incidence patterns for Vietnam veterans and non-veterans. Non-veterans have therefore been excluded from the comparison group for this section. Section 4.6 uses non-veterans as a comparison group for dapsone-exposed Vietnam veterans.

Table 4.6 summarises the analyses of cancer incidence in dapsone-exposed Vietnam veterans and those not exposed to dapsone. Section 3.6 describes the statistical methods used.

Cancers for all sites combined

There were 509 cancer cases identified among the Vietnam veterans. The expected number of cancer cases among the dapsone-exposed Vietnam veterans and those not exposed to dapsone can be calculated assuming similar age groups and calendar-year-specific cancer incidence rates for both subgroups (see Section C.1). The expected number of cancer cases is 263.5 for the dapsone-exposed Vietnam veterans and 245.5 for Vietnam veterans not exposed to dapsone.

The corresponding observed numbers are 247 and 262 incident cancer cases. The estimated relative cancer incidence rate between these two groups is therefore 0.88; that is, the cancer incidence rate in dapsone-exposed Vietnam veterans is 88 per cent of that in other Vietnam veterans. A 95 per cent confidence interval for the relative rate, assuming Poisson variation, is 0.74 to 1.05. This includes unity, so the data are not inconsistent with equal cancer incidence rates for dapsone-exposed Vietnam veterans and those not exposed to dapsone. The maximum likelihood test statistic (2.1, $p > 0.05$) confirms this.

The first line of the body of Table 4.6 provides summary statistics for this analysis. Box 3.1 and Section C.4 provide further statistical discussion of the analysis.

Specific sites of cancer

Table 4.6 also summarises similar analyses for 28 specific sites of cancer. For most sites, the 95 per cent confidence interval includes unity, and so the data are not inconsistent with equal cancer incidence rates for dapsone-exposed Vietnam veterans and those not exposed to dapsone.

For no site of cancer is the lower end of the 95 per cent confidence interval above unity; that is, no confidence intervals suggest that cancer incidence is statistically significantly elevated in dapsone-exposed Vietnam veterans compared with other Vietnam veterans. With the exception of cancer of the prostate, no estimated relative cancer incidence rate is particularly high: all are less than 2.

For cancer of the prostate the confidence interval includes unity, even though the statistical test is nominally significant at the 5 per cent level. There were only two cancer cases in the unexposed subgroup, so the exact binomial confidence interval is preferred to the asymptotic test statistic. The confidence interval is wide, ranging from 0.9 to greater than 10. There is therefore little power to detect even a large elevated relative rate for prostatic cancer incidence.

The reported incidence of cancers with no site specified was similar regardless of dapsone exposure.

For two sites of cancer—cancer of the testis and skin melanoma—the upper end of the 95 per cent confidence interval is below unity; that is, the lower incidence rates for these sites among dapsone-exposed Vietnam veterans compared with other Vietnam veterans is nominally statistically significant. Nominally statistically significant test statistics without corroborating evidence from their exact 95 per cent confidence intervals occurred for cancer of the thyroid and for myelocytic leukemia. The nominal statistical significance of the asymptotic test statistics can be discounted as an artefact of there being few cancer cases of these sites.

Further analyses

It is possible that cancer incidence patterns could differ for National Service conscripts and for Australian Regular Army volunteers. These two groups of Vietnam veterans also have markedly different age profiles. Accordingly, the foregoing analyses were repeated for three different study populations drawn from the Vietnam veterans.

The first study population was Vietnam veterans aged less than 26 in 1970 (Table 4.7). This study population comprised almost all National Servicemen and the Australian Regular Army servicemen of similar age. The second study population was National Service Vietnam veterans (Table 4.8), and the third was Australian Regular Army Vietnam veterans (Table 4.9).

Vietnam veterans aged less than 26 in 1970

In the age-restricted study population, the overall cancer incidence rate for dapsone-exposed Vietnam veterans is estimated to be 0.73 times that for Vietnam veterans not exposed to dapsone. The 95 per cent confidence interval is from 0.57 to 0.94. Because there are fewer cancer cases in the restricted study population, this confidence interval is slightly wider than that for all cancers in Table 4.6 (0.74 to 1.05). It does, however, exclude unity, so dapsone exposure is nominally associated with reduced cancer incidence.

The estimated relative cancer incidence rates for cancer of the testis and skin melanoma are more extreme in the age-restricted study population. Both are statistically significantly less in the dapsone-exposed subgroup than in the subgroup not exposed to dapsone.

In the unrestricted study population, the only site of cancer for which there was a suggestion of a possible association with dapsone exposure was cancer of the prostate. This cancer is predominantly a cancer of elderly men, so it is not surprising that there are too few cases in the age-restricted study population for further analysis.

For no other site of cancer does the relative cancer incidence rate appear markedly higher in the dapsone-exposed subgroup compared with the unexposed subgroup. With the exception of prostatic cancer, all estimated relative rates are less than 2.

National Service Vietnam veterans

The relative rates among National Service Vietnam veterans are similar to those among the age-restricted study population. In particular, the 'All cancers' incidence rate among the dapsone-exposed subgroup is 0.68 times that among the unexposed subgroup. The confidence interval is from 0.50 to 0.92, so dapsone-exposed National Service Vietnam veterans experienced lower cancer incidence than National Servicemen who did not serve in Vietnam. The relative rates for cancer of the testis and skin melanoma are also statistically significantly lower in the dapsone-exposed subgroup.

Most estimated relative cancer incidence rates are less than 2. The three exceptions are cancer of the prostate, rectum cancer and other lymphoid and histocytic cancers. The last two estimates are between 2 and 3, with the lower end of the 95 per cent confidence interval well below unity (0.3 and 0.2 respectively) and the upper end well in excess of 10. The very wide confidence intervals for these cancers reflect the fact that very few incident cancer cases of these sites were identified.

Australian Regular Army Vietnam veterans

The 'All cancers' incidence rates are similar for the dapsone-exposed and unexposed subgroups among Australian Regular Army Vietnam veterans. The estimated relative rate is 1.00, with a 95 per cent confidence interval from 0.81 to 1.23. The only confidence interval that suggested different rates in the two subgroups was that for myelocytic leukemia. All leukemias and cancer of the thyroid had nominally statistically significant test statistics. The estimated cancer incidence rate for each of these sites of cancer was less in the dapsone-exposed subgroup than in the subgroup not exposed to dapsone.

Cancer incidence rates in the dapsone-exposed subgroup were more than twice those in the unexposed subgroup for eight sites of cancer. None of the rates were statistically significantly higher, and the confidence intervals for the relative rates were all wide and included unity. The eight sites were soft tissue and other sarcomas (and its constituent sites—bone and connective tissue), cancer of the prostate, cancer of the kidney, Non-Hodgkin's lymphoma (and one constituent site—lympho- and reticulo-sarcoma), and Hodgkin's disease.

The cancers found to have nominally statistically significant differences among the National Service study population—cancer of the testis and skin melanoma—have unexceptional relative rates in the Australian Regular Army study population. Conversely, the only cancer with a nominally statistically significant difference in the Australian Regular Army study population—myelocytic leukemia—had an unexceptional relative rate in the National Service study population. Yet the estimated rate for each of these cancer sites was less in the dapsone-exposed subgroup in both the study populations.

4.3 Trends in cancer incidence with total dapsone dose

If dapsone exposure were to lead to cancer in some servicemen, higher doses of dapsone would be expected to be associated with higher incidence than would be the case for those receiving lower doses of dapsone. The analyses in this section assess whether a dose–response relationship between total dapsone dose and cancer incidence exists.

Figure 4.2 shows the distribution of Vietnam veterans for five categories of total dapsone dose. Table 4.10 shows the observed and expected number of cancers among Vietnam veterans, classified by total dapsone dose. The dose–response estimates (Table 4.11) are the estimated average relative risk between dapsone-exposed Vietnam veterans differing by 5 grams in their exposure to dapsone. This estimate has been calculated by Poisson regression within the dapsone-exposed Vietnam veterans only.

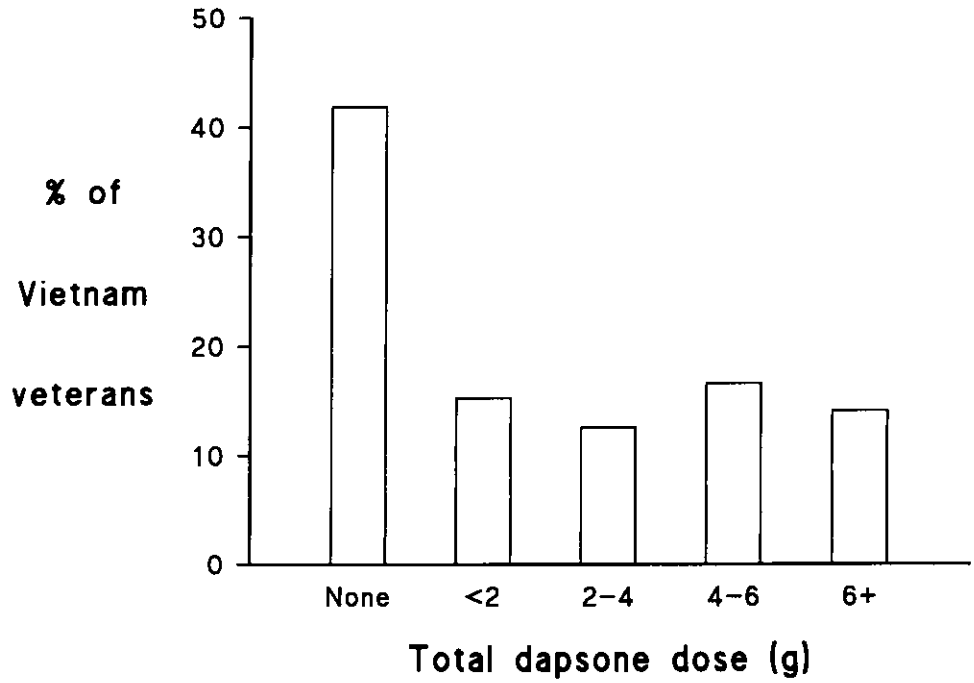

Figure 4.2 *Total dapsone exposure of Vietnam veterans*

This is a standard method of analysis of dose response in bio-assay. It allows for the possibility that the cancer risk associated with a zero dose of dapsone is not the same as that obtained by extrapolating to zero dose the trend seen in servicemen who received dapsone. Poisson regression also enables estimation of asymptotic 95 per cent confidence intervals for the average relative risk. The test statistic is an asymptotic chi-square test statistic with 1 degree of freedom.

Trend estimates are indeterminate for cancer sites with no cancer cases among the dapsone-exposed servicemen. They are also indeterminate for cancer sites where only one dapsone dose level has cancer cases, and this dose level is either 2–4 grams or 4–6 grams. The test statistic is also unavailable when there are none or only one dapsone dose level with cancer cases.

For no site of cancer is the dose response statistically significantly different from no trend in the cancer risk with increasing dapsone dose; that is, from a dose–response estimate of unity. Similar results hold when the study population is restricted to National Service Vietnam veterans (Tables 4.12 and 4.13) and to Australian Regular Army Vietnam veterans (Tables 4.14 and 4.15).

4.4 Vietnam veterans with malaria compared with other veterans

There were only eight cancer cases among the servicemen who contracted malaria. For none of the 29 sites of cancer was there a nominally statistically significant difference in the cancer incidence rates between Vietnam veterans who had had malaria and those who had not (Table 4.16).

The low number of cancer cases among the servicemen who had had malaria precludes further analysis (such as stratification by service type).

4.5 Cancer incidence among Vietnam veterans compared with non-veterans

The 'All cancers' incidence rates were similar for Vietnam veterans and non-veterans (Table 4.17). The estimated relative rate is 0.99, very close to equal incidence rates (for which the value would be exactly 1). The 95 per cent confidence interval is from 0.89 to 1.10, suggesting that even if there were a difference in the rates it must be small.

For no site of cancer does the 95 per cent confidence interval suggest that cancer incidence rates definitely differ between Vietnam veterans and non-veterans. For each site the test statistic is not statistically significant at the 5 per cent level. For all except two cancer sites the estimated relative rates are less than 2; the exceptions are nasopharyngeal cancer, with an estimated relative rate of 5.8 and 95 per cent confidence interval from 0.6 to greater than 10, and primary liver cancer, with an estimated relative rate of 3.0 and a 95 per cent confidence interval of 0.3 to greater than 10.

Analogous analyses were performed for the study population restricted to National Servicemen only. The overall cancer incidence rate was similar for Vietnam veterans compared with non-veterans (Table 4.18). The estimated relative rate was 1.05, with a 95 per cent confidence interval from 0.87 to 1.28. Three sites of cancers showed statistically significantly higher cancer incidence among National Service Vietnam veterans compared with non-veterans: cancer of the pancreas (estimated relative rate of 11 with a 95 per cent confidence interval from 1.4 to over 10); cancer of the lung (estimated relative rate of 3.9 with a 95 per cent confidence interval from 1.5 to 10); and cancer of the brain (estimated relative risk of 3.0 with a 95 per cent confidence interval from 1.1 to 8.2).

Corresponding analyses for the study population restricted to the Australian Regular Army showed no sites of cancer with statistically significantly higher cancer incidence rates for Vietnam veterans compared with non-veterans (Table 4.19).

4.6 Dapsone-exposed Vietnam veterans compared with non-veterans

For completeness, the study population was restricted to dapsone-exposed Vietnam veterans, with non-veterans as the comparison group. Analyses like those in Sections 4.2 and 4.5 were carried out for National Service and Australian Regular Army combined (Table 4.20), for National Service alone (Table 4.21) and for Australian Regular Army alone (Table 4.22). The estimated relative rates are as expected given the results for Section 4.2 (in which dapsone-exposed Vietnam veterans are compared with other Vietnam veterans) and Section 4.5 (in which Vietnam veterans are compared with non-veterans).

4.7 Vietnam conflict era servicemen compared with other Australian males

Cancer incidence among the study population in 1982 to 1984 was compared with that among Australian males in 1982. Age- and gender-specific cancer incidence rates for the Australian population in 1982 are given in Giles et al. (1987). This enables the expected number of cancers in the study population to be estimated for each site of cancer, except that rates for the subsites of non-Hodgkin's lymphoma were unavailable.

The analysis was restricted to incidence in 1982 to 1984 for two reasons. First, cancer incidence in this period should be comparable with that for Australia in 1982. Second, this was the longest period for which all cancer registries had complete registrations. In earlier and later years at least one registry had no data or only partial coverage of incident cases in its jurisdiction.

Tables 4.23 to 4.25 show the observed and expected numbers of cancers for the study cohort for 1982 to 1984. The estimated relative cancer incidence rate for the study cohort compared with the rest of the Australian male population is the ratio of these two numbers; it is also shown.

Confidence intervals for the estimated rate have been calculated using the Byar formula (Breslow & Day 1987, p. 69), which closely approximates the exact confidence intervals based on the Poisson distribution (Breslow & Day 1987, p. 71).

Maximum likelihood test statistics to assess whether the data are consistent with equal rates in the study cohort and the Australian male population are also given in the tables. These test statistics have an asymptotic chi-square distribution with 1 degree of freedom.

For all sites combined, there were similar numbers of observed and expected cancers. The relative rate was 1.05, with a 95 per cent confidence interval from 0.97 to 1.13 (Table 4.23). These data are consistent with the cancer incidence rates in the study cohort being similar to those in the Australian male population. This also means that the matching process between persons in the study cohort and the cancer registries appears to neither omit nor spuriously generate matches.

For most sites of cancer, the observed and expected cancers were similar, suggesting that cancer incidence rates in the study cohort between 1982 and 1984 were similar to those in the Australian male population (Table 4.23). For four sites of cancer, however, there were statistically significantly more cancers in the study cohort than expected given the incidence rates in the Australian male population. In descending order of relative incidence rates, these were as follows:

- larynx, with an estimated relative incidence rate of 1.7 and a 95 per cent confidence interval from 1.0 to 2.6;
- bladder, with an estimated relative incidence rate of 1.5 and a 95 per cent confidence interval from 1.1 to 2.0;
- oral, with an estimated relative incidence rate of 1.3 and a 95 per cent confidence interval from 1.0 to 1.7;
- skin melanoma, with an estimated relative incidence rate of 1.3 and a 95 per cent confidence interval from 1.0 to 1.5.

Among Vietnam veterans the higher incidence for bladder cancer was even more pronounced. For no other cancer site were there statistically significantly different incidence rates among Vietnam veterans compared with the Australian male population (Table 4.24).

There were no statistically significant differences in cancer incidence rates for dapsone-exposed Vietnam veterans compared with the Australian male population (Table 4.25).

4.8 Trends in cancer incidence with latency period

Relative cancer incidence rate with dapsone exposure

Of the 247 cancer cases among Vietnam veterans exposed to dapsone, 36 were registered before 1980, 88 between 1980 and 1984, and 123 in 1985 or later. Of the 262 cancer cases among Vietnam veterans not exposed to dapsone, 37, 90 and 135 respectively were registered in these three periods. The relative risk of cancer for dapsone-exposed Vietnam veterans compared with other Vietnam veterans was 0.85, 0.92 and 0.86 respectively for the three periods. These risks are not statistically significantly different from each other (chi-square test statistic = 0.1 for 2 degrees of freedom, $p > 0.5$).

For none of the 29 sites of cancer analysed in this report was there a statistically significant difference between these three periods in the relative cancer incidence rate for dapsone exposure. This held for all Vietnam veterans and for the Australian Regular Army and National Service subgroups separately.

About half (51 per cent) of all cancers were registered in 1985 or later. These cancers have a minimum of 13 years' latency between the latest possible dapsone exposure (March 1972) and registration of the cancer. Their maximum latency period is 24 years, latencies of up to 18 years being typical.

Relative cancer incidence rate with Vietnam service

Of the 509 cancer cases among Vietnam veterans, 73 were registered before 1980, 178 between 1980 and 1984, and 258 in 1985 or later. Of the 1,129 cancer cases among non-veterans, 188, 406 and 535 respectively were registered in these three periods. The relative risk of cancer for Vietnam veterans compared with non-veterans was 0.97, 0.97 and 1.02 respectively. These risks are not statistically significantly different from each other (chi-square test statistic = 0.2 for 2 degrees of freedom, $p > 0.5$).

For none of the 29 sites of cancer analysed in this report was there a statistically significant difference between the three periods in the relative cancer incidence rate for Vietnam service. This held for all servicemen and for the Australian Regular Army and National Service subgroups separately.

Table 4.1 *Number of servicemen, Vietnam veterans and dapsone-exposed Vietnam veterans, by type of service and year of birth*

	Dapsone-exposed Vietnam veterans		All Vietnam veterans		All servicemen		
Year of birth	NS	ARA	NS	ARA	NS	ARA	Total
1953	0	0	0	1	43	2,124	2,167
1952	0	118	0	173	1,159	3,842	5,001
1951	22	472	28	741	4,609	5,748	10,357
1950	344	901	500	1,201	4,742	4,519	9,261
1949	1,490	1,226	2,188	1,464	6,754	3,572	10,326
1948	2,729	1,284	3,328	1,710	7,718	3,288	11,006
1947	3,582	1,084	3,840	1,874	8,283	3,287	11,570
1946	2,394	909	3,562	1,790	8,019	3,056	11,075
1945	1,334	678	5,339	1,559	14,601	2,649	17,250
1944	1	575	2	1,247	2	2,316	2,318
1943	1	489	1	1,029	1	2,075	2,076
1942	0	412	0	892	1	1,826	1,827
1941	0	388	0	815	0	1,788	1,788
1940	0	334	0	714	0	1,636	1,636
1939	0	311	0	701	0	1,508	1,508
1938	0	244	0	552	2	1,277	1,279
1937	0	249	0	594	0	1,191	1,191
1936	0	211	0	496	1	1,013	1,014
1935	0	194	0	464	0	927	927
1930–34	0	735	0	1,670	0	3,660	3,660
1925–29	0	506	0	1,267	0	3,393	3,393
1920–24	0	189	0	446	0	2,256	2,256
1915–19	0	21	0	75	0	1,364	1,364
1910–14	0	1	0	9	0	849	849
Before 1910	0	0	2[a]	0	5[a]	303	308
Total	11,897	11,531	18,790	21,484	55,940	59,467	115,407

[a] These are presumably coding errors in the dates recorded on magnetic tape; these records do not affect the analyses in later sections.

Note: 'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 4.2 *Number of servicemen, by service type, service in Vietnam, total dapsone dose and treatment for malaria*

Service type	Veteran status	Dapsone dose (mg)	Malaria	Number
NS	Non-veteran	0	no	37,150
NS	Vietnam veteran	0	no	6,779
NS	Vietnam veteran	0	yes	114
NS	Vietnam veteran	1–1,999	no	3,106
NS	Vietnam veteran	1–1,999	yes	119
NS	Vietnam veteran	2,000–3,999	no	2,534
NS	Vietnam veteran	2,000–3,999	yes	82
NS	Vietnam veteran	4,000–5,999	no	3,399
NS	Vietnam veteran	4,000–5,999	yes	94
NS	Vietnam veteran	6,000+	no	2,539
NS	Vietnam veteran	6,000+	yes	24
ARA	Non-veteran	0	no	37,983
ARA	Vietnam veteran	0	no	9,785
ARA	Vietnam veteran	0	yes	168
ARA	Vietnam veteran	1–1,999	no	2,781
ARA	Vietnam veteran	1–1,999	yes	108
ARA	Vietnam veteran	2,000–3,999	no	2,325
ARA	Vietnam veteran	2,000–3,999	yes	82
ARA	Vietnam veteran	4,000–5,999	no	3,083
ARA	Vietnam veteran	4,000–5,999	yes	87
ARA	Vietnam veteran	6,000+	no	2,991
ARA	Vietnam veteran	6,000+	yes	74
Total				115,407

Note: 'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 4.3 *Number of cancer registrations for males, by State and calendar year of registration*

Year	New South Wales (and ACT)	Victoria	Queensland	Western Australia	South Australia	Tasmania
1972	4,405	-	-	-	-	-
1973	4,692	-	-	-	-	-
1974	5,135	-	-	-	-	-
1975	5,509	-	-	-	-	-
1976	6,053	-	-	-	-	-
1977	6,343	-	-	-	259	-
1978	6,709	-	-	-	321	564
1979	7,160	-	-	-	440	595
1980	7,592	-	-	-	590	685
1981	7,893	-	-	-	1,005	661
1982	8,358	6,710	4,641	1,813	2,202	661
1983	8,849	6,860	4,771	1,903	2,303	741
1984	9,058	7,139	4,833	1,913	2,428	725
1985	4,079[a]	7,281	5,189	-	2,554	745
1986	991[a]	7,246	-	-	2,540	750
1987	1,029[a]	7,460	-	-	2,841	776[a]
1988	836[a]	-	-	-	2,896	544[a]
1989	419[a]	-	-	-	3,002	183[a]
Total	95,110	42,696	19,434	5,629	23,381	7,630

[a] Incomplete coverage of incident cases.

Table 4.4 *Number of cancers identified in the study population as exact or partial matches, by ICD-9 classification*

ICD-9 code	Description	Number	Per cent
172	Skin melanoma	329	20.0
162	Lung	223	13.6
153	Colon	105	6.4
154	Rectum	86	5.3
186	Testis	83	5.1
188	Bladder	81	4.9
200, 202	Non-Hodgkin's lymphoma	75	4.6
140	Lip	66	4.0
185	Prostate	65	4.0
151	Stomach	45	2.7
189	Kidney	40	2.5
157	Pancreas	38	2.3
191	Brain	38	2.3
161	Larynx	33	2.0
201	Hodgkin's disease	33	2.0
205	Myelocytic leukemia	32	2.0
	Other specified site	214	13.1
195–199	Site not specified	52	3.2
140–208	Total	1,638	100.0

Table 4.5 *Incident cancer cases and person-years at risk, by Vietnam service and age group*

	Vietnam veterans		Non-veterans		All servicemen	
Age group	Cancers	At risk	Cancers	At risk	Cancers	At risk
15–19	0	1,118	2	25,742	2	26,860
20–24	6	59,722	16	182,745	22	242,467
25–29	21	157,175	60	303,832	81	461,007
30–34	54	176,134	122	325,421	176	501,555
35–39	118	186,514	191	312,242	309	498,756
40–44	97	135,475	108	165,597	205	301,072
45–49	58	42,620	74	54,396	132	97,016
50–54	56	25,001	88	40,716	144	65,717
55–59	54	13,710	120	33,801	174	47,511
60–64	34	6,163	141	26,618	175	32,781
65–69	9	1,575	108	17,404	117	18,979
70–74	2	235	71	9,528	73	9,763
75–79	0	28	28	3,880	28	3,908
80–84	0	10	0	705	0	715
85+	0	0	0	33	0	33
Total	509	805,480	1,129	1,502,660	1,638	2,308,140

Table 4.6 *Observed and expected cancers for National Service and Australian Regular Army Vietnam veterans of all ages, by dapsone exposure*

Site of cancer	Dapsone		No dapsone		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	247	263.5	262	245.5	0.88	(0.74 , 1.05)	2.1
Oral	16	21.3	27	21.7	0.6	(0.3 , 1.1)	2.7
Lip	9	12.2	13	9.8	0.6	(0.2 , 1.3)	1.9
Nasopharyngeal	2	2.3	2	1.7	0.8	(0.1 , >10)	0.1
Stomach	6	6.1	6	5.9	1.0	(0.3 , 3.0)	0.0
Colon	15	13.8	14	15.2	1.2	(0.6 , 2.4)	0.2
Rectum	12	11.1	12	12.9	1.2	(0.5 , 2.6)	0.1
Primary liver	1	1.5	2	1.5	0.5	(0.0 , 9.8)	0.3
Pancreas	7	5.8	6	7.2	1.4	(0.5 , 4.3)	0.4
Nasal	0	0.4	1	0.6	0.0	(0.0 , >10)	1.1
Larynx	1	2.6	5	3.4	0.3	(0.0 , 2.3)	2.0
Lung	28	27.3	31	31.7	1.1	(0.6 , 1.8)	0.0
Soft tissue	7	6.3	3	3.7	1.4	(0.3 , 8.3)	0.2
Bone	2	1.8	1	1.2	1.3	(0.1 , >10)	0.0
Connective tissue	5	4.5	2	2.5	1.4	(0.2 , >10)	0.2
Skin melanoma	56	67.9	65	53.1	0.7	(0.5 , 1.0)	4.7*
Prostate	7	3.9	2	5.1	4.5	(0.9 , >10)	4.4*
Testis	10	16.0	16	10.0	0.4	(0.2 , 0.9)	5.7*
Bladder	13	13.0	14	14.0	1.0	(0.5 , 2.1)	0.0
Kidney	6	5.2	6	6.8	1.3	(0.4 , 4.1)	0.2
Brain	11	9.5	6	7.5	1.4	(0.5 , 3.9)	0.5
Thyroid	0	1.5	3	1.5	0.0	(0.0 , 1.7)	4.1*
Non-H lymphoma	19	15.2	9	12.8	1.8	(0.8 , 3.9)	2.1
Lympho- & reticulo-	15	11.6	7	10.4	1.9	(0.8 , 4.7)	2.2
Other lymphoid	4	3.6	2	2.4	1.3	(0.2 , >10)	0.1
Hodgkin's disease	7	6.6	4	4.4	1.2	(0.3 , 5.5)	0.1
Leukemia	7	10.5	13	9.5	0.5	(0.2 , 1.2)	2.4
Myelocytic leukemia	3	6.4	9	5.6	0.3	(0.1 , 1.2)	4.0*
Site not specified	6	6.5	6	5.5	0.9	(0.3 , 2.7)	0.1

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$).

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.7 *Observed and expected cancers for National Service and Australian Regular Army Vietnam veterans aged less than 26 years in 1970, by dapsone exposure*

Site of cancer	Dapsone		No dapsone		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	137	156.1	117	97.9	0.73	(0.57, 0.94)	6.0*
Oral	11	10.1	5	5.9	1.3	(0.4 , 3.7)	0.2
Lip	9	8.8	5	5.2	1.1	(0.4 , 3.2)	0.0
Nasopharyngeal	2	1.9	1	1.1	1.2	(0.1 , >10)	0.0
Stomach	2	3.2	3	1.8	0.4	(0.0 , 3.2)	1.2
Colon	4	6.1	6	3.9	0.4	(0.1 , 1.8)	1.8
Rectum	5	4.2	2	2.8	1.7	(0.3 , >10)	0.4
Primary liver	0	0.6	1	0.4	0.0	(0.0 , >10)	2.0
Pancreas	4	3.7	4	4.3	1.1	(0.2 , 6.1)	0.0
Nasal	0		0		-		
Larynx	0	1.1	2	0.9	0.0	(0.0 , 3.1)	3.0
Lung	7	9.3	9	6.7	0.6	(0.2 , 1.5)	1.4
Soft tissue	5	5.4	3	2.6	0.8	(0.2 , 5.1)	0.1
Bone	1	1.4	1	0.6	0.4	(0.0 , >10)	0.3
Connective tissue	4	4.1	2	1.9	1.0	(0.1 , >10)	0.0
Skin melanoma	39	49.6	40	29.4	0.6	(0.4 , 0.9)	5.9*
Prostate	2	1.1	0	0.9	∞	(0.2 , ∞)	2.4
Testis	8	14.2	14	7.8	0.3	(0.1 , 0.8)	7.1**
Bladder	7	6.2	3	3.8	1.4	(0.3 , 8.4)	0.3
Kidney	1	2.2	4	2.8	0.3	(0.0 , 3.2)	1.3
Brain	9	7.3	3	4.7	1.9	(0.5 , >10)	1.0
Thyroid	0	0.6	1	0.4	0.0	(0.0 , >10)	2.0
Non-H lymphoma	12	10.0	5	7.0	1.7	(0.6 , 4.8)	1.0
Lympho- & reticulo-	8	6.5	3	4.5	1.9	(0.5 , >10)	0.9
Other lymphoid	4	3.5	2	2.5	1.4	(0.2 , >10)	0.2
Hodgkin's disease	5	4.9	2	2.1	1.1	(0.2 , >10)	0.0
Leukemia	6	6.2	4	3.8	0.9	(0.2 , 4.4)	0.0
Myelocytic leukemia	3	4.2	4	2.8	0.5	(0.1 , 2.9)	0.9
Site not specified	3	4.4	4	2.6	0.4	(0.1 , 2.6)	1.2

Population: National Service and Australian Regular Army Vietnam veterans less than 26 years old in 1970.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.8 *Observed and expected cancers for National Service Vietnam veterans, by dapsone exposure*

Site of cancer	Dapsone		No dapsone		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	83	98.7	80	64.3	0.68	(0.50 , 0.92)	6.2*
Oral	3	3.7	3	2.3	0.6	(0.1 , 4.6)	0.4
Lip	2	3.1	3	1.9	0.4	(0.0 , 3.6)	1.0
Nasopharyngeal	1	1.3	1	0.7	0.6	(0.0 , >10)	0.1
Stomach	2	3.3	3	1.7	0.3	(0.0 , 3.0)	1.4
Colon	3	3.9	4	3.1	0.6	(0.1 , 3.5)	0.5
Rectum	4	3.0	1	2.0	2.6	(0.3 , >10)	0.9
Primary liver	0		0		-		
Pancreas	4	3.1	3	3.9	1.7	(0.3 , >10)	0.4
Nasal	0		0		-		
Larynx	0	1.1	2	0.9	0.0	(0.0 , 3.1)	3.0
Lung	7	7.7	6	5.3	0.8	(0.3 , 2.4)	0.2
Soft tissue	3	3.4	2	1.6	0.7	(0.1 , 8.3)	0.2
Bone	1	1.4	1	0.6	0.4	(0.0 , >10)	0.3
Connective tissue	2	2.0	1	1.0	0.9	(0.0 , >10)	0.0
Skin melanoma	23	33.2	30	19.8	0.5	(0.3 , 0.8)	8.1**
Prostate	2	1.1	0	0.9	∞	(0.2 , ∞)	2.2
Testis	4	7.4	7	3.6	0.3	(0.1 , 1.1)	4.5*
Bladder	5	4.4	2	2.6	1.5	(0.2 , >10)	0.2
Kidney	0	1.3	3	1.7	0.0	(0.0 , 2.3)	3.4
Brain	6	4.9	2	3.1	1.9	(0.3 , >10)	0.6
Thyroid	0		0		-		
Non-H lymphoma	5	4.2	4	4.8	1.4	(0.3 , 7.1)	0.3
Lympho- & reticulo-	2	1.9	3	3.1	1.0	(0.1 , 9.1)	0.0
Other lymphoid	3	2.3	1	1.7	2.3	(0.2 , >10)	0.6
Hodgkin's disease	1	2.2	2	0.8	0.2	(0.0 , 3.6)	2.0
Leukemia	4	3.9	2	2.1	1.1	(0.2 , >10)	0.0
Myelocytic leukemia	3	3.1	2	1.9	0.9	(0.1 , >10)	0.0
Site not specified	2	3.1	3	1.9	0.4	(0.0 , 3.7)	0.9

Population: National Service Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.9 *Observed and expected cancers for Australian Regular Army Vietnam veterans, by dapsone exposure*

Site of cancer	Dapsone		No dapsone		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	164	164.0	182	182.0	1.00	(0.81 , 1.23)	0.0
Oral	13	17.5	24	19.5	0.6	(0.3 , 1.2)	2.3
Lip	7	8.9	10	8.1	0.6	(0.2 , 1.7)	0.9
Nasopharyngeal	1	1.0	1	1.0	1.1	(0.0 , >10)	0.0
Stomach	4	2.9	3	4.1	1.9	(0.3 , >10)	0.7
Colon	12	10.0	10	12.0	1.4	(0.6 , 3.4)	0.7
Rectum	8	8.2	11	10.8	1.0	(0.4 , 2.4)	0.0
Primary liver	1	1.5	2	1.5	0.5	(0.0 , 9.9)	0.3
Pancreas	3	2.5	3	3.5	1.4	(0.2 , >10)	0.2
Nasal	0	0.4	1	0.6	0	(0.0 , >10)	1.1
Larynx	1	1.6	3	2.4	0.5	(0.0 , 6.4)	0.4
Lung	21	19.7	25	26.3	1.1	(0.6 , 2.0)	0.2
Soft tissue	4	2.8	1	2.2	3.2	(0.3 , >10)	1.3
Bone	1	0.4	0	0.6	∞	(0.1 , ∞)	1.6
Connective tissue	3	2.3	1	1.7	2.2	(0.2 , >10)	0.5
Skin melanoma	33	34.9	35	33.1	0.9	(0.6 , 1.4)	0.2
Prostate	5	2.8	2	4.2	3.7	(0.6 , >10)	2.8
Testis	6	8.5	9	6.5	0.5	(0.2 , 1.4)	1.7
Bladder	8	8.7	12	11.3	0.9	(0.4 , 2.1)	0.1
Kidney	6	3.9	3	5.1	2.7	(0.6 , >10)	2.1
Brain	5	4.4	4	4.6	1.3	(0.3 , 6.6)	0.2
Thyroid	0	1.5	3	1.5	0.0	(0.0 , 1.8)	4.1*
Non-H lymphoma	14	10.5	5	8.5	2.3	(0.8 , 6.3)	2.8
Lympho- & reticulo-	13	9.3	4	7.7	2.7	(0.8 , >10)	3.4
Other lymphoid	1	1.2	1	0.8	0.7	(0.0 , >10)	0.1
Hodgkin's disease	6	4.4	2	3.6	2.5	(0.4 , >10)	1.4
Leukemia	3	6.6	11	7.4	0.3	(0.1 , 1.2)	3.9*
Myelocytic leukemia	0	3.3	7	3.7	0.0	(0.0 , 0.6)	9.1**
Site not specified	4	3.3	3	3.7	1.5	(0.2 , 9.9)	0.2

Population: Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.10 *Observed and expected cancers for National Service and Australian Regular Army Vietnam veterans, by level of dapsone exposure*

Site of cancer		Total dapsone dose (g)				
		None	0–2	2–4	4–6	6+
All	Obs	262	52	63	69	63
	Exp	245.5	68.3	56.8	70.3	68.1
Oral	Obs	27	3	5	5	3
	Exp	21.7	5.5	4.6	5.5	5.8
Lip	Obs	13	0	2	5	2
	Exp	9.8	3.1	2.6	3.4	3.2
Nasopharyngeal	Obs	2	0	2	0	0
	Exp	1.7	0.6	0.5	0.6	0.6
Stomach	Obs	6	2	1	2	1
	Exp	5.9	1.5	1.3	1.6	1.6
Colon	Obs	14	1	7	4	3
	Exp	15.2	3.6	3.0	3.5	3.7
Rectum	Obs	12	1	3	4	4
	Exp	12.9	2.9	2.4	2.7	3.1
Primary liver	Obs	2	0	0	1	0
	Exp	1.5	0.4	0.3	0.4	0.4
Pancreas	Obs	6	3	1	2	1
	Exp	7.2	1.5	1.3	1.3	1.7
Nasal	Obs	1	0	0	0	0
	Exp	0.6	0.1	0.1	0.1	0.1
Larynx	Obs	5	1	0	0	0
	Exp	3.4	0.7	0.6	0.6	0.7
Lung	Obs	31	6	6	6	10
	Exp	31.7	7.1	5.9	6.8	7.5
Soft tissue	Obs	3	3	0	1	3
	Exp	3.7	1.6	1.3	1.9	1.5
Bone	Obs	1	1	0	0	1
	Exp	1.2	0.5	0.4	0.6	0.4
Connective tissue	Obs	2	2	0	1	2
	Exp	2.5	1.1	1.0	1.3	1.1
Skin melanoma	Obs	65	12	13	16	15
	Exp	53.1	17.6	14.7	18.9	16.8
Prostate	Obs	2	4	0	1	2
	Exp	5.1	1.0	0.9	0.9	1.2
Testis	Obs	16	1	1	5	3
	Exp	10.0	4.3	3.4	4.8	3.7

Table 4.10 (continued) *Observed and expected cancers for National Service and Australian Regular Army Vietnam veterans, by level of dapsone exposure*

Site of cancer		Total dapsone dose (g)				
		None	0–2	2–4	4–6	6+
Bladder	Obs	14	1	4	3	5
	Exp	14.0	3.3	2.8	3.3	3.6
Kidney	Obs	6	0	5	1	0
	Exp	6.8	1.4	1.2	1.2	1.4
Brain	Obs	6	3	2	4	2
	Exp	7.5	2.4	2.0	2.7	2.4
Thyroid	Obs	3	0	0	0	0
	Exp	1.5	0.4	0.3	0.4	0.4
Non-H lymphoma	Obs	9	6	7	4	2
	Exp	12.8	4.2	3.3	4.2	3.5
Lympho- & reticulo-	Obs	7	6	5	2	2
	Exp	10.4	3.3	2.5	3.2	2.7
Other lymphoid	Obs	2	0	2	2	0
	Exp	2.4	0.9	0.8	1.1	0.8
Hodgkin's disease	Obs	4	0	4	2	1
	Exp	4.4	1.8	1.4	1.9	1.5
Leukemia	Obs	13	2	0	2	3
	Exp	9.5	2.6	2.2	2.8	2.8
Myelocytic leukemia	Obs	9	1	0	2	0
	Exp	5.6	1.6	1.4	1.7	1.7
Site not specified	Obs	6	0	2	2	2
	Exp	5.5	1.7	1.4	1.8	1.6

Population: National Service and Australian Regular Army servicemen who served in Vietnam.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in each exposure group.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.11 *Estimated dose response (multiplicative change in relative risk for a 5 gram higher dapsone dose) for National Service and Australian Regular Army dapsone-exposed servicemen*

Site of cancer	Dose response	95% confidence interval	Test statistic
All	1.1	(0.8 , 1.5)	0.6
Oral	0.9	(0.3 , 2.7)	0.0
Lip	2.6	(0.5 , >10)	1.5
Nasopharyngeal	0.3	(0.0 , 8.7)	0.5
Stomach	0.7	(0.1 , 3.9)	0.2
Colon	1.1	(0.4 , 3.4)	0.1
Rectum	2.1	(0.6 , 7.6)	1.3
Primary liver	2.4	(0.0 , >10)	0.1
Pancreas	0.5	(0.1 , 2.4)	0.8
Nasal	-		
Larynx	0.0	(0.0 , ∞)	-
Lung	1.4	(0.6 , 3.2)	0.6
Soft tissue	1.1	(0.2 , 5.9)	0.0
Bone	1.1	(0.0 , >10)	0.0
Connective tissue	1.1	(0.2 , 8.1)	0.0
Skin melanoma	1.2	(0.7 , 2.2)	0.4
Prostate	0.4	(0.1 , 2.3)	0.9
Testis	3.0	(0.7 , >10)	2.2
Bladder	2.1	(0.6 , 7.3)	1.3
Kidney	0.5	(0.1 , 3.1)	0.5
Brain	0.9	(0.2 , 3.2)	0.1
Thyroid	-		
Non-H lymphoma	0.5	(0.2 , 1.4)	1.9
Lympho- & reticulo-	0.4	(0.1 , 1.3)	2.5
Other lymphoid	1.0	(0.1 , 9.2)	0.0
Hodgkin's disease	1.2	(0.2 , 6.6)	0.1
Leukemia	1.8	(0.3 , 9.9)	0.5
Myelocytic leukemia	0.7	(0.1 , 8.1)	0.1
Site not specified	2.7	(0.4 , >10)	1.1

Population: Australian Regular Army and National Service servicemen who served in Vietnam.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in each exposure group.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

Test statistic is for dose response being consistent with no effect.

Table 4.12 *Observed and expected cancers for National Service Vietnam veterans, by level of dapsone exposure*

Site of cancer		Total dapsone dose (g)				
		None	0–2	2–4	4–6	6+
All	Obs	80	22	17	24	20
	Exp	64.3	26.4	21.7	28.8	21.8
Oral	Obs	3	1	1	1	0
	Exp	2.3	0.9	0.8	1.1	0.9
Lip	Obs	3	0	1	1	0
	Exp	1.9	0.8	0.7	0.9	0.7
Nasopharyngeal	Obs	1	0	1	0	0
	Exp	0.7	0.3	0.3	0.4	0.3
Stomach	Obs	3	1	0	1	0
	Exp	1.7	0.9	0.7	1.0	0.7
Colon	Obs	4	0	3	0	0
	Exp	3.1	1.0	0.9	1.1	1.0
Rectum	Obs	1	0	1	1	2
	Exp	2.0	0.8	0.7	0.8	0.7
Primary liver	Obs	0	0	0	0	0
	Exp					
Pancreas	Obs	3	2	0	1	1
	Exp	3.9	0.9	0.7	0.7	0.8
Nasal	Obs	0	0	0	0	0
	Exp					
Larynx	Obs	2	0	0	0	0
	Exp	0.9	0.5	0.3	0.3	0.2
Lung	Obs	6	2	1	2	2
	Exp	5.3	2.1	1.7	2.2	1.8
Soft tissue	Obs	2	1	0	0	2
	Exp	1.6	0.9	0.7	1.1	0.7
Bone	Obs	1	0	0	0	1
	Exp	0.6	0.4	0.3	0.5	0.2
Connective tissue	Obs	1	1	0	0	1
	Exp	1.0	0.5	0.4	0.6	0.5
Skin melanoma	Obs	30	5	6	5	7
	Exp	19.8	8.6	7.3	9.8	7.5
Prostate	Obs	0	1	0	1	0
	Exp	0.9	0.3	0.3	0.3	0.3
Testis	Obs	7	1	0	3	0
	Exp	3.6	2.2	1.6	2.3	1.4

Table 4.12 (continued) *Observed and expected cancers for National Service Vietnam veterans, by level of dapsone exposure*

Site of cancer		Total dapsone dose (g)				
		None	0–2	2–4	4–6	6+
Bladder	Obs	2	1	1	1	2
	Exp	2.6	1.1	1.0	1.3	1.1
Kidney	Obs	3	0	0	0	0
	Exp	1.7	0.4	0.3	0.3	0.3
Brain	Obs	2	3	1	1	1
	Exp	3.1	1.4	1.1	1.5	1.0
Thyroid	Obs	0	0	0	0	0
	Exp					
Non-H lymphoma	Obs	4	2	1	2	0
	Exp	4.8	1.2	0.9	1.2	0.9
Lympho- & reticulo-	Obs	3	2	0	0	0
	Exp	3.1	0.6	0.4	0.5	0.5
Other lymphoid	Obs	1	0	1	2	0
	Exp	1.7	0.7	0.5	0.7	0.4
Hodgkin's disease	Obs	2	0	1	0	0
	Exp	0.8	0.6	0.5	0.7	0.4
Leukemia	Obs	2	1	0	2	1
	Exp	2.1	1.0	0.8	1.2	0.9
Myelocytic leukemia	Obs	2	1	0	2	0
	Exp	1.9	0.8	0.7	0.9	0.7
Site not specified	Obs	3	0	0	1	1
	Exp	1.9	0.8	0.7	0.9	0.6

Population: National Service servicemen who served in Vietnam.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in each exposure group.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.13 *Estimated dose response (multiplicative change in relative risk for a 5 gram higher dapsone dose) for National Service dapsone-exposed servicemen*

Site of cancer	Dose response	95% confidence interval	Test statistic
All	1.1	(0.7 , 1.8)	0.1
Oral	0.3	(0.0 , 4.9)	0.7
Lip	1.0	(0.0 , >10)	0.0
Nasopharyngeal	0.4	(0.0 , >10)	0.2
Stomach	0.4	(0.0 , 10)	0.4
Colon	0.3	(0.0 , 4.9)	0.7
Rectum	5.7	(0.4 , >10)	2.0
Primary liver	-		
Pancreas	0.7	(0.1 , 6.2)	0.1
Nasal	-		
Larynx	-		
Lung	1.2	(0.2 , 6.5)	0.1
Soft tissue	3.4	(0.2 , >10)	0.8
Bone	∞	(0.0 , ∞)	-
Connective tissue	0.9	(0.0 , >10)	0.0
Skin melanoma	1.3	(0.5 , 3.3)	0.3
Prostate	0.3	(0.0 , 8.0)	0.5
Testis	1.3	(0.1 , >10)	0.1
Bladder	1.7	(0.2 , >10)	0.3
Kidney	-		
Brain	0.4	(0.1 , 2.7)	1.0
Thyroid	-		
Non-H lymphoma	0.4	(0.1 , 3.4)	0.7
Lympho- & reticulo-	0.0	(0.0 , ∞)	-
Other lymphoid	1.9	(0.1 , >10)	0.2
Hodgkin's disease	0.4	(0.0 , >10)	0.1
Leukemia	1.7	(0.2 , >10)	0.2
Myelocytic leukemia	0.7	(0.1 , 9.2)	0.1
Site not specified	>10	(0.2 , ∞)	2.2

Population: National Service servicemen who served in Vietnam.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in each exposure group.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

Test statistic is for dose response being consistent with no effect.

Table 4.14 *Observed and expected cancers for Australian Regular Army Vietnam veterans, by level of dapsone exposure*

Site of cancer		Total dapsone dose (g)				
		None	0–2	2–4	4–6	6+
All	Obs	182	30	46	45	43
	Exp	182.0	41.4	34.9	41.6	46.2
Oral	Obs	24	2	4	4	3
	Exp	19.5	4.4	3.7	4.4	5.0
Lip	Obs	10	0	1	4	2
	Exp	8.1	2.2	1.8	2.4	2.5
Nasopharyngeal	Obs	1	0	1	0	0
	Exp	1.0	0.2	0.2	0.2	0.3
Stomach	Obs	3	1	1	1	1
	Exp	4.1	0.7	0.6	0.6	0.9
Colon	Obs	10	1	4	4	3
	Exp	12.0	2.5	2.2	2.4	2.9
Rectum	Obs	11	1	2	3	2
	Exp	10.8	2.1	1.8	1.9	2.4
Primary liver	Obs	2	0	0	1	0
	Exp	1.5	0.4	0.3	0.4	0.4
Pancreas	Obs	3	1	1	1	0
	Exp	3.5	0.6	0.5	0.5	0.8
Nasal	Obs	1	0	0	0	0
	Exp	0.6	0.1	0.1	0.1	0.1
Larynx	Obs	3	1	0	0	0
	Exp	2.4	0.4	0.3	0.3	0.5
Lung	Obs	25	4	5	4	8
	Exp	26.3	5.1	4.3	4.7	5.7
Soft tissue	Obs	1	2	0	1	1
	Exp	2.2	0.7	0.6	0.8	0.8
Bone	Obs	0	1	0	0	0
	Exp	0.6	0.1	0.1	0.1	0.1
Connective tissue	Obs	1	1	0	1	1
	Exp	1.7	0.6	0.5	0.6	0.6
Skin melanoma	Obs	35	7	7	11	8
	Exp	33.1	8.8	7.4	9.3	9.3
Prostate	Obs	2	3	0	0	2
	Exp	4.2	0.7	0.6	0.6	0.8
Testis	Obs	9	0	1	2	3
	Exp	6.5	2.1	1.7	2.4	2.3

Table 4.14 (continued) *Observed and expected cancers for Australian Regular Army Vietnam veterans, by level of dapsone exposure*

Site of cancer		Total dapsone dose (g)				
		None	0–2	2–4	4–6	6+
Bladder	Obs	12	0	3	2	3
	Exp	11.3	2.2	1.9	2.1	2.5
Kidney	Obs	3	0	5	1	0
	Exp	5.1	1.0	0.8	0.9	1.1
Brain	Obs	4	0	1	3	1
	Exp	4.6	1.1	0.9	1.1	1.3
Thyroid	Obs	3	0	0	0	0
	Exp	1.5	0.4	0.3	0.4	0.4
Non-H lymphoma	Obs	5	4	6	2	2
	Exp	8.5	2.7	2.2	3.0	2.6
Lympho- & reticulo-	Obs	4	4	5	2	2
	Exp	7.7	2.4	2.0	2.7	2.3
Other lymphoid	Obs	1	0	1	0	0
	Exp	0.8	0.3	0.2	0.3	0.3
Hodgkin's disease	Obs	2	0	3	2	1
	Exp	3.6	1.1	0.9	1.2	1.2
Leukemia	Obs	11	1	0	0	2
	Exp	7.4	1.6	1.4	1.6	2.0
Myelocytic leukemia	Obs	7	0	0	0	0
	Exp	3.7	0.8	0.7	0.8	1.0
Site not specified	Obs	3	0	2	1	1
	Exp	3.7	0.8	0.7	0.8	1.0

Population: Australian Regular Army servicemen who served in Vietnam.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in each exposure group.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.15 *Estimated dose response (multiplicative change in relative risk for a 5 gram higher dapsone dose) for Australian Regular Army dapsone-exposed servicemen*

Site of cancer	Dose response	95% confidence interval	Test statistic
All	1.1	(0.8 , 1.5)	0.3
Oral	1.1	(0.3 , 3.5)	0.0
Lip	3.3	(0.5 , >10)	1.8
Nasopharyngeal	0.3	(0.0 , >10)	0.2
Stomach	0.9	(0.1 , 7.2)	0.0
Colon	1.4	(0.4 , 4.9)	0.3
Rectum	1.4	(0.3 , 6.5)	0.2
Primary liver	2.1	(0.0 , >10)	0.1
Pancreas	0.3	(0.0 , 4.3)	0.8
Nasal	-		
Larynx	0.0	(0.0 , ∞)	-
Lung	1.5	(0.6 , 3.8)	0.7
Soft tissue	0.5	(0.1 , 4.6)	0.4
Bone	0.0	(0.0 , ∞)	-
Connective tissue	1.2	(0.1 , >10)	0.0
Skin melanoma	1.1	(0.5 , 2.4)	0.1
Prostate	0.5	(0.1 , 3.5)	0.5
Testis	6.0	(0.6 , >10)	3.0
Bladder	2.4	(0.5 , >10)	1.2
Kidney	0.5	(0.1 , 2.8)	0.7
Brain	2.3	(0.3 , >10)	0.7
Thyroid	-		
Non-H lymphoma	0.5	(0.1 , 1.5)	1.7
Lympho- & reticulo-	0.5	(0.1 , 1.6)	1.4
Other lymphoid	0.3	(0.0 , >10)	0.3
Hodgkin's disease	1.2	(0.2 , 7.3)	0.1
Leukemia	2.2	(0.2 , >10)	0.4
Myelocytic leukemia	-		
Site not specified	1.4	(0.2 , >10)	0.1

Population: Australian Regular Army servicemen who served in Vietnam.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in each exposure group.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

Test statistic is for dose response being consistent with no effect.

Table 4.16 *Observed and expected cancers for National Service and Australian Regular Army Vietnam veterans of all ages, by whether the serviceman had contracted malaria while in Vietnam*

Site of cancer	Malaria		No malaria		Relative rate	95% confidence interval
	Obs	Exp	Obs	Exp		
All	8	9.8	501	499.2	0.8	(0.4 , 1.6)
Oral	0	0.8	43	42.2	0.0	(0.0 , 3.7)
Lip	0	0.5	22	21.5	0.0	(0.0 , 5.7)
Nasopharyngeal	0	0.1	4	3.9	0.0	(0.0 , >10)
Stomach	0	0.2	12	11.8	0.0	(0.0 , >10)
Colon	2	0.4	27	28.6	5.2	(0.6 , >10)
Rectum	1	0.4	23	23.6	2.5	(0.1 , >10)
Primary liver	0	0.1	3	2.9	0.0	(0.0 , >10)
Pancreas	0	0.3	13	12.7	0.0	(0.0 , >10)
Nasal	0	0.0	1	1.0	0.0	(0.0 , >10)
Larynx	0	0.1	6	5.9	0.0	(0.0 , >10)
Lung	0	0.9	59	58.1	0.0	(0.0 , 3.2)
Soft tissue	0	0.2	10	9.8	0.0	(0.0 , >10)
Bone	0	0.1	3	2.9	0.0	(0.0 , >10)
Connective tissue	0	0.2	7	6.8	0.0	(0.0 , >10)
Skin melanoma	5	2.7	116	118.3	1.9	(0.8 , 4.7)
Prostate	0	0.2	9	8.8	0.0	(0.0 , >10)
Testis	0	0.6	26	25.4	0.0	(0.0 , 5.1)
Bladder	0	0.5	27	26.5	0.0	(0.0 , 6.6)
Kidney	0	0.3	12	11.7	0.0	(0.0 , >10)
Brain	0	0.4	17	16.6	0.0	(0.0 , 8.1)
Thyroid	0	0.1	3	2.9	0.0	(0.0 , >10)
Non-H lymphoma	0	0.6	28	27.4	0.0	(0.0 , 5.6)
Lympho- & reticulo-	0	0.4	22	21.6	0.0	(0.0 , 7.8)
Other lymphoid	0	0.2	6	5.8	0.0	(0.0 , >10)
Hodgkin's disease	0	0.2	11	10.8	0.0	(0.0 , >10)
Leukemia	0	0.4	20	19.6	0.0	(0.0 , 8.5)
Myelocytic leukemia	0	0.2	12	11.8	0.0	(0.0 , >10)
Site not specified	0	0.2	12	11.8	0.0	(0.0 , >10)

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

The relative rate compares incidence among those who contracted malaria and those who did not.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.17 *Observed and expected cancers for National Service and Australian Regular Army servicemen of all ages, by service in Vietnam*

Site of cancer	Vietnam		No Vietnam		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	509	511.3	1129	1126.7	0.99	(0.89 , 1.10)	0.0
Oral	43	43.9	84	83.1	1.0	(0.7 , 1.4)	0.0
Lip	22	23.9	44	42.1	0.9	(0.5 , 1.5)	0.2
Nasopharyngeal	4	2.0	1	3.0	5.8	(0.6 , >10)	3.2
Stomach	12	13.2	33	31.8	0.9	(0.5 , 1.7)	0.2
Colon	29	29.5	76	75.5	1.0	(0.6 , 1.5)	0.0
Rectum	24	25.2	62	60.8	0.9	(0.6 , 1.5)	0.1
Primary liver	3	1.7	2	3.3	3.0	(0.3 , >10)	1.5
Pancreas	13	10.2	25	27.8	1.4	(0.7 , 2.8)	1.0
Nasal	1	1.8	3	2.2	0.4	(0.0 , 5.3)	0.6
Larynx	6	8.5	27	24.5	0.6	(0.3 , 1.6)	1.0
Lung	59	63.5	164	159.5	0.9	(0.7 , 1.2)	0.5
Soft tissue	10	10.2	19	18.8	1.0	(0.4 , 2.1)	0.0
Bone	3	3.5	7	6.5	0.8	(0.1 , 3.5)	0.1
Connective tissue	7	6.7	12	12.3	1.1	(0.4 , 2.7)	0.0
Skin melanoma	121	113.6	208	215.4	1.1	(0.9 , 1.4)	0.7
Prostate	9	9.1	56	55.9	1.0	(0.5 , 2.0)	0.0
Testis	26	31.0	57	52.0	0.8	(0.5 , 1.2)	1.3
Bladder	27	24.5	54	56.5	1.2	(0.7 , 1.8)	0.4
Kidney	12	12.1	28	27.9	1.0	(0.5 , 1.9)	0.0
Brain	17	12.7	21	25.3	1.6	(0.9 , 3.1)	2.1
Thyroid	3	3.4	8	7.6	0.9	(0.1 , 3.5)	0.1
Non-H lymphoma	28	26.2	47	48.8	1.1	(0.7 , 1.8)	0.2
Lympho- & reticulo-	22	17.0	25	30.0	1.6	(0.9 , 2.8)	2.2
Other lymphoid	6	9.2	22	18.8	0.6	(0.2 , 1.4)	1.8
Hodgkin's disease	11	10.5	22	22.5	1.1	(0.5 , 2.2)	0.0
Leukemia	20	18.6	32	33.4	1.1	(0.6 , 2.0)	0.2
Myelocytic leukemia	12	11.6	20	20.4	1.0	(0.5 , 2.1)	0.0
Site not specified	12	15.6	40	36.4	0.7	(0.4 , 1.3)	1.3

Population: National Service and Australian Regular Army servicemen.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

Relative rate compares incidence among Vietnam veterans with that among non-veterans.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.18 *Observed and expected cancers for National Service servicemen, by service in Vietnam*

Site of cancer	Vietnam		No Vietnam		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	163	157.5	290	295.5	1.05	(0.87 , 1.28)	0.3
Oral	6	10.7	24	19.3	0.5	(0.2 , 1.1)	3.5
Lip	5	8.7	20	16.3	0.5	(0.2 , 1.2)	2.7
Nasopharyngeal	2	0.8	0	1.2	∞	(0.4 , ∞)	3.6
Stomach	5	3.6	5	6.4	1.8	(0.5 , 6.2)	0.9
Colon	7	8.7	16	14.3	0.7	(0.3 , 1.8)	0.5
Rectum	5	5.5	11	10.5	0.9	(0.3 , 2.5)	0.1
Primary liver	0		0		-		
Pancreas	7	3.1	1	4.9	11.0	(1.4 , >10)	8.0**
Nasal	0	0.8	2	1.2	0.0	(0.0 , 4.9)	2.1
Larynx	2	1.3	2	2.7	2.2	(0.2 , >10)	0.6
Lung	13	6.8	6	12.2	3.9	(1.5 , 10)	8.3**
Soft tissue	5	5.4	10	9.6	0.9	(0.3 , 2.6)	0.1
Bone	2	1.9	3	3.1	1.1	(0.1 , 9.9)	0.0
Connective tissue	3	3.6	7	6.4	0.8	(0.1 , 3.3)	0.2
Skin melanoma	53	50.3	93	95.7	1.1	(0.8 , 1.5)	0.2
Prostate	2	1.2	1	1.8	2.8	(0.1 , >10)	0.8
Testis	11	16.5	37	31.5	0.6	(0.3 , 1.1)	3.0
Bladder	7	7.5	12	11.5	0.9	(0.4 , 2.3)	0.1
Kidney	3	2.8	6	6.2	1.1	(0.2 , 5.3)	0.0
Brain	8	4.2	7	10.8	3.0	(1.1 , 8.2)	4.3*
Thyroid	0	1.7	5	3.3	0.0	(0.0 , 1.6)	4.1*
Non-H lymphoma	9	8.1	13	13.9	1.2	(0.5 , 2.8)	0.1
Lympho- & reticulo-	5	3.9	5	6.1	1.6	(0.4 , 5.4)	0.5
Other lymphoid	4	4.2	8	7.8	0.9	(0.2 , 3.4)	0.0
Hodgkin's disease	3	4.6	11	9.4	0.6	(0.1 , 2.1)	0.9
Leukemia	6	5.5	11	11.5	1.1	(0.4 , 3.0)	0.1
Myelocytic leukemia	5	4.4	7	7.6	1.2	(0.4 , 3.9)	0.1
Site not specified	5	3.5	5	6.5	1.8	(0.5 , 6.3)	0.9

Population: National Service servicemen.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

Relative rate compares incidence among Vietnam veterans with that among non-veterans.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.19 *Observed and expected cancers for Australian Regular Army servicemen, by service in Vietnam*

Site of cancer	Vietnam		No Vietnam		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	346	352.9	839	832.1	0.97	(0.86 , 1.10)	0.2
Oral	37	33.7	60	63.3	1.2	(0.8 , 1.7)	0.5
Lip	17	15.4	24	25.6	1.2	(0.6 , 2.2)	0.3
Nasopharyngeal	2	1.3	1	1.7	2.7	(0.1 , >10)	0.7
Stomach	7	9.5	28	25.5	0.7	(0.3 , 1.5)	0.9
Colon	22	20.1	60	61.9	1.1	(0.7 , 1.8)	0.2
Rectum	19	19.6	51	50.4	1.0	(0.6 , 1.6)	0.0
Primary liver	3	1.7	2	3.3	2.8	(0.3 , >10)	1.3
Pancreas	6	6.7	24	23.3	0.9	(0.4 , 2.1)	0.1
Nasal	1	0.8	1	1.2	1.4	(0.0 , >10)	0.0
Larynx	4	7.0	25	22.0	0.5	(0.1 , 1.4)	1.9
Lung	46	56.7	158	147.3	0.8	(0.5 , 1.1)	2.9
Soft tissue	5	4.7	9	9.3	1.1	(0.4 , 3.3)	0.0
Bone	1	1.6	4	3.4	0.5	(0.0 , 5.2)	0.4
Connective tissue	4	3.0	5	6.0	1.6	(0.3 , 7.3)	0.5
Skin melanoma	68	62.7	115	120.3	1.1	(0.8 , 1.5)	0.7
Prostate	7	7.8	55	54.2	0.9	(0.4 , 2.0)	0.1
Testis	15	14.6	20	20.4	1.0	(0.5 , 2.0)	0.0
Bladder	20	17.0	42	45.0	1.3	(0.7 , 2.1)	0.7
Kidney	9	9.3	22	21.7	1.0	(0.4 , 2.1)	0.0
Brain	9	8.9	14	14.1	1.0	(0.4 , 2.3)	0.0
Thyroid	3	1.6	3	4.4	2.8	(0.4 , >10)	1.6
Non-H lymphoma	19	18.1	34	34.9	1.1	(0.6 , 1.9)	0.1
Lympho- & reticulo-	17	13.2	20	23.8	1.5	(0.8 , 2.9)	1.7
Other lymphoid	2	4.9	14	11.1	0.3	(0.0 , 1.4)	2.9
Hodgkin's disease	8	6.1	11	12.9	1.6	(0.6 , 3.9)	0.9
Leukemia	14	13.5	21	21.5	1.1	(0.5 , 2.1)	0.0
Myelocytic leukemia	7	7.4	13	12.6	0.9	(0.4 , 2.3)	0.0
Site not specified	7	12.1	35	29.9	0.5	(0.2 , 1.1)	3.4

Population: Australian Regular Army servicemen.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

Relative rate compares incidence among Vietnam veterans with that among non-veterans.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.20 *Observed and expected cancers for National Service and Australian Regular Army Vietnam veterans, by dapsone-exposed Vietnam veterans and non-veterans*

Site of cancer	Dapsone		No Vietnam		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	247	260.3	1129	1115.7	0.94	(0.82 , 1.08)	0.8
Oral	16	21.0	84	79.0	0.7	(0.4 , 1.2)	1.6
Lip	9	12.4	44	40.6	0.7	(0.3 , 1.4)	1.3
Nasopharyngeal	2	0.8	1	2.2	5.4	(0.3 , >10)	2.0
Stomach	6	6.7	33	32.3	0.9	(0.4 , 2.1)	0.1
Colon	15	14.9	76	76.1	1.0	(0.6 , 1.8)	0.0
Rectum	12	12.5	62	61.5	1.0	(0.5 , 1.8)	0.0
Primary liver	1	0.4	2	2.6	3.5	(0.1 , >10)	0.9
Pancreas	7	4.4	25	27.6	1.7	(0.8 , 4.0)	1.5
Nasal	0	0.9	3	2.1	0.0	(0.0 , 3.9)	2.2
Larynx	1	3.6	27	24.4	0.3	(0.0 , 1.5)	2.8
Lung	28	29.5	164	162.5	0.9	(0.6 , 1.4)	0.1
Soft tissue	7	6.4	19	19.6	1.1	(0.5 , 2.7)	0.1
Bone	2	2.3	7	6.7	0.9	(0.1 , 4.5)	0.0
Connective tissue	5	4.2	12	12.8	1.3	(0.5 , 3.7)	0.2
Skin melanoma	56	59.5	208	204.5	0.9	(0.7 , 1.2)	0.3
Prostate	7	4.2	56	58.8	1.8	(0.8 , 3.9)	1.7
Testis	10	17.8	57	49.2	0.5	(0.2 , 0.9)	5.3*
Bladder	13	12.2	54	54.8	1.1	(0.6 , 2.0)	0.1
Kidney	6	5.7	28	28.3	1.1	(0.4 , 2.6)	0.0
Brain	11	7.2	21	24.8	1.8	(0.9 , 3.8)	2.4
Thyroid	0	1.3	8	6.7	0.0	(0.0 , 2.4)	2.8
Non-H lymphoma	19	14.6	47	51.4	1.4	(0.8 , 2.4)	1.6
Lympho- & reticulo-	15	9.0	25	31.0	2.1	(1.1 , 3.9)	4.6*
Other lymphoid	4	5.6	22	20.4	0.7	(0.2 , 2.0)	0.6
Hodgkin's disease	7	6.4	22	22.6	1.1	(0.5 , 2.6)	0.1
Leukemia	7	9.0	32	30.0	0.7	(0.3 , 1.7)	0.6
Myelocytic leukemia	3	5.5	20	17.5	0.5	(0.1 , 1.6)	1.7
Site not specified	6	8.2	40	37.8	0.7	(0.3 , 1.6)	0.8

Population: National Service and Australian Regular Army servicemen, excluding unexposed Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$).

Relative rate compares incidence among dapsone-exposed Vietnam veterans with that among non-veterans.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.21 *Observed and expected cancers for National Service Vietnam veterans, by dapsone-exposed Vietnam veterans and non-veterans*

Site of cancer	Dapsone		No Vietnam		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	83	92.5	290	280.5	0.87	(0.68, 1.11)	1.3
Oral	3	6.8	24	20.2	0.4	(0.1 , 1.2)	3.4
Lip	2	5.4	20	16.6	0.3	(0.0 , 1.3)	3.6
Nasopharyngeal	1	0.3	0	0.7	∞	(0.1 , ∞)	2.4
Stomach	2	1.9	5	5.1	1.1	(0.1 , 6.8)	0.0
Colon	3	5.0	16	14.0	0.5	(0.1 , 1.8)	1.2
Rectum	4	3.7	11	11.3	1.1	(0.3 , 3.7)	0.0
Primary liver	0	0.0	0	0.0	-		
Pancreas	4	1.4	1	3.6	10	(1.0 , >10)	5.9*
Nasal	0	0.6	2	1.4	0.0	(0.0 , 8.6)	1.4
Larynx	0	0.3	2	1.7	0.0	(0.0 , >10)	0.7
Lung	7	3.6	6	9.4	3.1	(1.0 , 9.1)	3.9*
Soft tissue	3	3.5	10	9.5	0.8	(0.1 , 3.1)	0.1
Bone	1	1.2	3	2.8	0.8	(0.0 , 9.8)	0.0
Connective tissue	2	2.3	7	6.7	0.8	(0.1 , 4.3)	0.1
Skin melanoma	23	28.2	93	87.8	0.8	(0.5 , 1.2)	1.3
Prostate	2	0.9	1	2.1	4.8	(0.2 , >10)	1.8
Testis	4	10.2	37	30.8	0.3	(0.1 , 0.9)	6.2*
Bladder	5	5.0	12	12.0	1.0	(0.4 , 2.9)	0.0
Kidney	0	1.2	6	4.8	0.0	(0.0 , 2.6)	2.6
Brain	6	2.5	7	10.5	3.6	(1.2 , 11)	4.9*
Thyroid	0	1.0	5	4.0	0.0	(0.0 , 3.4)	2.2
Non-H lymphoma	5	4.9	13	13.1	1.0	(0.4 , 2.9)	0.0
Lympho- & reticulo-	2	1.9	5	5.1	1.1	(0.1 , 6.7)	0.0
Other lymphoid	3	3.0	8	8.0	1.0	(0.2 , 4.2)	0.0
Hodgkin's disease	1	2.8	11	9.2	0.3	(0.0 , 2.0)	1.9
Leukemia	4	3.4	11	11.6	1.2	(0.3 , 4.1)	0.1
Myelocytic leukemia	3	2.7	7	7.3	1.2	(0.2 , 5.2)	0.1
Site not specified	2	1.7	5	5.3	1.2	(0.1 , 7.4)	0.1

Population: National Service servicemen, excluding unexposed Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$).

Relative rate compares incidence among dapsone-exposed Vietnam veterans with that among non-veterans.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.22 *Observed and expected cancers for Australian Regular Army Vietnam veterans, by dapsone-exposed Vietnam veterans and non-veterans*

Site of cancer	Dapsone		No Vietnam		Relative rate	95% confidence interval	Test statistic
	Obs	Exp	Obs	Exp			
All	164	167.5	839	835.5	0.98	(0.83 , 1.15)	0.1
Oral	13	14.4	60	58.6	0.9	(0.5 , 1.6)	0.2
Lip	7	7.0	24	24.0	1.0	(0.4 , 2.3)	0.0
Nasopharyngeal	1	0.6	1	1.4	2.5	(0.0 , >10)	0.4
Stomach	4	4.8	28	27.2	0.8	(0.2 , 2.3)	0.2
Colon	12	9.4	60	62.6	1.3	(0.7 , 2.5)	0.8
Rectum	8	8.8	51	50.2	0.9	(0.4 , 1.9)	0.1
Primary liver	1	0.4	2	2.6	3.5	(0.1 , >10)	0.9
Pancreas	3	2.9	24	24.1	1.0	(0.2 , 3.4)	0.0
Nasal	0	0.3	1	0.7	0.0	(0.0 , >10)	0.7
Larynx	1	3.2	25	22.8	0.3	(0.0 , 1.8)	2.2
Lung	21	26.0	158	153.0	0.8	(0.5 , 1.2)	1.2
Soft tissue	4	2.8	9	10.2	1.6	(0.4 , 5.8)	0.6
Bone	1	1.1	4	3.9	0.9	(0.0 , 9.4)	0.0
Connective tissue	3	1.7	5	6.3	2.2	(0.3 , >10)	1.0
Skin melanoma	33	31.1	115	116.9	1.1	(0.7 , 1.6)	0.1
Prostate	5	3.2	55	56.8	1.6	(0.6 , 4.0)	0.9
Testis	6	7.5	20	18.5	0.7	(0.3 , 1.8)	0.5
Bladder	8	7.2	42	42.8	1.1	(0.5 , 2.4)	0.1
Kidney	6	4.5	22	23.5	1.4	(0.6 , 3.5)	0.5
Brain	5	4.9	14	14.1	1.0	(0.4 , 2.9)	0.0
Thyroid	0	0.1	3	2.9	0.0	(0.0 , >10)	0.2
Non-H lymphoma	14	9.9	34	38.1	1.6	(0.8 , 2.9)	1.9
Lympho- & reticulo-	13	7.3	20	25.7	2.3	(1.1 , 4.6)	4.9*
Other lymphoid	1	2.6	14	12.4	0.3	(0.0 , 2.2)	1.5
Hodgkin's disease	6	3.8	11	13.2	1.9	(0.7 , 5.2)	1.5
Leukemia	3	5.8	21	18.2	0.5	(0.1 , 1.5)	2.0
Myelocytic leukemia	0	2.9	13	10.1	0.0	(0.0 , 0.9)	6.5*
Site not specified	4	6.5	35	32.5	0.6	(0.1 , 1.6)	1.3

Population: Australian Regular Army servicemen, excluding unexposed Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

For each five-year age group and single calendar year, the calculation of the expected number of cancers assumes equal incidence rates in both groups.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$).

Relative rate compares incidence among dapsone-exposed Vietnam veterans with that among non-veterans.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

'Obs' denotes observed; 'Exp' denotes expected.

Table 4.23 *Observed and expected incident cancers between 1982 and 1984 for National Service and Australian Regular Army servicemen*

Site of cancer	Observed	Expected	Relative rate	95% confidence interval	Test statistic
All	616	588.7	1.05	(0.97, 1.13)	1.3
Oral	62	46.2	1.3	(1.0 , 1.7)	4.8*
Lip	31	26.2	1.2	(0.8 , 1.7)	0.8
Nasopharyngeal	2	3.6	0.6	(0.1 , 2.0)	0.8
Stomach	13	20.9	0.6	(0.3 , 1.1)	3.4
Colon	38	46.6	0.8	(0.6 , 1.1)	1.7
Rectum	33	27.8	1.2	(0.8 , 1.7)	0.9
Primary liver	1	3.9	0.3	(0.0 , 1.4)	3.0
Pancreas	11	13.4	0.8	(0.4 , 1.5)	0.5
Nasal	2	2.5	0.8	(0.1 , 2.9)	0.1
Larynx	19	11.3	1.7	(1.0 , 2.6)	4.4*
Lung	79	82.9	1.0	(0.8 , 1.2)	0.2
Soft tissue	10	10.0	1.0	(0.5 , 1.8)	0.0
Bone	2	3.7	0.5	(0.1 , 2.0)	0.9
Connective tissue	8	6.3	1.3	(0.5 , 2.5)	0.4
Skin melanoma	94	75.2	1.3	(1.0 , 1.5)	4.4*
Prostate	31	35.1	0.9	(0.6 , 1.3)	0.5
Testis	24	27.4	0.9	(0.6 , 1.3)	0.4
Bladder	45	29.9	1.5	(1.1 , 2.0)	6.6*
Kidney	19	15.9	1.2	(0.7 , 1.9)	0.6
Brain	18	20.6	0.9	(0.5 , 1.4)	0.3
Thyroid	5	4.9	1.0	(0.3 , 2.4)	0.0
Non-H lymphoma	23	25.5	0.9	(0.6 , 1.4)	0.3
Hodgkin's disease	11	10.4	1.1	(0.5 , 1.9)	0.0
Leukemia	19	14.2	1.3	(0.8 , 2.1)	1.5
Myelocytic leukemia	10	9.2	1.1	(0.5 , 2.0)	0.1

Population: National Service and Australian Regular Army servicemen.

Notes: Observed cancers from Australian cancer registrations, 1982–84.

Expected cancers calculations use Australian male five-year age-specific rates for 1982 (Giles et al. 1987).

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$).

Relative rate compares incidence among the study cohort with that among other Australian males.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

Table 4.24 *Observed and expected incident cancers between 1982 and 1984 for National Service and Australian Regular Army Vietnam veterans*

Site of cancer	Observed	Expected	Relative rate	95% confidence interval	Test statistic
All	194	170.5	1.14	(0.98, 1.31)	3.1
Oral	22	15.6	1.4	(0.9 , 2.1)	2.3
Lip	9	9.0	1.0	(0.5 , 1.9)	0.0
Nasopharyngeal	2	1.3	1.5	(0.2 , 5.4)	0.3
Stomach	6	5.2	1.1	(0.4 , 2.5)	0.1
Colon	12	13.7	0.9	(0.5 , 1.5)	0.2
Rectum	10	7.3	1.4	(0.7 , 2.5)	0.9
Primary liver	0	1.0	0.0	(0.0 , 3.5)	2.1
Pancreas	4	3.6	1.1	(0.3 , 2.9)	0.0
Nasal	0	0.7	0.0	(0.0 , 5.0)	1.5
Larynx	4	3.4	1.2	(0.3 , 3.0)	0.1
Lung	22	19.7	1.1	(0.7 , 1.7)	0.2
Soft tissue	3	3.4	0.9	(0.2 , 2.6)	0.1
Bone	1	1.2	0.8	(0.0 , 4.5)	0.0
Connective tissue	2	2.2	0.9	(0.1 , 3.3)	0.0
Skin melanoma	30	25.8	1.2	(0.8 , 1.7)	0.6
Prostate	3	3.9	0.8	(0.2 , 2.2)	0.2
Testis	8	9.4	0.9	(0.4 , 1.7)	0.2
Bladder	17	7.5	2.3	(1.3 , 3.6)	8.8**
Kidney	5	4.6	1.1	(0.3 , 2.5)	0.0
Brain	9	7.2	1.2	(0.6 , 2.4)	0.4
Thyroid	2	1.9	1.0	(0.1 , 3.8)	0.0
Non-H lymphoma	7	8.1	0.9	(0.3 , 1.8)	0.1
Hodgkin's disease	5	3.6	1.4	(0.4 , 3.3)	0.5
Leukemia	6	3.8	1.6	(0.6 , 3.4)	1.1
Myelocytic leukemia	3	2.9	1.0	(0.2 , 3.0)	0.0

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1982–84.

Expected cancers calculations use Australian male five-year age-specific rates for 1982.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except that marked ** ($0.001 < p < 0.01$).

Relative rate compares incidence among Vietnam veterans with that among other Australia males.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

Table 4.25 *Observed and expected incident cancers between 1982 and 1984 for National Service and Australian Regular Army dapsone-exposed Vietnam veterans*

Site of cancer	Observed	Expected	Relative rate	95% confidence interval	Test statistic
All	93	85.0	1.09	(0.88, 1.34)	0.7
Oral	9	8.2	1.1	(0.5 , 2.1)	0.1
Lip	3	4.9	0.6	(0.1 , 1.8)	0.9
Nasopharyngeal	2	0.7	2.7	(0.3 , 9.7)	1.5
Stomach	2	2.4	0.8	(0.1 , 3.0)	0.1
Colon	6	6.7	0.9	(0.3 , 1.9)	0.1
Rectum	3	3.4	0.9	(0.2 , 2.6)	0.0
Primary liver	0	0.5	0.0	(0.0 , 7.4)	1.0
Pancreas	3	1.7	1.8	(0.4 , 5.2)	0.8
Nasal	0	0.4	0.0	(0.0 , 9.2)	0.8
Larynx	0	1.5	0.0	(0.0 , 2.4)	3.1
Lung	11	8.7	1.3	(0.6 , 2.3)	0.6
Soft tissue	2	1.9	1.0	(0.1 , 3.7)	0.0
Bone	0	0.7	0.0	(0.0 , 5.0)	1.5
Connective tissue	2	1.2	1.7	(0.2 , 6.0)	0.4
Skin melanoma	12	14.3	0.8	(0.4 , 1.5)	0.4
Prostate	3	1.5	2.0	(0.4 , 5.7)	1.1
Testis	4	5.6	0.7	(0.2 , 1.8)	0.5
Bladder	7	3.7	1.9	(0.8 , 3.9)	2.4
Kidney	3	2.3	1.3	(0.3 , 3.8)	0.2
Brain	5	3.9	1.3	(0.4 , 3.0)	0.3
Thyroid	0	1.0	0.0	(0.0 , 3.6)	2.1
Non-H lymphoma	5	4.3	1.2	(0.4 , 2.7)	0.1
Hodgkin's disease	3	2.1	1.4	(0.3 , 4.2)	0.4
Leukemia	2	2.0	1.0	(0.1 , 3.6)	0.0
Myelocytic leukemia	1	1.6	0.6	(0.0 , 3.5)	0.3

Population: National Service and Australian Regular Army Vietnam veterans who took dapsone.

Notes: Observed cancers from Australian cancer registrations, 1982–84.

Expected cancers calculations use Australian male five-year age-specific rates for 1982.

Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

Relative rate compares incidence among dapsone-exposed Vietnam veterans with that among other Australian males.

Test statistic enables assessment of whether data are consistent with equal rates in both groups.

5 Cancer incidence for different sites of cancer

Most tables in Chapter 4 compare cancer incidence in two subgroups of servicemen for up to 29 sites of cancer. Although this facilitates finding which sites of cancer show similar relative incidence patterns for particular subgroups, it is also of interest to look at the subgroup comparisons for each particular site of cancer.

Accordingly, the data in several tables in Chapter 4 have been collated into separate tables for each of the 29 sites of cancer. For each site of cancer, the observed number of incident cancers, the estimated relative rate and its confidence interval and the corresponding asymptotic test statistics are given for dapsone-exposed Vietnam veterans compared with other veterans (from Section 4.2), for malaria-exposed veterans compared with other veterans (from Section 4.4), for Vietnam veterans compared with non-veterans (from Section 4.5), and for the study cohort compared with the Australian male population (from Section 4.7). The first and third comparisons are shown for National Service and for Australian Regular Army separately as well as combined. The estimated dose response (and its confidence interval) with dapsone dose (from Section 4.3) is also shown.

The estimated relative cancer incidence rate among Vietnam veterans has also been plotted for five levels of total dapsone use. The observed and expected cancers are tabulated in Section 4.3. Where feasible, the asymptotic 95 per cent confidence interval based on the expected number of cancers has also been plotted.

5.1 All cancers

With one exception, all comparisons between subgroups show no statistically significant difference in cancer incidence. For most comparisons, the confidence interval for the relative cancer incidence rate is narrow, so the study has reasonable power to detect differences between most subgroups.

The nominally statistically significant comparison was for dapsone-exposed National Servicemen compared with other National Servicemen: the estimated cancer incidence is lower for the dapsone-exposed Servicemen than for the unexposed Servicemen. This is inconsistent with dapsone increasing the risk of cancer. It is, however, unlikely that dapsone is protective against cancer: first, there is no plausible biological explanation for such an effect; second, the estimated dose response for the relationship between the amount of dapsone consumed and later cancer incidence, although not statistically significant, is positive (Table 5.1). Figure 5.1 suggests that the cancer incidence rate is similar for each of the dapsone dose groups.

The cancer incidence between 1982 and 1984 for the study cohort is close to that expected given 1982 male age-specific cancer incidence rates. The observed incidence in the study cohort is only 5 per cent higher than in the Australian population, and

the 95 per cent confidence interval is narrow (from 0.97 to 1.13). This is consistent with the 1982 to 1984 cancer incidence among servicemen who were in the Australian Army between 1965 and 1972 being similar to that in other Australian males of a similar age. It also suggests that the matching process has neither undercounted nor overcounted the number of cancer cases in the study cohort.

If dapsone were to be associated with particular sites of cancer, it is possible that no overall increase in cancer incidence would be detectable, even though there was an increase for the particular cancer sites. Accordingly, incidence for particular cancer sites was examined.

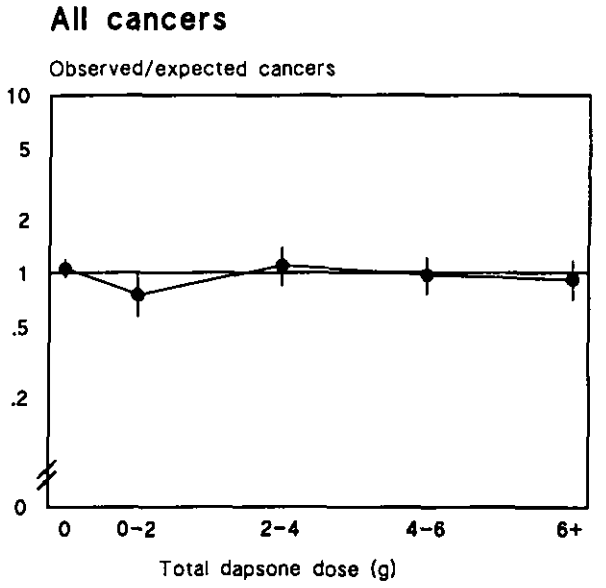

Figure 5.1 ***All sites cancer incidence among Vietnam veterans, by total dapsone dose***

Conclusion: Overall cancer incidence appears to be independent of dapsone exposure and service in Vietnam.

Table 5.1 also shows that the reported incidence of cancers with no site specified is similar for the different subgroups; that is, there is no evidence that cancers of persons in different subgroups have a different chance of having their primary site being either indeterminable or undetermined. If such differences did exist they could bias the comparisons between subgroups for sites of cancer where the primary site was known.

Conclusion: The incidence of cancers with site not specified appears to be independent of dapsone exposure and service in Vietnam.

5.2 Hodgkin's disease and non-Hodgkin's lymphoma

Animal studies and a statistically significant result for men in Brinton et al. (1984) suggest that lymphomas may be associated with dapsone exposure. In this study no statistically significant differences were found for cancers classified as either ICD 200 (lympho- and reticulo-sarcoma), ICD 201 (Hodgkin's disease), ICD 202 (other lymphoid and histocytic) or ICD 200 and 202 combined (non-Hodgkin's lymphoma).

The estimated relative cancer incidence rates for dapsone exposure within the entire Vietnam veteran cohort were 1.9, 1.2 and 1.3 for cancers classified as ICD 200, 201 and 202 respectively. The confidence intervals for these estimates are very wide, however, meaning that estimates as large as these can be expected. Some estimates are less than unity and some greater than unity for National Service and Australian Regular Army Vietnam veterans, so the estimates do not show a consistent pattern between subcohorts of the study population.

The estimated dose response is also not consistent for these sites of cancer. It is 0.4, 1.2 and 1.0 respectively for cancers classified as ICD 200, 201 and 202. Other studies (for example, Hardell et al. 1981 and Hardell & Bengtsson 1983) have suggested that these cancers may be associated with exposure to phenoxy herbicides.

The Selected Cancers Cooperative Study Group (1990a) summarised data from several studies of United States servicemen. The Group found a 50 per cent statistically significant excess risk for non-Hodgkin's lymphoma among men who had served in the United States military in Vietnam compared with men who had not served in the United States military. It considered, however, that this was not related to Agent Orange exposure. The upper confidence limit from this current study (1.8) is consistent with the risk estimated in the Group's United States study, although the lower confidence limit is below a relative risk of unity; that is, the data from this study are too few to decide whether either of these two possibilities is untenable.

Cancer incidence in 1982 to 1984 for these cancers in the study cohort is close to that for the Australian male population, so under- or over-enumeration seems unlikely.

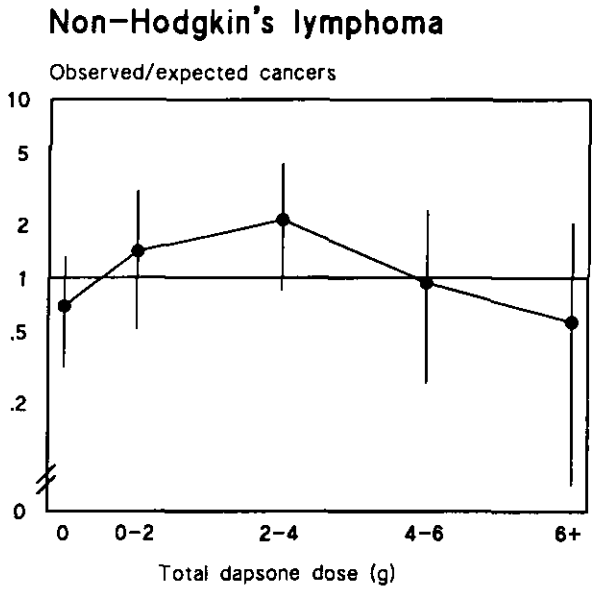

Figure 5.2 *Non-Hodgkin's lymphoma incidence among Vietnam veterans, by total dapsone dose*

Conclusion: The incidence of non-Hodgkin's lymphoma and Hodgkin's disease appears to be independent of dapsone exposure and service in Vietnam.

5.3 Leukemia

Because dapsone can affect white blood cells it is plausible that it may cause leukemia. The greatest difference within the study cohort was for Australian Regular Army dapsone-exposed Vietnam veterans compared with other Australian Regular Army Vietnam veterans. But this was a negative association. By contrast, the trend with dapsone dose was positive, although not statistically significant. This pattern was not seen among National Service Vietnam veterans.

The estimated relative risk for Vietnam veterans compared with non-veterans was close to unity for both National Service and Australian Regular Army servicemen. The study cohort had incidence rates similar to those for the Australian male population between 1982 and 1984.

The results for a major subtype of leukemia—myelocytic leukemia—are similar to those for leukemia as a whole.

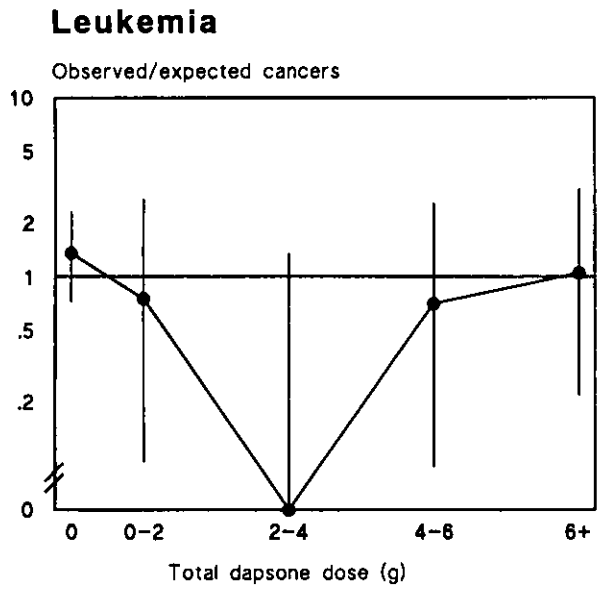

Figure 5.3 *Leukemia incidence among Vietnam veterans, by total dapsone dose*

Conclusion: Leukemia incidence appears to be independent of dapsone exposure and service in Vietnam.

5.4 Soft tissue and other sarcomas

Hardell and Sandstrom (1979) were the first to suggest that soft tissue and other sarcomas may be associated with exposure to phenoxy herbicides. The Selected Cancers Cooperative Study Group (1990b), however, found no excess risk for these cancers among men who had served in the United States military in Vietnam. No statistically significant differences were found in this current study.

There is no suggestion in these data that cancer incidence might differ for Vietnam veterans compared with non-veterans. Cancer incidence in 1982 to 1984 for the study cohort is close to that for the Australian male population, so under- or over-enumeration seems unlikely.

Nevertheless, the relative risk with dapsone exposure is estimated to be 1.4 within the cohort of Vietnam veterans. The 95 per cent confidence interval for this estimate is wide (0.3 to 8.3), so it is unsurprising that the estimate is not close to unity. The estimated relative cancer incidence rate is inconsistent for National Service and Australian Regular Army Vietnam veterans: it is less than 1 among National Servicemen but greater than 1 for the other group.

The dose–response estimate is close to that for no association of cancer incidence with dapsone dose, although there were only seven such cancer cases among the dapsone-exposed Vietnam veterans.

The estimates are similar for the two subsites—bone (ICD 170) and connective tissue (ICD 171). Therefore the suggestion by Fingerhut et al. (1991) of an increased risk for ICD 171 but not ICD 170 for chemical workers exposed to herbicides is not apparent in these data.

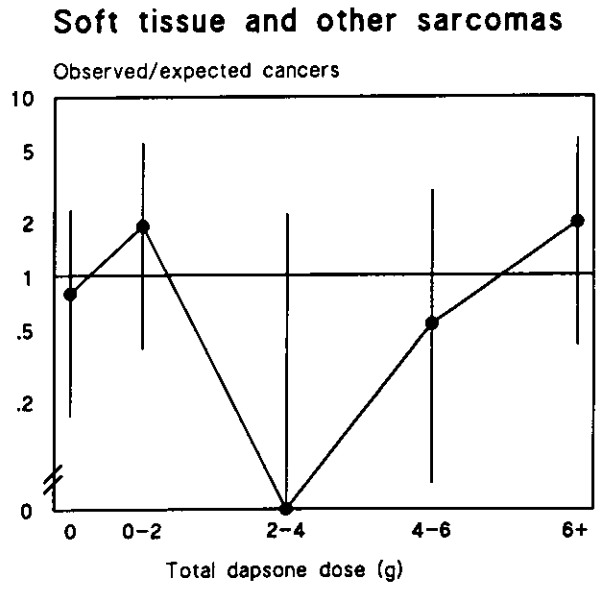

Figure 5.4 *Soft tissue and other sarcoma incidence among Vietnam veterans, by total dapsone dose*

Conclusion: The incidence of soft tissue and other sarcomas appears to be independent of dapsone exposure and service in Vietnam.

5.5 Cancers of the mouth and respiratory system

Brinton et al. (1984) found that oral cancer mortality was elevated among those of their patients who had leprosy. None of the comparisons within the study cohort was statistically significant. The estimated relative cancer incidence with dapsone dose was less than unity for all Vietnam veterans, and for National Servicemen and for those in the Australian Regular Army. The estimated dose response was

negative. Inconsistent directions of the estimated risk for service in Vietnam were found for the National Service and Australian Regular Army subgroups.

The study cohort had a statistically significantly higher incidence of oral cancer than in the Australian population between 1982 and 1984. This could reflect a higher incidence of smoking in the study cohort compared with the rest of the Australian population, and this is consistent with the statistically significantly higher incidence for larynx cancer and the higher incidence for lip cancer. The incidence rates for lung and pancreatic cancers are, however, not elevated. It is unlikely that smoking differences could result in increased incidence for some of these sites of cancers but not the others.

Conclusion: The incidence of oral cancer appears to be independent of dapsone exposure and service in Vietnam.

Phenoxy herbicide exposure has been reported to be associated with nasopharyngeal and nasal cancer (Hardell et al. 1982). In this study cohort only five and four cancers respectively were detected for these sites. Accordingly, the 95 per cent confidence intervals for estimated cancer incidence rates are very wide, and no comparisons between subgroups are statistically significant.

Conclusion: There are too few data to assess variation in nasopharyngeal and nasal cancer incidence.

Although not mentioned in the medical literature as being possibly associated with either dapsone exposure or service in Vietnam, the pattern of cancer incidence observed for lip and larynx cancers was similar to that for oral cancer. Since lip cancer is a substantial subset of oral cancer, the similarity of the results is not unexpected.

Lung cancer was not mentioned in the medical literature as being possibly associated with either dapsone exposure or service in Vietnam. Most relative cancer incidence rates for this site of cancer are close to unity and are not statistically significant. Tobacco smoking is, however, a potent risk factor for lung cancer, with a relative risk in excess of 10. This means that even small differences in smoking behaviour between subgroups could induce large apparent differences in lung cancer incidence. Accordingly, it is not possible to come to any conclusions about any relationship between lung cancer incidence and dapsone exposure or service in Vietnam.

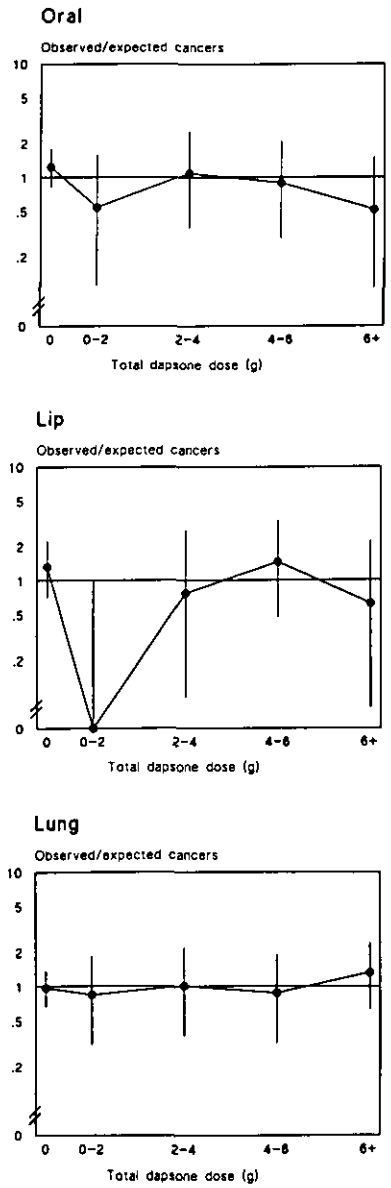

Figure 5.5 ***Oral, lip and lung cancer incidence among Vietnam veterans, by total dapsone dose***

Conclusion: The incidence of lip and larynx cancer appears to be independent of dapsone exposure and service in Vietnam. No conclusions can be drawn about lung cancer.

5.6 Cancers of the digestive system

Axelson et al. (1980) have suggested that phenoxy herbicide exposure may be associated with stomach cancer. There are no a priori hypotheses about a link between cancer incidence from other digestive cancers and either dapsone exposure or service in Vietnam.

No consistent or unusual patterns were seen for stomach, colon or rectum cancer in this study cohort. Cancer incidence in the cohort was similar to that in the Australian male population between 1982 and 1984.

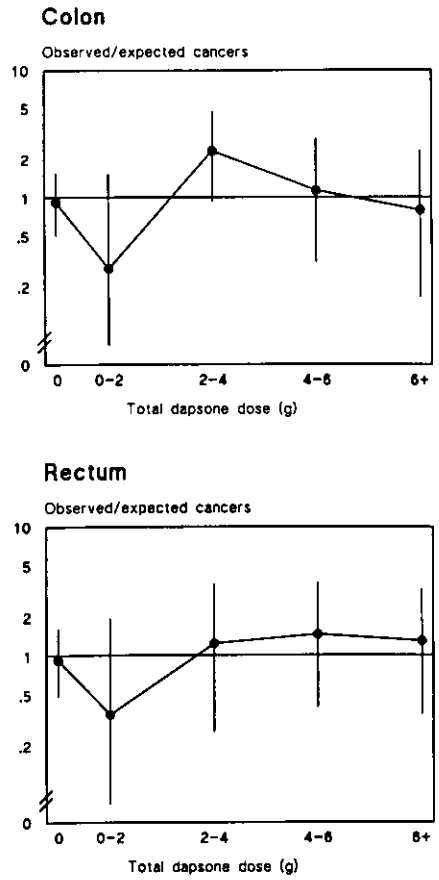

Figure 5.6 *Colon and rectum cancer incidence among Vietnam veterans, by total dapsone dose*

Conclusion: Stomach, colon and rectum cancer incidence appears to be independent of dapsone exposure and service in Vietnam.

5.7 Skin melanoma

Skin melanoma was not hypothesised as being associated with either dapsone use or Vietnam service.

Skin melanoma incidence was statistically significantly lower for dapsone-exposed National Service Vietnam veterans compared with other National Service Vietnam veterans. The estimated dose response was, however, inconsistent with this and not statistically significant. Among the Australian Regular Army Vietnam veterans, the estimated incidence was slightly lower for those exposed to dapsone compared with those not exposed but this negative association was not statistically significant.

The estimated relative risk of skin melanoma incidence for Vietnam veterans compared with non-veterans was close to unity for both National Service and Australian Regular Army servicemen. The study cohort had statistically significantly higher incidence rates than the Australian male population between 1982 and 1984.

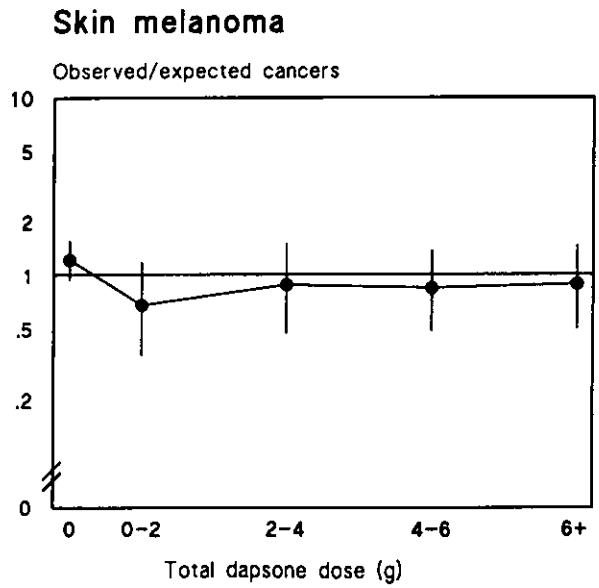

Figure 5.7 *Skin melanoma incidence among Vietnam veterans, by total dapsone dose*

Conclusion: Skin melanoma incidence appears to be independent of dapsone exposure and service in Vietnam.

5.8 Cancers of other organs

Of the cancers of the remaining organs, those of the liver (as a primary), testis, bladder, kidney and thyroid were mentioned in the medical literature as possibly being positively associated with either dapsone exposure or service in Vietnam.

In this study, a positive association with dapsone exposure was seen for only one of the five sites, kidney cancer. This positive association was inconsistent, being positive among the Australian Regular Army Vietnam veterans and negative among the National Service Vietnam veterans. There was little difference in cancer incidence between Vietnam veterans and non-veterans for this cancer.

Primary liver, testis and thyroid cancer each showed strong estimated negative associations with dapsone exposure, although only that for testis cancer was statistically significant. For both primary liver and testis cancer, however, the estimated dose response with dapsone dose was positive, and so was contrary to the result for dapsone exposure. No thyroid cancers were detected among dapsone-exposed Vietnam veterans, so dose response could not be assessed for this site of cancer.

The only large associations with Vietnam service were a positive association for primary liver cancer and a negative association for thyroid cancer, although neither of these was statistically significant. Of these five sites of cancer, only bladder cancer had a statistically significantly higher incidence in the study cohort than in the Australian male population.

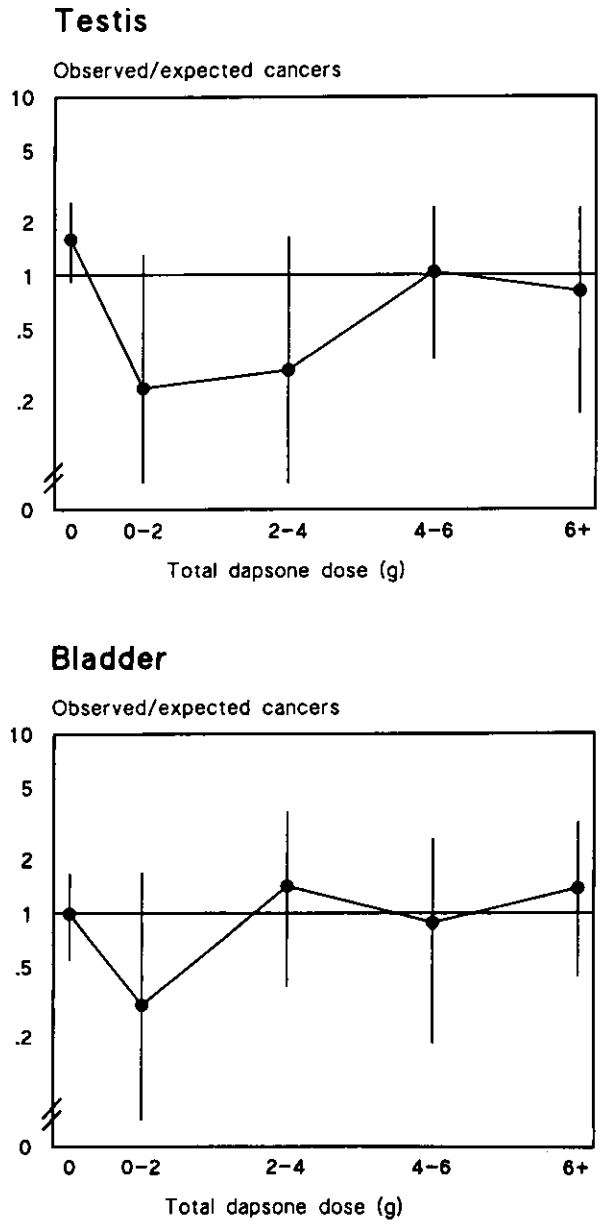

Figure 5.8 ***Testis and bladder cancer incidence among Vietnam veterans, by total dapsone dose***

Conclusion: Testis, bladder and kidney cancer incidence appears to be independent of dapsone exposure and service in Vietnam. There are too few data to assess variation in primary liver and thyroid cancer incidence.

For the remaining three sites of cancer, cancer of the pancreas, prostate and brain, no associations with either dapsone exposure or Vietnam service were identified in the medical literature. Although apparently not associated with dapsone exposure, in this study cancer of the pancreas seemed to be associated with Vietnam service among the National Service servicemen only. No such effect was apparent among the Australian Regular Army servicemen. A similar pattern was observed for brain cancer.

This pattern was also seen for lung cancer (see Section 5.5); both lung and pancreas, but not brain, cancers are associated with smoking of tobacco. However, the increased risk was not apparent among Australian Regular Army servicemen. Increased smoking of tobacco confined to National Service Vietnam veterans compared with non-veterans seems unlikely.

Dapsone exposure was positively associated with each of these sites of cancer, although not statistically significantly so. In each case the dose response was negative, suggesting that there is no underlying association between dapsone exposure and these sites of cancer.

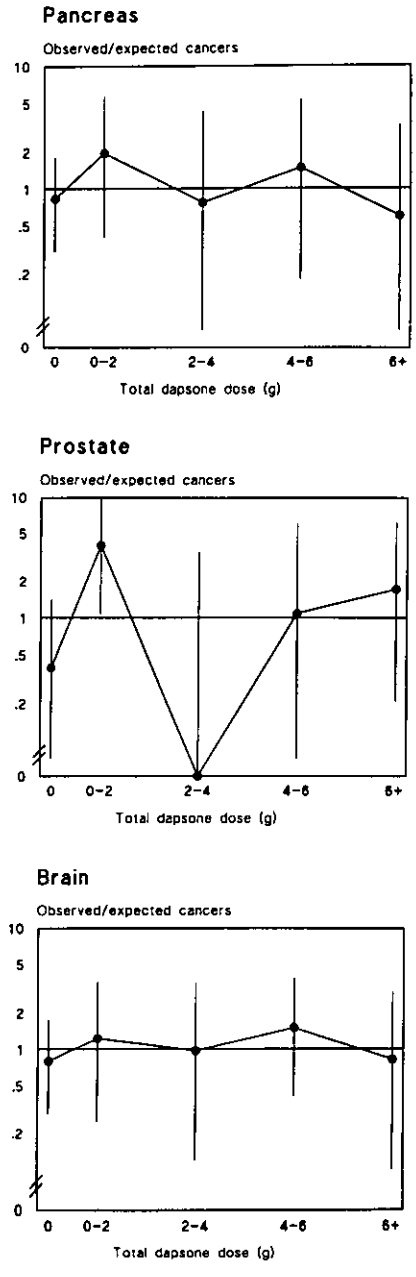

Figure 5.9 ***Pancreas, prostate and brain cancer incidence among Vietnam veterans, by total dapsone dose***

Conclusion: Pancreas, prostate and brain cancer incidence appears to be independent of dapsone exposure and service in Vietnam.

5.9 Conclusion

Cancer incidence and dapsone exposure

Total cancer incidence

The 'All cancers' relative cancer incidence rate for dapsone-exposed servicemen compared with other Vietnam veterans was 0.88 (Table 4.6). The 95 per cent confidence interval for the relative rate is 0.74 to 1.05, which includes equal incidence rates in both groups. The upper limit shows that the data from this study are inconsistent with a markedly higher total cancer incidence among dapsone-exposed servicemen compared with other Vietnam veterans; that is, there is no evidence from this study of an excess of overall cancer occurrence in those Vietnam veterans who had taken dapsone.

Most servicemen who took dapsone took a total (cumulative) dose of less than 5 grams. Dapsone-exposed servicemen whose total dose of dapsone differed by 5 grams were estimated to have a 1.1-fold difference in their total cancer incidence rate (Table 4.11). The 95 per cent confidence interval, 0.8 to 1.5, includes no difference in cancer incidence for servicemen exposed to different doses of dapsone. The upper limit of this confidence interval shows that the data from this study are inconsistent with large differences in total cancer incidence for servicemen exposed to different total doses of dapsone; that is, Vietnam veterans who took more dapsone did not appear to be much more likely to develop cancer than those who took less dapsone.

Different sites of cancer

Figure 5.10 shows the estimated relative cancer incidence rates for dapsone-exposed Vietnam veterans compared with unexposed Vietnam veterans for all sites and for 22 other groupings of sites. The sites are ordered by their estimated relative cancer incidence rates. The figure also shows 95 per cent confidence intervals for each estimate.

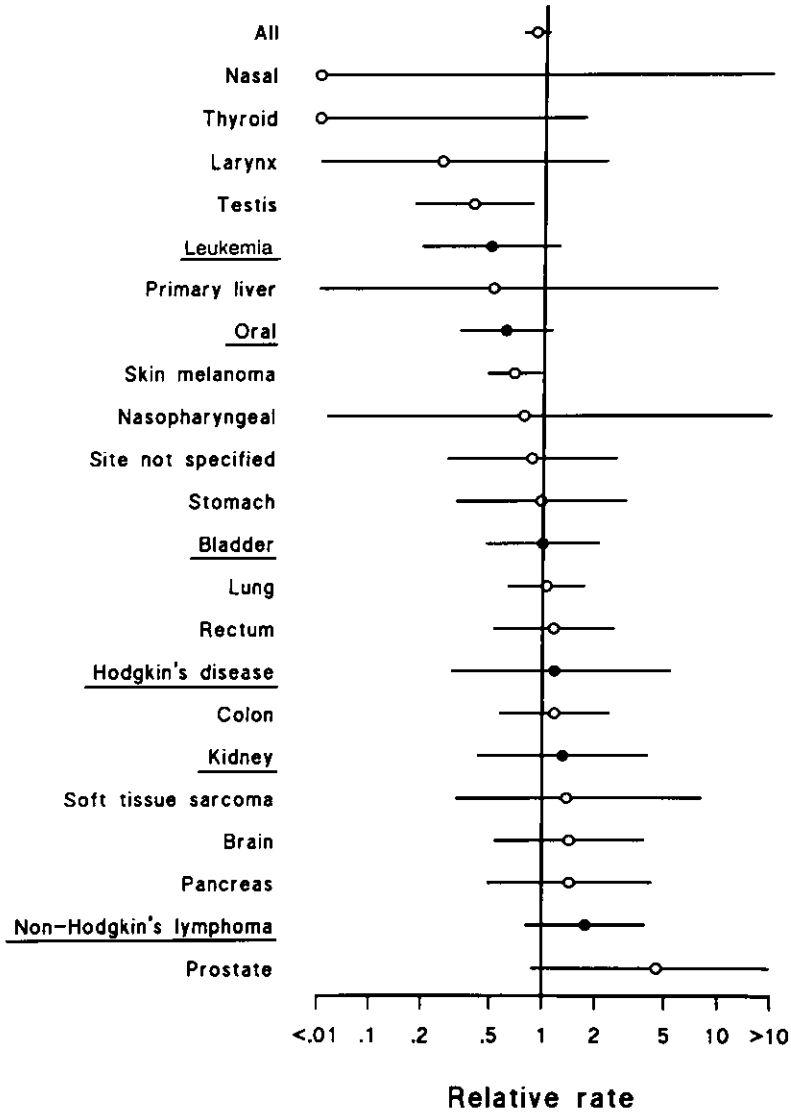

Figure 5.10 *Cancer incidence rate of dapsone-exposed Vietnam veterans compared with other Vietnam veterans, by cancer site*

Note: Equal rates in the two groups corresponds to a relative rate of 1. The estimated relative rate is shown, together with its exact 95% confidence interval (from Table 4.6). Sites of a priori interest in terms of dapsone exposure are underlined, with the estimated relative rate shown as a solid circle. The estimated rates are adjusted for age of the servicemen and for calendar year of cancer registration.

For none of the 28 sites of cancer examined was the cancer incidence among the dapsone-exposed servicemen statistically significantly greater than that among other Vietnam veterans (Figure 5.10; Table 4.6). For no site of cancer examined was there a statistically significant dose–response relationship between the total amount of dapsone received and cancer incidence (Table 4.11).

For one cancer, that of the testis, the rate of occurrence was much less than expected. Its incidence was nominally statistically significantly lower for the dapsone-exposed servicemen compared with other Vietnam veterans (Table 4.6). The dose-response relationship with dapsone exposure was, however, contradictory (Table 4.11). More importantly, there is no plausible biological explanation for a protective effect of dapsone exposure. With so many sites of cancer being examined, it is to be expected that one or more sites with no underlying relationship with cancer incidence would show nominally statistically significant variation in cancer incidence. Accordingly, it is unlikely that dapsone exposure protects against testicular cancer.

Specific sites of cancer

Six sites of cancer—non-Hodgkin's lymphoma, kidney, Hodgkin's disease, bladder, oral and leukemia—were of particular interest because previous research, independent of this study, had suggested that they might be associated with dapsone exposure. None of these sites had, however, shown particularly marked relationships with dapsone exposure in these other data sets. (These six sites are underlined in Figure 5.10.) This was also the case in this study, as shown in the following table.

Relative cancer incidence rates and dose responses among Vietnam veterans compared with non-veterans: specific sites

	Dapsone-exposed compared with other Vietnam veterans		Dose response with 5g total dose of dapsone	
Cancer site	**Relative rate**	**95% CI**	**Relative rate**	**95% CI**
Non-Hodgkin's lymphoma (ICD 200, 202)	1.8	(0.8, 3.9)	0.5	(0.2, 1.4)
Kidney (ICD 189)	1.3	(0.4, 4.1)	0.5	(0.1, 3.1)
Hodgkin's disease (ICD 201)	1.2	(0.3, 5.5)	1.2	(0.2, 6.6)
Bladder (ICD 188)	1.0	(0.5, 2.1)	2.1	(0.6, 7.3)
Oral (ICD 140–146, 149)	0.6	(0.3, 1.1)	0.9	(0.3, 2.7)
Leukemia (ICD 204–208)	0.5	(0.2, 1.2)	1.8	(0.3, 9.9)

For none of these six sites was the cancer incidence particularly high among dapsone-exposed servicemen compared with other Vietnam veterans. None of the relative rates was statistically significantly different from equal cancer incidence rates in the two groups of servicemen. The dose–response relationships were also unremarkable.

The observed relative rates are similar to those for total cancer incidence and for other sites of cancer. If dapsone exposure were causing some cancers, increased cancer incidence should be apparent among some or all of these six specific sites of cancer, even if the elevation in rates was not statistically significant. Cancer incidence for these six sites of cancer, individually and collectively, cannot be taken as definite evidence that dapsone exposure has led to an increased number of cancers.

The wide confidence intervals for some comparisons show, however, that this study has low power to detect differences in cancer incidence for some sites of cancer. The study's maximum latency period between dapsone exposure and registration of a cancer is 24 years, so an increase in cancer incidence 20 or more years after exposure to dapsone may not be detected.

Cancer incidence and malaria

Had there been an association between dapsone exposure and cancer incidence, a possible complication could have been that servicemen who had had malaria may be predisposed to cancer. No association was found between dapsone exposure and cancer incidence. Moreover, so far as could be ascertained with only eight cancer cases among servicemen who had had malaria, cancer incidence appeared not to be associated with having had malaria.

Cancer incidence and Vietnam service

Total cancer incidence

The overall relative cancer incidence rate for Vietnam veterans compared with non-veterans (those who had not been posted to Vietnam) was 0.99 (Table 4.17). The 95 per cent confidence interval for the relative rate is 0.89 to 1.10, which includes equal incidence rates in both groups. The upper limit shows that the data from this study are inconsistent with a markedly higher total cancer incidence among Vietnam veterans compared with non-veterans.

Different sites of cancer

Figure 5.11 shows the estimated relative cancer incidence rates for Vietnam veterans compared with non-veterans for all sites and for 22 other groupings of sites. The sites are ordered by their estimated relative cancer incidence rates. The figure also shows 95 per cent confidence intervals for each estimate.

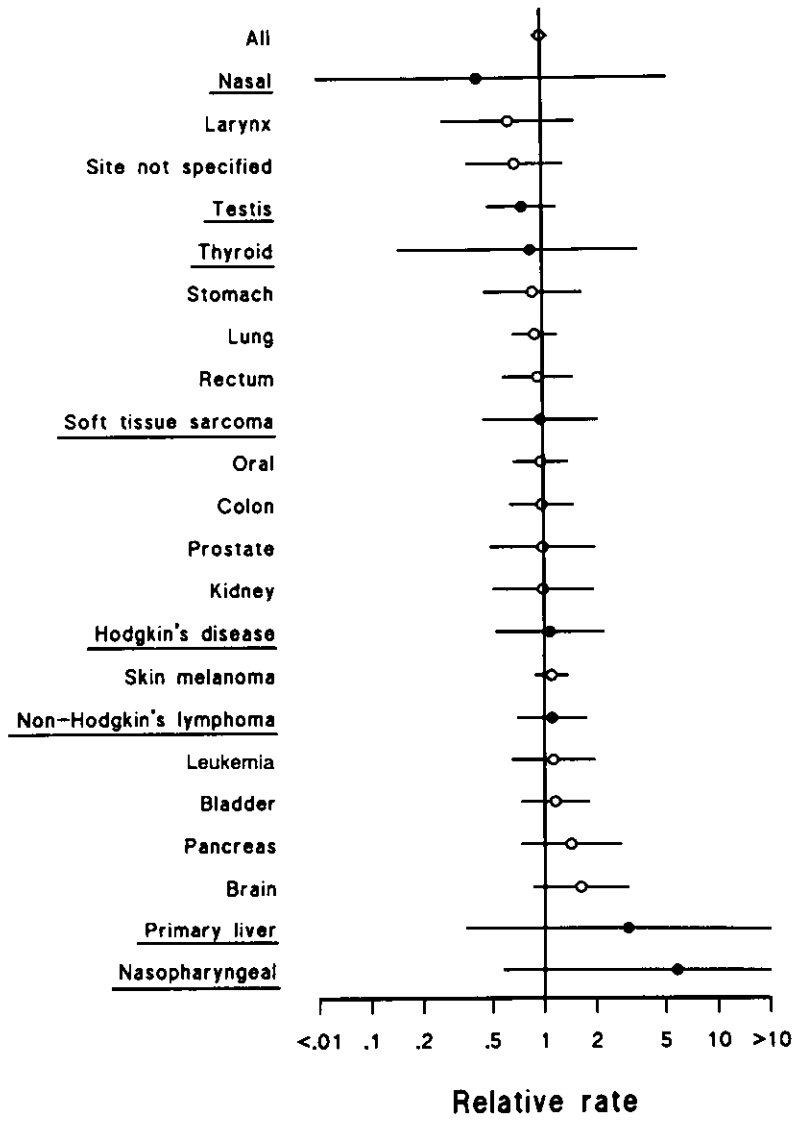

Figure 5.11 *Cancer incidence rate of Vietnam veterans compared with non-veterans, by cancer site*

Note: Equal rates in the two groups corresponds to a relative rate of 1. The estimated relative rate is shown, together with its exact 95% confidence interval (from Table 4.17). Sites of a priori interest in terms of herbicide exposure are underlined, with the estimated relative rate shown as a solid circle. The estimated rates are adjusted for age of the servicemen and for calendar year of cancer registration.

For none of the 28 sites of cancer examined was the cancer incidence among Vietnam veterans statistically significantly greater than that among non-veterans (Figure 5.11; Table 4.17). This was also true for servicemen who had served as volunteers in the Australian Regular Army (Table 4.19). Among those who served as National Servicemen, three sites of cancer—pancreas, lung and brain—showed statistically significantly higher incidence among Vietnam veterans compared with non-veterans (Table 4.18), as follows.

Relative cancer incidence rates among Vietnam veterans compared with non-veterans: selected sites

	National Service		Australian Regular Army	
Cancer site	Relative rate	95% CI	Relative rate	95% CI
Pancreas (ICD 157)	11.0	(1.4 , >10.0)	0.9	(0.4, 2.1)
Lung (ICD 162)	3.9	(1.5 , 10.0)	0.8	(0.5, 1.1)
Brain (ICD 191)	3.0	(1.1 , 8.2)	1.0	(0.4, 2.3)

There was nothing in the medical literature to link these three sites of cancer with Vietnam service. Curiously, any increased risk is apparently confined to National Servicemen because the estimated risks for these sites of cancer among members of the Australian Regular Army are not greater than unity. This could, however, occur if there were some relevant aspect of Vietnam service that differed substantially between these two groups of servicemen.

A statistical issue is that these three nominally statistically significant results have occurred when testing for differences at 29 sites in the two service groups. With so many tests, it is to be expected that, even if there were no real underlying difference, chance would result in a few being nominally statistically significant. For 58 tests, the expected number of nominally statistically significant raised estimates is 1.4, and observing three such results is not unusual.

Specific sites of cancer

Eight sites of cancer—nasopharyngeal, primary liver, non-Hodgkin's lymphoma, Hodgkin's disease, soft tissue and other sarcoma, thyroid, testis and nasal—were of particular interest because previous research, independent of this study, had nominated them as possibly being associated with herbicide exposure. (These sites are underlined in Figure 5.11.) Relative cancer incidence rates for these sites of cancer (Table 4.17) are shown in the following table.

If herbicide exposure were causing some cancers and if Vietnam veterans were exposed to herbicides, increased cancer incidence should be apparent among some or all of the specific sites of cancer, even if the elevation in rates was not statistically significant. For no site is cancer incidence among Vietnam veterans statistically significantly different from that among non-veterans. The two highest and the lowest estimated relative rates are based on five or fewer cancer cases, and the confidence

Relative cancer incidence rates among Vietnam veterans compared with non-veterans: specific sites

	Vietnam veterans compared with non-veterans	
Cancer site	**Relative rate**	**95% CI**
Nasopharyngeal (ICD 147)	5.8	(0.6, >10.0)
Primary liver (ICD 155)	3.0	(0.3, >10.0)
Non-Hodgkin's lymphoma (ICD 200, 202)	1.1	(0.7, 1.8)
Hodgkin's disease (ICD 201)	1.1	(0.5, 2.2)
Soft tissue and other sarcoma (ICD 170–171)	1.0	(0.4, 2.1)
Thyroid (ICD 193)	0.9	(0.1, 3.5)
Testis (ICD 186)	0.8	(0.5, 1.2)
Nasal (ICD 160)	0.4	(0.0, 5.3)

intervals are correspondingly wide. The other five estimated rates, based on more than 10 cancer cases, are close to unity. Cancer incidence for these five sites, individually and collectively, cannot be taken as definite evidence that posting to Vietnam has led to an increased number of cancers.

The wide confidence intervals for some comparisons show, however, that this study has low power to detect differences in cancer incidence for some sites of cancer. The study's maximum latency period between dapsone exposure and registration of a cancer is 24 years, so an increase in cancer incidence 20 or more years after exposure to dapsone may not be detected.

Limitations of the study

This study is of all Australian Army servicemen of the Vietnam conflict era. It has used all available information from Australian cancer registries to identify cancers registered between 1972 and 1989 in the study cohort. It is therefore as comprehensive as possible.

Despite this, few cancers were identified for some sites of cancer. This means that the corresponding confidence intervals for the relative rates were wide and only limited conclusions can be made for these sites. For these sites the data from this study are consistent with equal cancer incidence in the two groups being compared, but they cannot rule out an increased incidence.

The study cohort—National Servicemen and Australian Regular Army members—was enumerated by the Australian Veterans' Health Studies for its study of mortality among National Servicemen. The study cohort is known to be complete and to have correct identification of Vietnam veterans.

Data on the use of dapsone for treatment and prevention of malaria were collated from historical sources. The reliability of the data on exposure to dapsone as a preventive measure depends on knowing postings information for each Vietnam veteran. This information had been checked, and corrected as necessary, by the

Australian Veterans' Health Studies for its calculation of combat indices. It is known, however, that some servicemen spent some time not with their posted unit. This could lead to miscalculation of the total dapsone dose for such servicemen. Nevertheless, the study team believes that such misclassification would be minor, especially in relation to dapsone exposure status.

The closeness of cancer incidence rates in the study cohort to those in the Australian male population in 1982 to 1984 suggests that the matching process was performed with good sensitivity and specificity.

The most recent cancers in the study were registered in 1989. This means that the longest possible latency between dapsone (or Vietnam service) exposure and cancer incidence is 24 years. This study cannot therefore detect cancers occurring with latencies longer than this. Indeed, the distribution of registration years for the cancer registries (Figure 4.1; Table 4.3) shows that the study data are concentrated on cancers occurring 10 to 15 years after dapsone exposure or Vietnam service. The study also has the most comprehensive data possible for cancers occurring earlier than this.

Table 5.1 *All cancers*

Site of cancer	Observed number of cancers: Exposed	Unexposed	Relative rate	95% CI	Test statistic
All cancers (ICD 140–208)					
Dapsone					
NS+ARA	247	262	0.88	(0.74, 1.05)	2.1
NS	83	80	0.68	(0.50, 0.92)	6.2*
ARA	164	182	1.00	(0.81, 1.23)	0.0
Trend with dose			1.1	(0.8 , 1.5)	0.6
Malaria	8	501	0.8	(0.4 , 1.6)	
Vietnam service					
NS+ARA	509	1129	0.99	(0.89, 1.10)	0.0
NS	163	290	1.05	(0.87, 1.28)	0.3
ARA	346	839	0.97	(0.86, 1.10)	0.2
All (1982–84)		616	1.05	(0.97, 1.13)	1.3
Site not specified (ICD 195–199)					
Dapsone					
NS+ARA	6	6	0.9	(0.3 , 2.7)	0.1
NS	2	3	0.4	(0.0 , 3.7)	0.9
ARA	4	3	1.5	(0.2 , 9.9)	0.2
Trend with dose			2.7	(0.4 , >10)	1.2
Malaria	0	12	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	12	40	0.7	(0.4 , 1.3)	1.3
NS	5	5	1.8	(0.5 , 6.3)	0.9
ARA	7	35	0.5	(0.2 , 1.1)	3.4
All (1982–84)		••			

•• Not available.

Note: Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except that marked * ($0.01 < p < 0.05$).

'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 5.2 *Hodgkin's disease and non-Hodgkin's lymphoma*

Site of cancer	Observed number of cancers: Exposed	Unexposed	Relative rate	95% CI	Test statistic
Lympho- & reticulo- sarcoma (ICD 200)					
Dapsone					
NS+ARA	15	7	1.9	(0.8 , 4.7)	2.2
NS	2	3	1.0	(0.1 , 9.1)	0.0
ARA	13	4	2.7	(0.8 , >10)	3.4
Trend with dose			0.4	(0.1 , 1.3)	2.5
Malaria	0	22	0.0	(0.0 , 7.8)	
Vietnam service					
NS+ARA	22	25	1.6	(0.9 , 2.8)	2.2
NS	5	5	1.6	(0.4 , 5.4)	0.5
ARA	17	20	1.5	(0.8 , 2.9)	1.7
All (1982–84)	**				
Hodgkin's disease (ICD 201)					
Dapsone					
NS+ARA	7	4	1.2	(0.3 , 5.5)	0.1
NS	1	2	0.2	(0.0 , 3.6)	2.0
ARA	6	2	2.5	(0.4 , >10)	1.4
Trend with dose			1.2	(0.2 , 6.6)	0.1
Malaria	0	11	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	11	22	1.1	(0.5 , 2.2)	0.0
NS	3	11	0.6	(0.1 , 2.1)	0.9
ARA	8	11	1.6	(0.6 , 3.9)	0.9
All (1982–84)	11		1.1	(0.5 , 1.9)	0.0
Other lymphoid (ICD 202)					
Dapsone					
NS+ARA	4	2	1.3	(0.2 , >10)	0.1
NS	3	1	2.3	(0.2 , >10)	0.6
ARA	1	1	0.7	(0.0 , >10)	0.1
Trend with dose			1.0	(0.1 , 9.2)	0.0
Malaria	0	6	0.0	(0.0 , >10)	

Table 5.2 (continued) *Hodgkin's disease and non-Hodgkin's lymphoma*

Site of cancer	Observed number of cancers: Exposed	Unexposed	Relative rate	95% CI	Test statistic
Vietnam service					
NS+ARA	6	22	0.6	(0.2 , 1.4)	1.8
NS	4	8	0.9	(0.2 , 3.4)	0.0
ARA	2	14	0.3	(0.0 , 1.4)	2.9
All (1982–84)		••			
Non-Hodgkin's lymphoma (ICD 200, 202)					
Dapsone					
NS+ARA	19	9	1.8	(0.8 , 3.9)	2.1
NS	5	4	1.4	(0.3 , 7.1)	0.3
ARA	14	5	2.3	(0.8 , 6.3)	2.8
Trend with dose			0.5	(0.2 , 1.4)	1.9
Malaria	0	28	0.0	(0.0 , 5.6)	
Vietnam service					
NS+ARA	28	47	1.1	(0.7 , 1.8)	0.2
NS	9	13	1.2	(0.5 , 2.8)	0.1
ARA	19	34	1.1	(0.6 , 1.9)	0.1
All (1982–84)		23	0.9	(0.6 , 1.4)	0.3

•• Not available.

Note: Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 5.3 Leukemia

Site of cancer	Observed number of cancers: Exposed	Observed number of cancers: Unexposed	Relative rate	95% CI	Test statistic
Leukemia (ICD 204–208)					
Dapsone					
NS+ARA	7	13	0.5	(0.2 , 1.2)	2.4
NS	4	2	1.1	(0.2 , >10)	0.0
ARA	3	11	0.3	(0.1 , 1.2)	3.9*
Trend with dose			1.8	(0.3 , 9.9)	0.5
Malaria	0	20	0.0	(0.0 , 8.5)	
Vietnam service					
NS+ARA	20	32	1.1	(0.6 , 2.0)	0.2
NS	6	11	1.1	(0.4 , 3.0)	0.1
ARA	14	21	1.1	(0.5 , 2.1)	0.0
All (1982–84)	19		1.3	(0.8 , 2.1)	1.5
Myelocytic leukemia (ICD 205)					
Dapsone					
NS+ARA	3	9	0.3	(0.1 , 1.2)	4.0*
NS	3	2	0.9	(0.1 , >10)	0.0
ARA	0	7	0.0	(0.0 , 0.6)	9.1**
Trend with dose			0.7	(0.1 , 8.1)	0.1
Malaria	0	12	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	12	20	1.0	(0.5 , 2.1)	0.0
NS	5	7	1.2	(0.4 , 3.9)	0.1
ARA	7	13	0.9	(0.4 , 2.3)	0.0
All (1982–84)	10		1.1	(0.5 , 2.0)	0.1

Note: Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 5.4 *Soft tissue and other sarcomas*

Site of cancer	Observed number of cancers: Exposed	Unexposed	Relative rate	95% CI	Test statistic
Soft tissue cancers (ICD 170–171)					
Dapsone					
NS+ARA	7	3	1.4	(0.3 , 8.3)	0.2
NS	3	2	0.7	(0.1 , 8.3)	0.2
ARA	4	1	3.2	(0.3 , >10)	1.3
Trend with dose			1.1	(0.2 , 5.9)	0.0
Malaria	0	10	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	10	19	1.0	(0.4 , 2.1)	0.0
NS	5	10	0.9	(0.3 , 2.6)	0.1
ARA	5	9	1.1	(0.4 , 3.3)	0.0
All (1982–84)	10		1.0	(0.5 , 1.8)	0.0
Bone (ICD 170)					
Dapsone					
NS+ARA	2	1	1.3	(0.1 , >10)	0.0
NS	1	1	0.4	(0.0 , >10)	0.3
ARA	1	0	∞	(0.1 , ∞)	1.6
Trend with dose			1.1	(0.0 , >10)	0.0
Malaria	0	3	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	3	7	0.8	(0.1 , 3.5)	0.1
NS	2	3	1.1	(0.1 , 9.9)	0.0
ARA	1	4	0.5	(0.0 , 5.2)	0.4
All (1982–84)	2		0.5	(0.1 , 2.0)	0.9
Connective tissue (ICD 171)					
Dapsone					
NS+ARA	5	2	1.4	(0.2 , >10)	0.2
NS	2	1	0.9	(0.0 , >10)	0.0
ARA	3	1	2.2	(0.2 , >10)	0.5
Trend with dose			1.1	(0.2 , 8.1)	0.0
Malaria	0	7	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	7	12	1.1	(0.4 , 2.7)	0.0
NS	3	7	0.8	(0.1 , 3.3)	0.2
ARA	4	5	1.6	(0.3 , 7.3)	0.5
All (1982–84)	8		1.3	(0.5 , 2.5)	0.4

Note: Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 5.5 *Cancers of the mouth and respiratory system*

Site of cancer	Observed number of cancers: Exposed	Unexposed	Relative rate	95% CI	Test statistic
Oral (ICD 140–146, 149)					
Dapsone					
NS+ARA	16	27	0.6	(0.3 , 1.1)	2.7
NS	3	3	0.6	(0.1 , 4.6)	0.4
ARA	13	24	0.6	(0.3 , 1.2)	2.3
Trend with dose			0.9	(0.3 , 2.7)	0.0
Malaria	0	43	0.0	(0.0 , 3.7)	
Vietnam service					
NS+ARA	43	84	1.0	(0.7 , 1.4)	0.0
NS	6	24	0.5	(0.2 , 1.1)	3.5
ARA	37	60	1.2	(0.8 , 1.7)	0.5
All (1982–84)	62		1.3	(1.0 , 1.7)	4.8*
Nasopharyngeal (ICD 147)					
Dapsone					
NS+ARA	2	2	0.8	(0.1 , >10)	0.1
NS	1	1	0.6	(0.0 , >10)	0.1
ARA	1	1	1.1	(0.0 , >10)	0.0
Trend with dose			0.3	(0.0 , 8.7)	0.5
Malaria	0	4	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	4	1	5.8	(0.6 , >10)	3.2
NS	2	0	∞	(0.4 , ∞)	3.6
ARA	2	1	2.7	(0.1 , >10)	0.7
All (1982–84)	2		0.6	(0.1 , 2.0)	0.8
Nasal (ICD 160)					
Dapsone					
NS+ARA	0	1	0.0	(0.0 , >10)	1.1
NS	0	0	-		
ARA	0	1	0.0	(0.0 , >10)	1.1
Trend with dose			-		
Malaria	0	1	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	1	3	0.4	(0.0 , 5.3)	0.6
NS	0	2	0.0	(0.0 , 4.9)	2.1
ARA	1	1	1.4	(0.0 , >10)	0.0
All (1982–84)	2		0.8	(0.1 , 2.9)	0.1

Table 5.5 (continued) *Cancers of the mouth and respiratory system*

Site of cancer	Observed number of cancers: Exposed	Observed number of cancers: Unexposed	Relative rate	95% CI	Test statistic
Lip (ICD 140)					
Dapsone					
NS+ARA	9	13	0.6	(0.2 , 1.3)	1.9
NS	2	3	0.4	(0.0 , 3.6)	1.0
ARA	7	10	0.6	(0.2 , 1.7)	0.9
Trend with dose			2.6	(0.5 , >10)	1.5
Malaria	0	22	0.0	(0.0 , 5.7)	
Vietnam service					
NS+ARA	22	44	0.9	(0.5 , 1.5)	0.2
NS	5	20	0.5	(0.2 , 1.2)	2.7
ARA	17	24	1.2	(0.6 , 2.2)	0.3
All (1982–84)	31		1.2	(0.8 , 1.7)	0.8
Larynx (ICD 161)					
Dapsone					
NS+ARA	1	5	0.3	(0.0 , 2.3)	2.0
NS	0	2	0.0	(0.0 , 3.1)	3.0
ARA	1	3	0.5	(0.0 , 6.4)	0.4
Trend with dose			0.0	(0.0 , ∞)	-
Malaria	0	6	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	6	27	0.6	(0.3 , 1.6)	1.0
NS	2	2	2.2	(0.2 , >10)	0.6
ARA	4	25	0.5	(0.1 , 1.4)	1.9
All (1982–84)	19		1.7	(1.0 , 2.6)	4.4*
Lung (ICD 162)					
Dapsone					
NS+ARA	28	31	1.1	(0.6 , 1.8)	0.0
NS	7	6	0.8	(0.3 , 2.4)	0.2
ARA	21	25	1.1	(0.6 , 2.0)	0.2
Trend with dose			1.4	(0.6 , 3.2)	0.6
Malaria	0	59	0.0	(0.0 , 3.2)	
Vietnam service					
NS+ARA	59	164	0.9	(0.7 , 1.2)	0.5
NS	13	6	3.9	(1.5 , 10)	8.3**
ARA	46	158	0.8	(0.5 , 1.1)	2.9
All (1982–84)	79		1.0	(0.8 , 1.2)	0.2

Note: Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 5.6 *Cancers of the digestive system*

Site of cancer	Observed number of cancers: Exposed	Observed number of cancers: Unexposed	Relative rate	95% CI	Test statistic
Stomach (ICD 151)					
Dapsone					
NS+ARA	6	6	1.0	(0.3 , 3.0)	0.0
NS	2	3	0.3	(0.0 , 3.0)	1.4
ARA	4	3	1.9	(0.3 , >10)	0.7
Trend with dose			0.7	(0.1 , 3.9)	0.2
Malaria	0	12	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	12	33	0.9	(0.5 , 1.7)	0.2
NS	5	5	1.8	(0.5 , 6.2)	0.9
ARA	7	28	0.7	(0.3 , 1.5)	0.9
All (1982–84)	13		0.6	(0.3 , 1.1)	3.4
Colon (ICD 153)					
Dapsone					
NS+ARA	15	14	1.2	(0.6 , 2.4)	0.2
NS	3	4	0.6	(0.1 , 3.5)	0.5
ARA	12	10	1.4	(0.6 , 3.4)	0.7
Trend with dose			1.1	(0.4 , 3.4)	0.1
Malaria	2	27	5.2	(0.6 , >10)	
Vietnam service					
NS+ARA	29	76	1.0	(0.6 , 1.5)	0.0
NS	7	16	0.7	(0.3 , 1.8)	0.5
ARA	22	60	1.1	(0.7 , 1.8)	0.2
All (1982–84)	38		0.8	(0.6 , 1.1)	1.7
Rectum (ICD 154)					
Dapsone					
NS+ARA	12	12	1.2	(0.5 , 2.6)	0.1
NS	4	1	2.6	(0.3 , >10)	0.9
ARA	8	11	1.0	(0.4 , 2.4)	0.0
Trend with dose			2.1	(0.6 , 7.6)	1.3
Malaria	1	23	2.5	(0.1 , >10)	
Vietnam service					
NS+ARA	24	62	0.9	(0.6 , 1.5)	0.1
NS	5	11	0.9	(0.3 , 2.5)	0.1
ARA	19	51	1.0	(0.6 , 1.6)	0.0
All (1982–84)	33		1.2	(0.8 , 1.7)	0.9

Note: Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$.

'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 5.7 *Skin melanoma*

Site of cancer	Observed number of cancers: Exposed	Observed number of cancers: Unexposed	Relative rate	95% CI	Test statistic
Skin melanoma (ICD 172)					
Dapsone					
NS+ARA	56	65	0.7	(0.5 , 1.0)	4.7*
NS	23	30	0.5	(0.3 , 0.8)	8.1**
ARA	33	35	0.9	(0.6 , 1.4)	0.2
Trend with dose			1.2	(0.7 , 2.2)	0.4
Malaria	5	116	1.9	(0.8 , 4.7)	
Vietnam service					
NS+ARA	121	208	1.1	(0.9 , 1.4)	0.7
NS	53	93	1.1	(0.8 , 1.5)	0.2
ARA	68	115	1.1	(0.8 , 1.5)	0.7
All (1982–84)	94		1.3	(1.0 , 1.5)	4.4*

Note: Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

Table 5.8 *Cancers of other organs*

Site of cancer	Observed number of cancers: Exposed	Observed number of cancers: Unexposed	Relative rate	95% CI	Test statistic
Primary liver (ICD 155)					
Dapsone					
NS+ARA	1	2	0.5	(0.0 , 9.8)	0.3
NS	0	0	-		
ARA	1	2	0.5	(0.0 , 9.9)	0.3
Trend with dose			2.4	(0.0 , >10)	0.1
Malaria	0	3	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	3	2	3.0	(0.3 , >10)	1.5
NS	0	0	-		
ARA	3	2	2.8	(0.3 , >10)	1.3
All (1982–84)	1		0.3	(0.0 , 1.4)	3.0
Testis (ICD 186)					
Dapsone					
NS+ARA	10	16	0.4	(0.2 , 0.9)	5.7*
NS	4	7	0.3	(0.1 , 1.1)	4.5*
ARA	6	9	0.5	(0.2 , 1.4)	1.7
Trend with dose			3.0	(0.7 , >10)	2.2
Malaria	0	26	0.0	(0.0 , 5.1)	
Vietnam service					
NS+ARA	26	57	0.8	(0.5 , 1.2)	1.3
NS	11	37	0.6	(0.3 , 1.1)	3.0
ARA	15	20	1.0	(0.5 , 2.0)	0.0
All (1982–84)	24		0.9	(0.6 , 1.3)	0.4
Bladder (ICD 188)					
Dapsone					
NS+ARA	13	14	1.0	(0.5 , 2.1)	0.0
NS	5	2	1.5	(0.2 , >10)	0.2
ARA	8	12	0.9	(0.4 , 2.1)	0.1
Trend with dose			2.1	(0.6 , 7.3)	1.3
Malaria	0	27	0.0	(0.0 , 6.6)	
Vietnam service					
NS+ARA	27	54	1.2	(0.7 , 1.8)	0.4
NS	7	12	0.9	(0.4 , 2.3)	0.1
ARA	20	42	1.3	(0.7 , 2.1)	0.7
All (1982–84)	45		1.5	(1.5 , 2.0)	6.6*

Table 5.8 (continued) *Cancers of other organs*

Site of cancer	Observed number of cancers: Exposed	Observed number of cancers: Unexposed	Relative rate	95% CI	Test statistic
Kidney (ICD 189)					
Dapsone					
NS+ARA	6	6	1.3	(0.4 , 4.1)	0.2
NS	0	3	0.0	(0.0 , 2.3)	3.4
ARA	6	3	2.7	(0.6 , >10)	2.1
Trend with dose			0.5	(0.1 , 3.1)	0.5
Malaria	0	12	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	12	28	1.0	(0.5 , 1.9)	0.0
NS	3	6	1.1	(0.2 , 5.3)	0.0
ARA	9	22	1.0	(0.4 , 2.1)	0.0
All (1982–84)		19	1.2	(0.7 , 1.9)	0.6
Thyroid (ICD 193)					
Dapsone					
NS+ARA	0	3	0.0	(0.0 , 1.7)	4.1*
NS	0	0			
ARA	0	3	0.0	(0.0 , 1.8)	4.1*
Trend with dose		-			
Malaria	0	3	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	3	8	0.9	(0.1 , 3.5)	0.1
NS	0	5	0.0	(0.0 , 1.6)	4.1*
ARA	3	3	2.8	(0.4 , >10)	1.6
All (1982–84)		5	1.0	(0.3 , 2.4)	0.0
Pancreas (ICD 157)					
Dapsone					
NS+ARA	7	6	1.4	(0.5 , 4.3)	0.4
NS	4	3	1.7	(0.3 , >10)	0.4
ARA	3	3	1.4	(0.2 , >10)	0.2
Trend with dose			0.5	(0.1 , 2.4)	0.8
Malaria	0	13	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	13	25	1.4	(0.7 , 2.8)	1.0
NS	7	1	11	(1.4 , >10)	8.0**
ARA	6	24	0.9	(0.4 , 2.1)	0.1
All (1982–84)		11	0.8	(0.4 , 1.5)	0.5

Table 5.8 (continued) *Cancers of other organs*

Site of cancer	Observed number of cancers: Exposed	Observed number of cancers: Unexposed	Relative rate	95% CI	Test statistic
Prostate (ICD 185)					
Dapsone					
NS+ARA	7	2	4.5	(0.9 , >10)	4.4*
NS	2	0	∞	(0.2 , ∞)	2.2
ARA	5	2	3.7	(0.6 , >10)	2.8
Trend with dose			0.4	(0.1 , 2.3)	0.9
Malaria	0	9	0.0	(0.0 , >10)	
Vietnam service					
NS+ARA	9	56	1.0	(0.5 , 2.0)	0.0
NS	2	1	2.8	(0.1 , >10)	0.8
ARA	7	55	0.9	(0.4 , 2.0)	0.1
All (1982–84)		31	0.9	(0.6 , 1.3)	0.5
Brain (ICD 191)					
Dapsone					
NS+ARA	11	6	1.4	(0.5 , 3.9)	0.5
NS	6	2	1.9	(0.3 , >10)	0.6
ARA	5	4	1.3	(0.3 , 6.6)	0.2
Trend with dose			0.9	(0.2 , 3.2)	0.1
Malaria	0	17	0.0	(0.0 , 8.1)	
Vietnam service					
NS+ARA	17	21	1.6	(0.9 , 3.1)	2.1
NS	8	7	3.0	(1.1 , 8.2)	4.3*
ARA	9	14	1.0	(0.4 , 2.3)	0.0
All (1982–84)		18	0.9	(0.5 , 1.4)	0.3

Note: Poisson regression test statistics are asymptotically chi-square tests with 1 degree of freedom. All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

'NS' denotes National Service; 'ARA' denotes Australian Regular Army.

6 Conclusion

The study revealed no definite evidence that dapsone exposure was associated with an increase in total cancer incidence. Cancer incidence was assessed at six sites that had been suggested in previous publications as those for which an effect of dapsone was most likely. The study does not provide definite evidence of increased cancer incidence at these sites. Similar conclusions apply to the other 22 sites that were examined.

The study revealed no definite evidence that Vietnam service was associated with an increase in total cancer incidence. Cancer incidence was assessed at eight sites that had been suggested in previous publications as those for which an effect of exposure to herbicides was most likely. This study does not provide definite evidence of increased cancer incidence at these sites. Similar conclusions apply to the other 20 sites that were examined.

For those sites of cancer with few cases the confidence intervals were wide. The study results cannot therefore rule out an increased incidence at one or more of these sites.

The most recent cancer registration used in this study was for 1989, 24 years after first exposure to dapsone or service in Vietnam. Accordingly, this study cannot detect cancers that may arise at greater latencies after exposure to dapsone or Vietnam service.

Appendix A: Protocol for an epidemiological study of cancer in servicemen of the Vietnam era particularly in relation to the use of dapsone

A.1 Background

A.1.1 Use of dapsone in Vietnam

During the war in Vietnam, Australian forces used the drug dapsone for treatment and later for prevention of falciparum malaria. According to Black (1973), dapsone was highly effective as an anti-malarial, reducing the number of falciparum malaria cases in the Australian Army from 442 in 1968 to 32 in 1969 in a slightly larger force.

The earliest record so far found of the use of dapsone to treat falciparum malaria in Australian servicemen in Vietnam is dated August 1966. The drug was used for treatment of virtually all cases of falciparum malaria from September 1967 until the departure of Australian forces in 1972. The regimen included 25 mg per day for 30 days.

Dapsone was first used for malaria prophylaxis, also in a dose regimen of 25 mg per day, in a trial that began on 23 October 1968. From 17 November 1968 all Australian Army personnel in Vietnam received dapsone.

The use of dapsone led to serious adverse effects, leukopenia or agranulocytosis, in a small proportion of users. Once this effect was recognised, the drug was used only at times of threatened or actual outbreaks of falciparum malaria when the risk of death from falciparum malaria was considered to exceed that of death from the adverse effects. The requirement to maintain operational capability was also a major factor in decision making.

The administration of dapsone to all Australian Army members in Vietnam that had started in November 1968 continued until 10 February 1970. The drug was again issued for prophylaxis, but only to units of 1 Australian Task Force (1ATF) and of the Australian Army Training Team (AATTV) located in Phuoc Tuy Province, from 5 August 1970 to 28 February 1971 and from 3 August 1971 until the departure of 1ATF.

The Department of Veterans' Affairs and the Official History Unit of the Australian War Memorial have each prepared an analysis of the use of dapsone by Australian forces in Vietnam. A synthesis of these documents is presented in Attachment I.

A.1.2 Events leading to this study

Some years later public concern arose about the health of Vietnam veterans and their families, especially as it may have been affected by exposure to herbicides, and in particular to Agent Orange. The Australian Veterans' Herbicide Studies, later renamed the Australian Veterans' Health Studies (AVHS), was established to investigate this concern. Amongst its activities was a cohort study of mortality of National Service (NS) Vietnam veterans from the time of their discharge from the Australian Army (or two years after enlistment, whichever occurred first) until the end of 1981. The study found that the cancer mortality to 1981 of former National Servicemen was very similar for those who had served in Vietnam and for those who had not (Fett et al. 1984).

The AVHS findings were included in evidence submitted to the Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam.

The Royal Commission reviewed expert opinion on diapasons potential for carcinogenicity. It gave particular weight to the evidence of Dr Philippe Shubik, whose written submission had stated 'On present evidence I am unable to say whether dapsone is actually carcinogenic in humans', but who had also selected dapsone as 'the most likely compound to pose a potential carcinogenic hazard' amongst all those considered by the Royal Commission.

While the Royal commission stated 'there is of course no evidence that dapsone is actually carcinogenic in man' (Evatt 1985, p. VIII-382) it recommended:

1. THAT government finance through NH&MRC studies of the carcinogenicity of dapsone.
2. THAT any Vietnam veteran suffering from cancer who may have taken dapsone should have his claim treated on the basis that a reasonable hypothesis exists connecting his disease with war service (p. XV-46).

(NH&MRC is the acronym for the National Health and Medical Research Council)

In March 1987 Mr Bob Hogg was appointed as a consultant to the Minister for Veterans' Affairs to co-ordinate the Government's response to the report of the Royal Commission. In October 1987 he reported, recommending:

v. that the Government immediately establish an epidemiological study into the possible health effects arising from the use of Dapsone (Hogg 1987, p. 46)

In the event, the Government accepted this recommendation only as it related to cancer, in effect the common aspect of the two recommendations.

Following the Government decision on the recommendations as they applied to dapsone and cancer, the Department of Veterans' Affairs (DVA) wrote to the NH&MRC concerning the recommendations for studies of carcinogenicity of dapsone. The NH&MRC passed the request for a study of cancer to the Australian Institute of Health (AIH), which was still being formed when the Royal Commission reported, as the most appropriate agency to conduct any epidemiological investigation.

The AIH in turn advised the DVA not to proceed immediately with an epidemiological study, but to determine whether the number of cancers likely to

have occurred among Vietnam veterans would justify a study at this stage, or whether the study should be deferred until sufficient cancers had accumulated. The DVA then commissioned the AIH to investigate this problem. In its report to the Department (Donovan 1989) the Institute estimated the power of the study in relation to cancer as a whole and to particular common cancers, and concluded that a study conducted in 1989–90 would have sufficient power to be worthwhile.

The Government accepted this advice and funded the study in the 1989 Budget. The Minister for Veterans' Affairs subsequently invited a number of scientific bodies to nominate experts who might, as a Scientific Advisory Committee, assure quality of the study.

A.1.3 Arrangement of protocol

This protocol presents the design of a study to examine the incidence of cancer among Vietnam veterans and non-veterans of the Vietnam era and the relationship of cancer incidence to Vietnam service and to use of dapsone in Vietnam. The study also includes an analysis of cancer deaths from the Australian Veterans' Health Studies' (AVHS) Mortality Study in relation to dapsone exposure.

This study design is followed by a section which contains information required by the Australian Institute of Health Ethics Committee.

In conclusion there are three appendices: Attachment I presents information on dapsone exposure and information relevant to calculating the dapsone consumption of individual servicemen, Attachment II identifies sources of information which can be used to identify malaria cases and Attachment III presents matching rules used to link names by the Soundex method.

Some sections of this protocol state that further developmental work is needed before study procedures can be specified precisely. For example, no decision can be made on criteria for matching individuals' records until samples of data are available to show sensitivity and specificity of possible procedures. All such procedures will be devised, tested, and documented as developmental work proceeds. They will be available for assessment by the Scientific Advisory as they are prepared.

A.2 Introduction

A.2.1 Purpose

The aim of this study is to estimate the magnitude of possible effects of Vietnam service and of the use of dapsone on the subsequent incidence of cancer among Australian Vietnam veterans of the Vietnam Conflict, using Australian servicemen of that era for comparison where appropriate.

A.2.2 Aims

The study has the following aims:

1. To examine whether service in Vietnam by Australian Army servicemen during the Vietnam Conflict has increased their overall risk of cancer (International Classification of Diseases codes 140–208);
2. To examine whether service in Vietnam by Australian Army servicemen during the Vietnam Conflict has increased their risk of cancer of a part of the body or of cancer of a particular morphology (of a particular cell type), focusing on:
   - non-Hodgkin's lymphoma (200,202)
   - Hodgkin's disease (201)
   - soft tissue and other sarcomas (170,171)
   - primary liver cancer (155)
   - leukemia (204–208)
   - oral cancer (140–146,149)
   - nasal cancer (160)
   - nasopharyngeal carcinoma (147)
   - bladder cancer (188).
3. To examine whether consumption of dapsone by Australian Army servicemen during the Vietnam conflict has increased their overall risk of cancer;
4. To examine whether consumption of dapsone by Australian Army servicemen during the Vietnam conflict has increased their risk of cancer of a part of the body or of cancer of a particular morphology (of a particular cell type), focusing on:
   - non-Hodgkin's lymphoma (200,202)
   - Hodgkin's disease (201)
   - soft tissue and other sarcomas (170,171)
   - primary liver cancer (155)
   - leukemia (204–208)
   - oral cancer (140–146,149)
   - nasal cancer (160)
   - nasopharyngeal carcinoma (147)
   - bladder cancer (188).

A.2.3 Comparisons of interest

For the time period for which cancer incidence data are obtained, the following groups will be compared in terms of their relative cancer incidence rates:

1. Vietnam veteran study subjects vs non-veteran study subjects;
2. Vietnam veteran study subjects exposed to dapsone vs Vietnam veteran study subjects not exposed to dapsone. This comparison will also be undertaken for study subjects who have consumed different total dosages of dapsone (e.g. nil vs low vs high);
3. Vietnam veteran study subjects exposed to dapsone vs non-veteran study subjects not exposed to dapsone. This comparison will also be undertaken for

study subjects who have consumed different total dosages of dapsone (e.g. nil vs low vs high);

Comparisons 2. and 3. will be conducted separately rather than combine unexposed Vietnam veterans with non-veterans into a single comparison group. This will avoid the possibility that non-comparability of these two groups might obscure a possible effect of dapsone on cancer incidence.

For the time period for which cancer mortality data are available from the AVHS Mortality Study, the following groups will be compared in terms of their relative cancer mortality rates:

1. Vietnam veteran study subjects exposed to dapsone vs Vietnam veteran study subjects not exposed to dapsone.
2. Vietnam veteran study subjects exposed to dapsone vs non-veteran study subjects not exposed to dapsone.

Both comparisons will also be undertaken for study subjects who have consumed different total dosages of dapsone (e.g. nil vs low vs high).

The comparison of Vietnam veteran vs non-veteran cancer mortality has already been presented in the AVHS Mortality Study report (Fett et al. 1984). In that study, there was no difference in cancer mortality up to 1981 between former National Service Vietnam veterans and non-veterans.

A.2.4 Definition of cancer

All cancers identified in Australian cancer registries through electronic linkage will be included in the study as it relates to overall risk of cancer, and these cancers plus those identified in the AVHS mortality study will be included when the risk of cancer in relation to dapsone exposure is being assessed.

A.2.5 Choice of study aims

Cancer types which will be examined in relation to Vietnam service have been chosen because they were studied in the Selected Cancers Study in the United States on the basis of review of the current evidence of possible associations between exposure to phenoxyherbicides and cholorophenols, and the risk of subsequently developing cancer (Selected Cancers Cooperative Study Group 1990a, 1990b, 1990c). The cancers studied will be non-Hodgkin's lymphoma, Hodgkin's disease, soft tissue and other sarcoma, nasal carcinoma, nasopharyngeal carcinoma and primary liver cancer.

Cancer types which will be examined in relation to dapsone have been chosen because of references in the scientific literature to a possible link between these cancers and dapsone (Brinton 1984; IARC 1987). The cancers studied will be non-Hodgkin's lymphoma, Hodgkin's disease, and oral and bladder cancer. Scientific reports which link these cancers to dapsone are summarised in the consultancy which preceded this study (Donovan 1989). Leukemia has also been included because dapsone can be toxic to bone marrow (Stickland & Hurdle 1970) and therefore may cause haematological malignancy.

Other common cancers will be studied where numbers available give reasonable power. Malignant melanoma is known to be related to exposure to sunlight, and so may be related to Vietnam service as well as to dapsone administration. Non-melanotic skin cancers are also related to exposure to sunlight, but are not registered so cannot be studied.

A.2.6 Overview of design of the study

This study has several components:

The incidence of cancer among Vietnam veterans will be compared with the incidence among Army servicemen who served in the same period but did not go to Vietnam. This analysis will be performed for all cancers combined and for specific types of cancers of concern. Study subjects will be all Army servicemen (Regular and National Service) who were eligible for Vietnam service in view of their period of Army service (i.e. greater than 365 days) and their calendar years of service, and served around the time when dapsone was used in Vietnam (i.e. served after 1 January 1965 and first enlisted in the Army before 1 March 1971) (see Section A.3.2).

The incidence of cancer will also be compared among Vietnam veterans with differing known levels of consumption of the anti-malaria drug, dapsone, and their cancer incidence compared with the cancer incidence of non-veteran study subjects. As with the Vietnam/no Vietnam analysis above, this analysis will be performed for all cancers combined and for specific types of cancers of concern (Section A.3.3 and Attachment I). A similar analysis will be conducted for cancer deaths identified by the AVHS Mortality Study.

Data identifying study subjects and giving details of their Army and Vietnam service will be obtained from the Army, with manual verification of data items from Army paper records as required (Section A.3.2).

Data on cancers will be obtained by computerised linkage of individually identified records on Army registers and State/Territory cancer registries. The linkage will be performed using validated matching criteria. Manual verification of source records held by the Army and cancer registries will be undertaken where computerised linkage suggests that pairs of records might represent the same person but differences in data on the two records prevent conclusive matching. Following this verification, computerised matching will be repeated and any partial matches remaining will be subjected to manual matching using criteria validated for manual matching. Cancers found through these linkages will be used for Vietnam veteran vs non-veteran comparisons as well as for comparisons within Vietnam veterans.

In addition to cancer registry searches, cases of cancer among study subjects will also be sought from departmental and hospital records of the Department of Veteran's Affairs. Cancers found only through DVA sources will be added to the cancer registry cases for comparisons within Vietnam veterans but will not be included in Vietnam veteran/non-veteran comparisons, to avoid bias (Section A.3.6).

Cancer deaths identified by the AVHS Mortality Study among former National Servicemen will be obtained from the AVHS data tapes (Section A.3.7).

Following the identification of cases of cancer among study subjects, data on date of diagnosis, topographical codes (International Classification of Diseases; ICD) and morphological codes of diagnosis will be obtained. The morphological codes will be converted to ICD O. This will allow analysis of data for all cases of soft tissue sarcoma (Section A.3.8).

Estimated dapsone consumption for each study subject will be calculated using information from the Australian Defence Force and from the Australian War Memorial on the pattern of usage of dapsone in Vietnam combined with Army information on the postings of individual members of the Army to specific units in Vietnam.

Cases of malaria which occurred in Vietnam will be identified from Defence, War Memorial and DVA records and a malaria register at Sydney University. These data will be combined with the cancer data obtained from the cancer registries to allow some statistical control for a possible association between malaria and cancer in determining whether there is an association between dapsone consumption and risk of cancer (Section A.3.4 and Attachment II).

A.2.7 Limitations

This study has several limitations in determining whether there is a link between Vietnam service and risk of cancer, dapsone consumption and risk of cancer, and malaria and risk of cancer. These limitations are common to all epidemiological studies:

- This study will only be able to identify statistical associations and will not be able to prove that any associations found are or are not causal associations.
- All statistical measures of association (e.g. relative risk) have a degree of imprecision which is partially reflected in statistical confidence intervals.
- The risk of cancer may be influenced by factors other than those measured in this study (i.e. in addition to Vietnam service and dapsone consumption, such as sunlight, tobacco, other chemicals, etc). If the frequency of these unmeasured factors differs among the comparison groups of interest (i.e. Vietnam veterans and non-veterans, dapsone exposed and non-dapsone exposed), statistical associations may be observed between Vietnam service or dapsone and cancer which are not attributable to Vietnam service or dapsone. Similarly, such confounding may obscure a real association between Vietnam service or dapsone and cancer. This possibility will need to be considered when interpreting the results.
- If a statistically significant increase in risk of cancer is observed in relation to Vietnam service in particular, it will probably not be possible to attribute this increased risk to any particular aspect of Vietnam service (e.g. chemicals) with current data. Even with additional data, this may still not be possible.

A.3 Data collection methods

A.3.1 Overview of data collection

The elements of data collection for this study are:

- identify the study population from Army records;
- obtain details of their Army service;
- obtain details of dapsone usage in Vietnam;
- combine Army data with dapsone usage data to calculate the dapsone consumption of individual soldiers;
- identify cases of malaria among the study population;
- link Army identifying information with cancer registry records of persons who have developed cancer to identify subjects who have developed cancer;
- identify additional cases of cancer from DVA departmental and hospital records;
- identify cancer deaths from the AVHS mortality study;
- convert morphological diagnoses for cancers to ICD O; and
- for purposes of analysis, prepare a computer file of records of individual servicemen with details of Army and Vietnam service, cancer details, dapsone exposure and malaria details.

A.3.2 Study population

Study subject selection criteria

The population to be studied will be:

- all males who were members of the Australian Army (both National Servicemen and Regulars) for more than 365 days who:
- served during the period 1 January 1965 to 1 March 1972 inclusive (and thus first enlisted before 1 March 1971) and who:
- did not die during Army service within two years of enlistment.

It is proposed to include non-veteran Army servicemen in the study to provide a comparison group with which to compare Vietnam veterans and to provide another comparison group with which to compare dapsone exposed Vietnam veterans.

The date 1 January 1965 is chosen because few Australian servicemen served in Vietnam before 1965 (see Table A.3.1) and dapsone was probably first used in August 1966. Servicemen who served before but did not serve after 1 January 1965 would tend to be considerably older than servicemen exposed to dapsone, and there are substantial numbers of servicemen who served 12 months after 1 January 1965 (and enlisted before 1 March 1971) to form a suitable comparison group. Dapsone came into widespread use as a malarial prophylactic in late 1968 (see Attachment I). Thus this criterion reduces the number of unexposed, relatively non-comparable servicemen in the study while retaining sufficient numbers of unexposed servicemen.

Table A.3.1 *Australian Army personnel in Vietnam on 1 January each year*

Year	Number of personnel
1962	0
1963	30[a]
1964	89[a]
1965	92[a]
1966	1,479
1967	4,303
1968	6,035
1969	7,171
1970	6,979
1971	6,300
1972	2,334
1973	179
1974	0

[a] Estimate.

Source: Senate Standing Committee on Science and the Environment (1982).

Twelve months is chosen because very few if any servicemen went to Vietnam within 12 months of enlistment. Similarly, very few servicemen who enlisted on or after 1 March 1971 served in Vietnam. (For example, in the AVHS Mortality Study, only 20 National Service Vietnam veterans were excluded because of this restriction, while 14,686 National Service non-veterans were excluded.) Thus, these criteria exclude servicemen who would not have been liable for Vietnam service because of their short period of service or because they enlisted too recently. The latter selection criterion was also used in the AVHS Mortality Study. Its use in the current study enhances the comparability of the two studies and makes data collection more practicable, while having negligible effect on the power of the study.

In the AVHS mortality study deaths (including cancer deaths) were ascertained among a more restricted group of servicemen: only National Servicemen who served for at least two years or were discharged alive after 12 months. This duration of service criterion was used to exclude all National Servicemen who had died in the first two years of service. In the AVHS Mortality Study, this criterion resulted in the exclusion of a further 321 National Servicemen. It is proposed to use this criterion in

the current study. If deaths in the first two years of Army service can be identified for Regular servicemen too, these servicemen will be excluded from the study group.

This restriction will be used to reduce, to some extent, the bias in cancer incidence rates arising from the inclusion in the denominator of person-years of follow-up of servicemen who are deceased. This restriction will not obscure any associations of interest as it is exceedingly unlikely that any potential carcinogenic effect of dapsone or Vietnam service would cause death from cancer within two years of commencing Army service.

Identification of subjects and obtaining Army data

Members of the study population will be identified from data tapes from the Central Army Records Office (CARO) and from the AVHS Mortality and Birth Defects studies. Comparisons of records from these three sources will be used to compile the most complete list possible of eligible servicemen and to identify records requiring verification by CARO. These data will provide:

- individual identifying information required for record linkage to determine cancer status;
- Army postings data to calculate dapsone consumption and duration and period of Vietnam service; and
- Army data for analysis as potential confounding variables and effect modifiers (Corps and National Service/Regular status).

In 1982 the since disbanded Melbourne Regional Computing Centre of the Department of Defence supplied AVHS with computer records of all Australian Army Vietnam veterans and non-veterans of the Vietnam Conflict era. These records have been located and show Army number, surname, forenames and date of birth for all servicemen of the Vietnam Conflict era. Of the 119,000 records, approximately 85 per cent show full name and date of birth, about 5 per cent show surname, initials and date of birth, and about 10 per cent show surname, initials and month and year of birth. (Transfer of data from the mortality study to the Institute has taken place under Section 30 (2) of the Australian Institute of Health Act.)

CARO has already provided the Institute with computer files which identify and give a history of postings for all members of the Army during the Vietnam conflict era.

Date of entry into the study

Cancer incidence data are only available from 1972 on, therefore the earliest useful date of commencement of follow-up is 1 January 1972. In relation to Vietnam veterans, since any potential carcinogenic effect of Vietnam service would probably take several years to cause cancer, it is reasonable to commence follow-up at the date of return from Vietnam (or date of last return for Vietnam veterans with multiple tours) if this date is after 1 January 1972.

In relation to non-veterans, the issue is more complicated. Since the occurrence of cancer in a serviceman prior to possible Vietnam service would have precluded him

from going to Vietnam, it would be desirable to exclude the period of Army service during which servicemen were liable for Vietnam service. For National Servicemen, this is clearly the first two years of Army service. For Regulars, who mostly served for longer than two years, this period could cover the entire period of their service. However, Regulars were in demand for Vietnam service. Thus, Regulars who enlisted during the period of the Vietnam Conflict would usually have gone to Vietnam within two years of enlistment if they were going to go. While there is no perfect solution, it is appropriate to commence follow-up for non-veterans at two years from the commencement of Army service.

The date of commencement of follow-up will be as follows:

- for both Regular and National Service Vietnam veterans, the date of departure from Vietnam (or date of last return for those with multiple tours) or 1 January 1972, whichever is later;
- for both Regular and National Service non-veterans, two years after the date of enlistment or 1 January 1972, whichever is later.

A.3.3 Summary analyses of characteristics of study subjects

Tabulations of selected characteristics of study subjects are presented below (Tables A.3.2, A.3.3). These tables give an indication of the number of subjects in the study and their age range.

Table A.3.2 *Number of records on the Service file by study subject status and Regular/National Service status*

Status	Subjects	Not subjects
Regulars	39,772	15,225
National servicemen	43,220	20,504

Note: Numbers are subject to revision.

Table A.3.3 *Number of study subjects classified by year of enlistment, Vietnam veteran status and Regular/National Service status*

Year of enlistment	Regular			National Service			All study subjects		
	VV	NV	All	VV	NV	All	VV	NV	All
Before 1947	218	544	762	0	0	0	218	544	762
1947	115	337	452	0	0	0	115	337	452
1948	205	606	811	0	0	0	205	606	811
1949	135	343	478	0	0	0	135	343	478
1950	202	303	505	0	0	0	202	303	505
1951	329	634	963	0	0	0	329	634	963
1952	455	607	1,062	0	0	0	455	607	1,062
1953	385	409	794	0	0	0	385	409	794
1954	291	264	555	0	0	0	291	264	555
1955	245	192	437	0	0	0	245	192	437
1956	298	214	512	0	0	0	298	214	512
1957	320	239	559	0	0	0	320	239	559
1958	619	448	1,067	0	0	0	619	448	1,067
1959	789	485	1,274	0	0	0	789	485	1,274
1960	521	697	1,218	0	0	0	521	697	1,218
1961	1,009	873	1,882	0	0	0	1,009	873	1,882
1962	1,127	760	1,887	1	0	1	1,128	760	1,888
1963	1,497	924	2,421	1	2	3	1,498	926	2,424
1964	1,501	880	2,381	0	2	2	1,501	882	2,383
1965	1,757	1,047	2,804	1,348	2,468	3,816	3,105	3,515	6,620
1966	1,812	1,051	2,863	2,567	4,962	7,529	4,379	6,013	10,392
1967	2,003	1,344	3,347	3,344	4,038	7,382	5,347	5,382	10,729
1968	1,881	1,822	3,703	3,439	4,209	7,648	5,320	6,031	11,351
1969	1,197	2,131	3,328	3,052	4,806	7,858	4,249	6,937	11,186
1970	432	2,460	2,892	1,871	5,210	7,081	2,303	7,670	9,973
1971	12	803	815	133	1,767	1,900	145	2,570	2,715
Total	19,355	20,417	39,772	15,756	27,464	43,220	35,111	47,881	82,992

VV = Vietnam veteran; NV = non-veteran.

Note: Numbers subject to revision.

A.3.4 Dapsone consumption

Use of dapsone in Vietnam

The Department of Veterans' Affairs and the Official History Unit of the Australian War Memorial have compiled analyses of the use of dapsone in treatment and in the prevention of falciparum malaria in Vietnam. These are summarised in Attachment I.

Determining individual subject's dapsone consumption

Computer algorithms will be developed to calculate estimates of total dapsone dose for all study subjects. Individual subject's Unit, dates of departure for and return from Special Overseas Service as recorded in the CARO tapes, with allowance for identified sea travel, will be used to determine dates in Vietnam. The individual's Unit and dates in Vietnam will then be used to impute the number of days that each subject took dapsone. Between these dates the standard dose of 25 mg per day will be assumed to allow a total dose to be estimated.

Checks on transfers between Units will be made on a sample of records of those who served after 5 August 1970; these will allow estimates of movement between Units with different dapsone regimens. Further detail is given in Attachment II, where limitations of the method also are discussed.

In addition, any Vietnam veteran with an episode of 'definite' or 'probable' falciparum malaria at a time when dapsone was not used is assumed to have taken an additional 750 mg of dapsone. Extension of this to those identified as 'possible' falciparum malaria cases will be examined.

An indication of the approximate number of Vietnam veterans who were exposed to dapsone is given in Table A.3.4.

Table A.3.4 *Number of Vietnam veteran subjects classified by year of birth and by exposure to dapsone*

Year of birth	Exposed to dapsone		Total
	No	Yes	
Before 1920	62	67	129
1920–924	169	257	426
1925–929	456	693	1,149
1930–934	580	958	1,538
1935–939	1,049	1,326	2,375
1940–944	1,674	2,138	3,812
1945	2,764	1,309	4,073
1946	2,539	2,141	4,680
1947	816	4,245	5,061
1948	363	4,322	4,685
1949	58	3,744	3,802
1950	0	2,049	2,049
1951	0	4	934
1952	0	379	379
1953	0	19	19
Total	10,530	24,581	35,111

Note: Numbers are subject to revision.

A.3.5 Data relating to malaria

The occurrence of malaria in individuals will be recorded wherever possible. Malaria data are required for two reasons. Firstly, this is a study relating to dapsone, and at various times the occurrence of malaria can be an indicator of possible failure to use the drug for prevention and/or of use of the drug in treatment. Secondly, malaria has been suggested as a cause of some cancers in Vietnam veterans, although the scientific case for this is weak.

Cases of malaria will be identified from the following sources:

- The Official History Unit of the Australian War Memorial (the majority of the cases);
- The Department of Defence for cases treated in military hospitals in Australia and the Department of Veterans' Affairs for Vietnam veterans who have made claims on the Department for malaria contracted in Vietnam; and

- The malaria register compiled by the late Professor R H Black of the University of Sydney, now held by Professor P Moodie.

As dapsone was only used to treat falciparum malaria, it is desirable to identify those cases of malaria which were falciparum. The type of malaria from which Vietnam veterans suffered is sometimes recorded in RAAMC Unit records and almost always in notifications of infectious diseases, which show diagnosis at both admission and discharge. It is not yet known what terms were used in Australian hospitals or in Professor Black's register. As the type is not always stated on records three categories of definite, probable and possible falciparum malaria will be used in the assignment of falciparum malaria to individuals as follows:

Definite: A Vietnam veteran recorded as having suffered falciparum malaria will be regarded as a definite case. The monthly medical report for November 1966 states 'The Australian Army forces in Vietnam had its first case of (vivax) malaria...'. If this can be verified by inspection of medical records of a sample of cases between January and October 1966, all cases of malaria up to October 1966 will be regarded as definite falciparum malaria.

Probable: As most malaria experienced by Australian troops in Vietnam (Black 1973) was falciparum malaria, a Vietnam veteran recorded to have suffered malaria unspecified as to type from November 1966 will be regarded as a probable falciparum malaria case.

Possible: 'Pyrexia of unknown origin—malaria?' and similar diagnoses also appear commonly in these source records. A Vietnam veteran recorded with such a diagnosis will be regarded for the purposes of the study as possibly having suffered falciparum malaria. Depending on numbers, it may be possible to check individual records to decide whether each case was or was not falciparum.

These three diagnostic categories of definite, probable and possible falciparum malaria will be used in relation to illnesses. Dapsone use in treatment will then be imputed from the dates of known use of the drug as established by a review of a sample of records of definite cases of falciparum malaria (refer Attachment II).

To date approximately 1100 episodes of malaria including identified recurrences have been recorded. This number exceeds the 907 known to Black (1972) but will, at this point, probably include some New Zealand Vietnam veterans who will be excluded as they are identified. In addition, the study will include illnesses likely to have been treated with anti-malarial drugs (e.g. 'PUO? malaria') whereas Black will not have included such cases.

A.3.6 Identifying cases of cancer among study subjects

As mentioned above, follow-up will commence from two years after enlistment or date of discharge, whichever occurred first. However, it should be noted that cancer will only be ascertained for the years for which cancer registrations are computerised (see below) or if the cancers were detected in the AVHS Mortality Study (as deaths from cancer; see Section A.2.6). Cancer cases will be identified by matching computerised data on cancer registrations (compiled by State and

Territory cancer registries) with the study subject file. Cancers detected by this matching will be included in Vietnam veteran/non-veteran comparisons.

Following this matching, additional cases of cancer among Vietnam veterans will be sought from sources such as DVA hospital and departmental records, which over-represent Vietnam veterans. Cancers found only in these latter sources and not found through linkage with State/Territory cancer registers will be flagged so that they are only included in statistical analyses within Vietnam veterans, i.e. analyses of the relationship between dapsone use and the risk of cancer where both the exposed and unexposed groups used in the analyses are Vietnam veterans. The inclusion of these additional cancers will improve statistical power. However, the inclusion of these cancers in Vietnam veteran/non-veteran comparisons would lead to estimates which are grossly biased and therefore uninformative in assessing whether Vietnam service or dapsone has increased the risk of cancer.

Cancers which occurred among subjects who were overseas and did not receive treatment in Australia will not be detected by this method. The number of cases missed for this reason will probably be very small, since in the AVHS Mortality Study only 0.75 per cent of study subjects were last known alive from Department of Immigration and Ethnic Affairs departure records up to 31 December 1981.

Coverage of electronic cancer data

The years for which cancer registrations are available vary across the States and Territories, and only for some years are data available in electronic form. A lag in cancer registration exists in most cancer registries, and the years for which each can supply data on electronic media are presented in Table A.3.5. Electronic data are only available for about one third to one half of the period of interest. Every effort will be made during the course of the study to obtain more recent electronic registry data when they become available.

It is estimated that a manual search of each registry for as yet unkeyed registrations relating to 120,000 Australian Army members from the Vietnam era would take 6 person years. This would double the cost of the study. A manual search has not been pursued at this time because of limitations on the capacity of registries to accommodate extra staff without disruption of their work, and because it would greatly lengthen the duration of the study.

Table A.3.5 *Coverage of State/Territory cancer registries*[a]

	Population coverage commences	Electronic coverage commences	Electronic coverage ceases
NSW (incl ACT)	1972	1972	1984[b]
Vic[c]	1982	1982	1986
Qld	1982	1982	1987
SA	1977	1977	1988[d]
WA	1981	1982?	1986
Tas	1978	1978	1968[e]
NT[f]	1981	1981	1986[g]

[a] This refers to complete coverage. Several registries have partial data beyond this (see below).

[b] Will have complete electronic data up to 1988 by June 1991.

[c] Data from a number of major hospitals are available in electronic form from 1960 to the commencement of population coverage in 1982.

[d] Partial electronic data are available for 1989.

[e] Partial electronic data are available for 1987 to 1989.

[f] Partial coverage started in 1977. These data are available in electronic form.

[g] Partial electronic data are available for 1987.

Record linkage procedures

Surname, given names and birthdates of all Vietnam veteran and non-veteran members of the study population will be compared with cancer registrations from all States and Territories. This matching will be done for the full set of years for which cancer registration data are available on electronic media.

To enable this matching, most State and Territory cancer registries will supply details of cancer registrations in males for the period for which they hold data in electronic form. The remaining cancer registries will provide data for matching to be undertaken at the Institute under the supervision of registry staff, who will then remove their cancer registry data from the Institute computer, or will undertake the linkage at the cancer registry.

- *Development of matching criteria*

A key element in the design of the study is the matching criterion used to decide if pairs of records represent the same person. The sensitivity and specificity of this criterion is a critically important determinant of the ability of this study to detect and effect of dapsone or Vietnam service, should such an effect be present.

The findings from the matching of the Service file (AVHS Mortality Study tape) with the DVA cancer file and the NSW cancer registry file will be applied to the development of criteria for matching service records with cancer registrations. The approach taken will be to examine the differences in identifying information in these

two files for pairs of records which are sufficiently similar for there to be a possibility that they represent the same person. The aspects identified for examination will include:

- the effect of standardisation of format of surname e.g. by removal of all apostrophes, spaces, and hyphens; by expressing all letters in upper case; by converting Mc and M' to Mac;
- testing use of Soundex codes rather than surnames. The rules used in establishing the codes are described further in Attachment III;
- the effect of allowing for familiar forms of common forenames, especially where these result in a change of initial, e.g. Tony for Anthony;
- the effect of allowing for omission of, transposition of, and errors in initials;
- the effect of allowing for transposition in day and month of birth, and for errors in components in dates of birth;
- other aspects as revealed by the comparison of the Service, DVA cancer file and NSW cancer registry data.

From a knowledge of the frequency of these and other discrepancies between the Service file and both DVA cancer records and NSW cancer records, a sequential search strategy will be devised. This strategy will be designed to identify an acceptably high proportion of true matches, while yielding an acceptably low proportion of matches which prove false.

The strategy will be applied to obtain lists of perfect matches, possible matches and non-matches between the service file and cancer registrations. Perfect matches will be accepted without further verification. Non-matches will be rejected without further verification. Identifying data for partial matches will be checked with the source paper records in CARO and the cancer registry.

To minimise the need for manual verification of possible matches, registries have been asked to supply AIH with all available identifying data on individuals.

- *Verification of possible matches*

Once electronic matching has been performed, the data for samples of records which match partially will be verified manually in CARO and cancer registry paper records using a standard inquiry form. If it is necessary to approach sources of cancer registrations, that will be done via the relevant registries.

- ***Final decisions on partial matches***

Once verified data have been returned from either the relevant cancer registry or CARO, the electronic matching procedure will be re-run. Following this, matching decisions on partial matches will be made using the manual matching criteria developed and extensively validated in the AVHS mortality study. This matching will be performed without knowledge of the dapsone consumption or the Vietnam veteran status of subjects. To decide that a pair of records match, the records will need to have the following similarities:

Surname: Exact match except for minor spelling variations, e.g. 'Mathews and Matthews'.

Given names: Consistent. For example, one name being identical with the other name absent, Anglicised or shortened, or the order of two matching names reversed. 'Fredrick Henry' and 'Fredrick George' do not match while Tony and Anthony do.

Birthdate: Identical, one digit different, two digits transposed or the following differences in the day field: 9 vs 10, 19 vs 20, 29 vs 30.

Once the criteria have been fully developed, they will be applied to the DVA cancer file to document the sensitivity and specificity of the matching procedure.

Where matching is undertaken at cancer registries instead of AIH, it will be necessary to use the electronic matching algorithm developed by each registry. Information on the validity of these algorithms will be obtained. Where manual matching is required following this electronic matching, the manual matching criteria presented above will be used.

A.3.7 Identifying cancer deaths from the AVHS Mortality Study

Data on cancer deaths identified in the AVHS Mortality Study will be obtained from data tapes from this study held by AIH. It is proposed to use Mortality Study data because of their ready availability and there potential contribution. The proposition that they should not be used in the current study because they are not independent of the current study is not relevant: the mortality data did not influence the choice of hypotheses for the current study.

Cancer mortality data from the AVHS Mortality Study will be analysed to see whether there is any association between cancer mortality and dapsone exposure. In the Mortality Study, no association was apparent between the risk of death from cancer during the period of that study (1967 to 1981) and Vietnam service. However, while this makes the possibility of an association between dapsone exposure and cancer mortality during that period unlikely (as cancer due to dapsone would be apparent in Vietnam veteran/non-veteran comparisons), it would be desirable to use available data to examine this issue.

It is recognised that cancer mortality data allow for less statistically powerful comparisons than cancer incidence data because cancer mortality is less common than cancer incidence, due to the potential for cure. The relationship between cancer incidence and mortality varies according to cancer type, age and calendar year of incidence (due to improvements in treatment). However, the period of observation of the Mortality Study (1967 to 1981) precedes the period of population and electronic coverage of the majority of State/Territory cancer registries (1981 on). Thus the Mortality Study provides a view of a latency period following Vietnam service which is largely unavailable with cancer registry data. However, there is some overlap in coverage of the Mortality Study and several cancer registries (NSW from 1972, SA from 1977, Tas from 1978) and the issue arises of how to use and interpret data from different sources covering the same population and period.

Mortality Study data will be analysed separately because mortality data are not directly comparable with cancer incidence data. In addition, the separate analysis of mortality and incidence data will ensure that any associations which might be observed among the incidence data will not be obscured by being combined with mortality data, which suggest no association between Vietnam service and risk of cancer.

A.3.8 Coding of cancer diagnoses

There is a potential for bias in the registration of soft tissue sarcoma because the International Classification of Diseases requires some soft tissue sarcomas to be classified to their topographical (or anatomical) site. For example, fibrosarcoma located in the lung should be coded to 'cancer of the lung, not otherwise specified' (ICD-9 162.9). However, such tumours may be incorrectly classified as 'soft tissue sarcoma' (ICD 171). It is possible that such incorrect coding may have occurred more often among Vietnam veterans because of the longstanding and public concern about a possible excess of soft tissue sarcoma among Vietnam veterans from exposure to Agent Orange. The resultant bias would lead to biased comparisons. Furthermore, the correct ICD coding of some soft tissue sarcomas to codes other than ICD 171 means that relying solely on the cancers coded to ICD 171 may underestimate the true number of soft tissue sarcomas, reducing the power of the study to detect a difference in soft tissue sarcoma.

Thus it will be necessary to check that all cases with ICD 171 have been correctly coded (and if not, recode them) as well as obtain morphological codes from cancer registries where available, in addition to topographical codes. The morphological codes which are not already ICD O will be converted to ICD O. In the analysis, comparisons will be made using the ICD-9 coded diagnoses and using the ICD O codes for soft tissue tumours.

More generally, it is possible that there has been incorrect coding of other cancers. To enhance the validity of comparisons within study subjects, narrative pathology reports could be sought for all cancers. Where these reports are obtained, the cancers would be recoded by a nosologist using ICD-9. Consultation with the cancer registries indicates that great care is taken in applying the ICD coding rules correctly and that there would be little, if any, advantage in recoding the pathology reports, even if they could be obtained.

A.3.9 Preparation of data for analysis

The cancer incidence among servicemen exposed to each of the putative risk and confounding factors, Vietnam service, malaria and use of dapsone, will then be compared by appropriate statistical methods.

A.4 Power of the study

A.4.1 Introduction

The scientific value of a study arises from its ability to test hypotheses and make estimates. The statistical power of a study to test an hypothesis is the probability that, if the hypothesis is false, the study will correctly identify it as false.

For example, suppose that a study is investigating the hypothesis that the risk of cancer is the same for two groups but, in reality, the risk for one group is double that for the other. Further suppose that there is only a 30 per cent chance that the study's estimate of the difference in risk will be statistically significant. In this case the power of the study is 30 per cent and such a study would be unlikely to detect a real difference in cancer risk. Suppose, on the other hand, that there was a 95 per cent chance that the study's estimate of the difference in risk will be statistically significant. In this case the power of the study is 95 per cent and in this case the study would probably detect a statistically significant difference.

The power of a study to detect a difference in cancer risk between two groups depends on the size of the two groups (in this case the number of person-years in each group during the study period), the size of the true cancer risk ratio between the two groups and the number of cancers observed in each group. In general, the power will increase with increases in each of these factors.

A.4.2 Study and comparison groups

Each of the power calculations relates to a pair of study and comparison groups. These are:

1. Vietnam veteran study subjects vs non-veteran study subjects;
2. Vietnam veteran study subjects exposed to dapsone vs Vietnam veteran study subjects not exposed to dapsone;
3. Vietnam veteran study subjects exposed to dapsone vs non-veteran study subjects not exposed to dapsone.

For each of these, the first is taken as the study group and the second as the comparison population.

A.4.3 Assumptions made in the power calculations

In calculating the power, two assumptions were made about these groups. These are:

1. All study subjects lived through the entire study period.

   This assumption was used to calculate the number of person-years for each group. Since the study group is relatively young, this should be a reasonable assumption. (See Section A.5.3 for further discussion of this issue.)

2. The age structure of the comparison group is the same as that of the study group.

   This assumption was used to calculate the expected number of cancers in each group. The overall cancer incidence rate was calculated by applying age specific

incidence rates to the age structure of the study group. This incidence rate was then applied to the total person hours in both the study and comparison group.

A.4.4 Cancer incidence rates

The most recent available national cancer incidence rates (for 1982; Giles et al. 1987) were assumed to apply to the study groups. This publication gives incidence rates for cancers grouped according to the three digit ICD-9 code. For soft tissue and other sarcoma, and cancer of the oral cavity, the relevant three digit ICD-9 code covers more cancers than just those under study. In these cases, the resulting power estimates will over-estimate the study power.

A.4.5 Cancer registry coverage

Cancer incidence data is collected by State and Territory cancer registries. The date at which electronic coverage of registry cancer data commenced varies between the registries and is shown in Table 3.5.

It was assumed that the proportion of the cancers occurring in the study group which would be listed on a register is the same as the proportion of the Australian population in the States where the registries are operating. For example, in 1978 there were registries collecting cancer incidence data electronically only in New South Wales and Tasmania. Approximately 39 per cent of the Australian male population lives in these two states. Therefore it was assumed that 39 per cent of the cancers which occurred in the study group in 1978 would be listed on a cancer registry.

The study involves matching the names of the study group against the names on the cancer register. This matching process was assumed to have about a 90 per cent success rate (i.e. 90 per cent sensitivity). In other words, it was assumed that only 90 per cent of the cancers in the study group could be matched to cancers listed on a register. The matching was assumed to have a specificity of 100 per cent, i.e. all cancers found in the register through matching were cancers of the study subjects concerned and not cancers of other people which were matched inadvertently. (The sensitivity and specificity of matching will be ascertained by comparison of the cancers found through the cancer registries and the cancers present in the DVA Cancer File.)

Finally, 1984 is the most recent year for which all the registries have complete data. The power calculations were done twice for each study and comparison group—once based on this incomplete coverage and then assuming complete registry coverage from 1984 to 1989.

A.4.6 The power calculations

The formulae for calculating the study power rely on the above assumptions. They also involve a number of approximations. These approximations are sufficiently accurate for all but very large and very small power estimates. For this reason, estimates of power below 10 per cent or above 99 per cent are shown in the table as a dash (-) or an asterisk (*) respectively.

The power calculations were done for a range of relative risk ratios. This was done by multiplying the cancer incidence for the study group calculated from the rates described above by the a series of risk ratios and calculating the study power for each result.

A.4.7 Study power

The following tables (A.4.1a to A.4.1f) present estimates of the statistical power of the study to detect differences in cancer incidence (ranging between relative risks of 1.2 and 2.5) between exposed and unexposed groups of study subjects. In Tables A.4.1a and A.4.1b the exposed group is Vietnam veterans and the unexposed group is non-veterans. In Tables A.4.1c and A.4.1d the exposed group is dapsone exposed Vietnam veterans and the unexposed group is Vietnam veterans who were not exposed to dapsone. In Tables 4.1e and A.4.1f the exposed group is dapsone exposed Vietnam veterans and the unexposed group is non-veterans.

The tables also present the number of cases of cancer expected to be found in the cancer register searches. Since DVA sources will also be searched to detect additional cases among Vietnam veterans, with these cases being used only for comparisons within Vietnam veterans, the estimates of power in Tables A.4.1c and A.4.1d are underestimates. However, the size of this underestimation is unknown.

Tables A.4.1a, A.4.1c and A.4.1e are based on the number of cases of cancer expected to be found with cancer registry coverage as indicated in Table A.3.5. Tables A.4.1b, A.4.1d and A.4.1f are based on the number of cases which would be expected if the cancer registries were searched up to the end of 1989. It is possible that more recent data will be able to be obtained for some States/Territories than indicated in Table A.3.5. If so, the actual power of the study will lie somewhere in between the estimates in Tables A.4.1a, A.4.1c and A.4.1e and the estimates in Tables A.4.1b, A.4.1d and A.4.1f.

These tables indicate that the study would have power to detect a small increase (20 per cent increase; relative risk of 1.2) in cancer incidence among Vietnam veterans compared with non-veterans and among Vietnam veterans exposed to dapsone compared with non-veterans. Because less than one third of Vietnam veterans were not exposed to dapsone (see Table A.3.5), comparisons within veterans are less powerful. The study would have power to detect a 40 per cent increase in cancer incidence among dapsone exposed Vietnam veterans compared with Vietnam veterans not exposed to dapsone.

The study has substantially less power to detect differences in incidence for specific sites of cancer. For non-Hodgkin's lymphoma, the study only has power to detect a doubling of incidence (100 per cent increase; relative risk of 2.0) among Vietnam veterans compared with non-veterans and among Vietnam veterans exposed to dapsone compared with non-veterans. The study would only be able to detect a very large increase (possibly relative risk of 3) in incidence of non-Hodgkin's lymphoma among dapsone exposed Vietnam veterans compared with Vietnam veterans not exposed to dapsone. In the US study of cancer among Vietnam veterans (Selected Cancers Cooperative Study Group 1990a, 1990b, 1990c) a relative risk of

1.47 was observed for non-Hodgkin's lymphoma. The current study would only have an approximately 30 per cent chance of detecting a similar relative risk for this cancer.

The power to detect increased incidence of cancer is higher for oral cancer than for non-Hodgkin's lymphoma, but for the other types of cancer under consideration, the power is less. Thus, the current study would only be able to detect large increases in risk for these cancers.

It should be noted that the limitations in power of the study are not due to limitations in design, but rather to limitations in size of study groups. Since all Australian Vietnam veterans are being studied, it is not possible to increase the power of the study by increasing the size of the study groups.

Table A.4.1 *Power of the study to detect various risk ratios for all cancers combined and for specific sites of cancer*

		Expected cancers[a]		Power for risk ratios[b]					
Site	**ICD-9**	**Exposed**	**Unexposed**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0**	**2.5**
(a) Vietnam veterans vs non-veterans based on *incomplete* cancer registry data after 1985									
All cancers combined	(140–208)	335	451	83	*	*	*	*	*
Oral cancer[c]	(140–146, 149)	30	39	17	39	71	90	98	*
Nasopharyngeal carcinoma	(147)	2	3	-	-	-	-	10	25
Primary liver cancer	(155)	2	3	-		-	-	-	20
Nasal carcinoma	(160)	2	2	-	-	-	-	-	11
Soft tissue and other sarcoma	(170–171)	8	11	-	-	19	33	47	76
Bladder cancer	(188)	14	19	-	17	36	57	74	95
Non-Hodgkin's lymphoma	(200, 202)	17	22	11	21	43	65	81	98
Hodgkin's disease	(201)	9	11	-	-	21	35	50	79
Leukemia	(204–208)	10	14	-	12	26	42	58	86
(b) Vietnam veterans vs non-veterans assuming *complete* cancer registry data up to 1989									
All cancers combined	(140–208)	557	738	96	*	*	*	*	*
Oral cancer[c]	(140–146, 149)	49	63	24	61	90	99	*	*
Nasopharyngeal carcinoma	(147)	4	5	-	-	-	12	19	39
Primary liver cancer	(155)	4	4	-	-	-	12	19	38
Nasal carcinoma	(160)	2	3	-	-	-	-	-	23

Table A.4.1 (continued) *Power of the study to detect various risk ratios for all cancers combined and for specific sites of cancer*

Site	ICD-9	Expected cancers[a]		Power for risk ratios[b]					
		Exposed	Unexposed	1.2	1.4	1.6	1.8	2.0	2.5
Soft tissue and other sarcoma	(170–171)	11	15	-	13	29	47	63	90
Bladder cancer	(188)	24	34	14	32	61	83	94	*
Non-Hodgkin's lymphoma	(200, 202)	26	35	15	34	65	86	96	*
Hodgkin's disease	(201)	12	16	-	14	30	48	65	90
Leukemia	(204–208)	15	21	-	19	40	61	78	97
(c) Dapsone exposed Vietnam veterans vs non-dapsone exposed Vietnam veterans based on *incomplete* cancer registry data after 1985									
All cancers combined	(140-208)	216	119	42	98	*	*	*	*
Oral cancer[c]	(140-146, 149)	20	11	-	-	14	32	53	89
Nasopharyngeal carcinoma	(147)	2	1	-	-	-	-	-	-
Primary liver cancer	(155)	1	1	-	-	-	-	-	-
Nasal carcinoma	(160)	1	1	-	-	-	-	-	-
Soft tissue and other sarcoma	(170-171)	6	2	-	-	-	-	-	16
Bladder cancer	(188)	9	5	-	-	-	-	13	39
Non-Hodgkin's lymphoma	(200, 202)	11	6	-	-	-	10	20	52
Hodgkin's disease	(201)	6	3	-	-	-	-	-	19
Leukemia	(204-208)	7	3	-	-	-	-	-	24
(d) Dapsone exposed Vietnam veterans vs non-dapsone exposed Vietnam veterans assuming *complete* cancer registry data up to 1989									
All cancers combined	(140-208)	358	199	60	*	*	*	*	*
Oral cancer[c]	(140-146, 149)	32	17	10	11	34	63	84	99
Nasopharyngeal carcinoma	(147)	2	1	-	-	-	-	-	-
Primary liver cancer	(155)	2	1	-	-	-	-	-	-
Nasal carcinoma	(160)	2	1	-	-	-	-	-	-

Table A.4.1 (continued) *Power of the study to detect various risk ratios for all cancers combined and for specific sites of cancer*

Site	ICD-9	Expected cancers[a]		Power for risk ratios[b]					
		Exposed	Unexposed	1.2	1.4	1.6	1.8	2.0	2.5
Soft tissue and other sarcoma	(170-171)	8	3	-	-	-	-	10	31
Bladder cancer	(188)	15	9	-	-	-	21	38	77
Non-Hodgkin's lymphoma	(200, 202)	17	9	-	-	11	26	45	84
Hodgkin's disease	(201)	8	3	-	-	-	-	11	34
Leukemia	(204-208)	10	5	-	-	-	-	18	49
(e) Dapsone exposed Vietnam veterans vs non-veterans based on *incomplete* cancer registry data after 1985									
All cancers combined	(140-208)	216	451	73	*	*	*	*	*
Oral cancer[c]	(140-146, 149)	20	39	14	31	58	79	91	*
Nasopharyngeal carcinoma	(147)	2	3	-	-	-	-	-	20
Primary liver cancer	(155)	1	3	-	-	-	-	-	15
Nasal carcinoma	(160)	1	2	-	-	-	-	-	-
Soft tissue and other sarcoma	(170-171)	6	11	-	-	17	28	40	67
Bladder cancer	(188)	9	19	-	14	28	44	59	86
Non-Hodgkin's lymphoma	(200, 202)	11	22	-	17	34	53	69	92
Hodgkin's disease	(201)	6	11	-	-	19	31	43	71
Leukemia	(204-208)	7	14	-	10	22	35	48	76
(f) Dapsone exposed Vietnam veterans vs non-veterans assuming *complete* cancer registry data up to 1989									
All cancers combined	(140-208)	358	738	90	*	*	*	*	*
Oral cancer[c]	(140-146, 149)	32	63	20	48	79	94	99	*
Nasopharyngeal carcinoma	(147)	2	5	-	-	-	-	16	33
Primary liver cancer	(155)	2	4	-	-	-	-	14	29
Nasal carcinoma	(160)	2	3	-	-	-	-	-	18

Table A.4.1 (continued) *Power of the study to detect various risk ratios for all cancers combined and for specific sites of cancer*

Site	ICD-9	Expected cancers[a]		Power for risk ratios[b]					
		Exposed	Unexposed	1.2	1.4	1.6	1.8	2.0	2.5
Soft tissue and other sarcoma	(170-171)	8	15	-	12	25	40	54	81
Bladder cancer	(188)	15	34	12	25	47	68	84	98
Non-Hodgkin's lymphoma	(200, 202)	17	35	13	28	52	74	88	99
Hodgkin's disease	(201)	8	16	-	13	26	41	56	83
Leukemia	(204-208)	10	21	-	16	33	51	67	91

[a] Number of cancers expected to be found on the cancer registries if no effect of service in Vietnam, based on 1982 incidence data and assuming 90% sensitivity and 100% specificity of matching.

[b] Power (%); * represents power > 99% and - represents power < 10%.

[c] Oral cancer contains some sites in addition to those under study. Therefore, these are slight over-estimates of the power for oral cancer.

A.5 Data analysis

A.5.1 Method of analysis of cancer incidence and mortality rates

Poisson regression (Breslow & Day 1987) will be used to examine the relationship between cancer incidence and mortality, and the risk factors. The response variable for these models is cancer incidence or cancer mortality, and the explanatory variables of key interest are Vietnam service status, dapsone use status, dapsone dose, malaria status, Army corps, calendar year of Vietnam service and duration of Vietnam service.

Poisson regression is now the standard method for analysis of cohort studies, and was used in the analysis of the AVHS Mortality Study (Fett et al. 1984; Adena et al. 1985). The method allows for unequal periods of follow-up, separate models for different classifications of cancers, comparison with external controls (e.g. the cancer incidence rates in the Australian population), control for possible confounding variables (e.g. age), testing for interactions and assessment of dose response (e.g. for duration of service in Vietnam or total dose of dapsone received). It will also be possible to restrict the analyses to cancers occurring after a defined latent period following service.

The parameter estimates from Poisson regression models can be expressed as relative cancer incidence rates. Confidence intervals, as well as statistical hypothesis tests, are readily available. The descriptions from such models can be easily understood by non-statisticians (see, for example, the analysis of road fatality rates in Anderson, Montesin & Adena 1989, or the analysis of death rates in regions of Victoria in Adena 1989).

After suitable summary of the data, these models can be fitted using standard statistical software, for example, GLIM (Payne 1985). The methods of data summary were developed for the AVHS Mortality Study (Fett et al. 1984), and so are immediately applicable.

A.5.2 Other analyses

Multi-way contingency tables will be used to display information relating to data quality. If appropriate, these tables will be analysed using log-linear models.

A.5.3 Issues to be considered in the analysis

Estimating cancer incidence rates

Estimates of cancer incidence rates for study subjects will be slightly biased because of lack of information on deaths among study subjects. This will lead to overestimation of the number of person-years of follow-up and hence underestimation of cancer incidence rates, although the magnitude of this effect will be small since the proportion of subjects who will have died will be small (<5%). The effect of this bias will be less when relative risks are estimated, as the bias in the exposure and control groups will tend to cancel, even if there are differences in mortality rates of exposed and unexposed subjects.

As mortality rates may differ for Regulars and National Servicemen, the analysis will need to be stratified by Regular/National Service status.

Cancer incidence rates for the general population, which will be used to calculate the number of cancers expected among the study population, will be calculated using cancer incidence data from the individual cancer registries for the calendar years which were searched to detect cancer cases among study subjects. In this way, expected cancer incidence will be as comparable as possible.

Calendar years of use of dapsone

The incidence of most cancers increases greatly with age and thus with time since service. Those who served before dapsone was used are thus older and will have higher cancer incidence than those who served later. In addition, among National Servicemen, nearly all members of each birth cohort served simultaneously, so that the birth cohorts exposed to malaria and dapsone were also largely separate. Thus, the ability to statistically control for secular trends in background cancer incidence will be limited.

Most Australians who served in Vietnam did so between 1966 and 1971 inclusive. Dapsone was used for treatment of falciparum malaria, the most common form of malaria in Australian Forces in Vietnam, in August 1966 and in virtually all cases from September 1967. Its use in prophylaxis from late 1968 was followed by a reduction in the incidence of falciparum malaria. Episodes of malaria and use of dapsone thus occurred at largely different times.

The study design and analysis must therefore take into account the present age distribution (or equivalently birth cohort distribution) and calendar period of service

in Vietnam (or equivalently length of time since return), which are both highly confounded with dapsone use and malaria, the risk factors to which Vietnam veterans were largely separately exposed.

Latency of any carcinogenic effect

Cancer occurs years after exposure to carcinogens. The length of this delay varies according to the type of carcinogen, the intensity of exposure and the type of cancer. To examine this issue, the risk of cancer will be expressed in terms of time since Vietnam service and exposure to dapsone, to see if the risk of cancer is increased for any particular period since exposure.

Multiple tests of statistical significance

The analysis will contain a number of tests of statistical significance. It should be noted that when many tests are performed, the chance that one or more of these tests will be significant through chance alone increases substantially. For example, at the p=0.05 level, on average one test out of 20 will be significant through chance alone.

However, statistically significant results for one of the prior hypotheses (presented as aims in Section A.2.2) have special importance because, while such results may have occurred by chance, they support the original hypothesis.

Separate analysis of National Servicemen and Regulars

During preparation of the protocol for the AVHS Mortality Study, Army sources indicated that, with the comparative shortage of Regular servicemen to serve in Vietnam, health status had a greater influence on the selective posting to Vietnam of Regulars than National Servicemen. This makes Regular Vietnam veterans less comparable with Regular non-veterans than National Service Vietnam veterans and non-veterans. It will therefore be necessary for analyses which compare Vietnam veterans with non-veterans to examine Regulars and National Servicemen separately and to take the potentially greater non-comparability of Regular Vietnam veterans and non-veterans into account when interpreting the data.

A.6 Reporting, privacy and confidentiality

A.6.1 Reporting

The Institute will prepare a report on the study for submission to the Minister for Veterans' Affairs. The report will first have been endorsed by the Scientific Advisory Committee. The Institute will publish this report as soon as the Minister agrees that is appropriate.

After publication of the report the Institute may also seek to publish, in scientific journals, shorter reports suitable for a professional audience. These publications also would be endorsed by the Scientific Advisory Committee prior to submission to the journals.

No individuals will be identified in any reports.

A.6.2 Privacy and confidentiality

The Epidemiological Studies (Confidentiality) Act 1981 explicitly provided that information relating to identifiable persons not be passed beyond the group carrying out the studies. This was to encourage Vietnam veterans to participate in the AVHS studies. The later Australian Institute of Health Act provides that studies done by the Institute are to be carried out under that Act, that the Epidemiological Studies (Confidentiality) Act does not apply to studies done by the Institute, and that the Institute may pass data on to others who would then be bound by the secrecy provisions of the Australian Institute of Health Act.

As the Institute may have the power to pass data relating to identifiable subjects to other investigators, it may need to declare that it will not exercise this power, to keep faith with Vietnam veterans.

It is accepted that cancer registries may require examination of this protocol by their own ethical advisers before they agree to use of their data.

This study would not be possible unless individuals' identities are known to the investigators. In accordance with the draft Guidelines for the Protection of Privacy in Medical Research, the following additional information is supplied.

Obtaining consent for access to records from all living ex-servicemen or cancer registrants is clearly not possible. This is in breach of Privacy Act (1988) Information Privacy Principle number 5. It is necessary to retain records in identifiable form to comply with Archives legislation and until a decision is made on future studies.

Because of the number of records accessed, all bodies supplying data will be asked to list in a register of access to records their participation in the study. Notation of individuals' records is not feasible.

The confidentiality provisions of the Australian Institute of Health Act will apply to all parts of this study, as will its standards for physical and computer access.

At the conclusion of the study, data and all other material will be stored or disposed of as required by the Archives Act.

Attachment I—Estimating dapsone consumption

This attachment outlines the usage of dapsone by Australian forces in Vietnam and how the dapsone consumption of individual servicemen will be calculated.

I.1 Dapsone Use by Australian Forces in Vietnam

I.1.1 Use of dapsone in treatment of malaria

The first record so far found of the use of dapsone for treatment of malaria dates from August 1966 when dapsone was used in combination with chloroquine and quinine to treat three cases of falciparum malaria. However the drug does not appear to have been used routinely as 12 soldiers with falciparum malaria were known to have been evacuated to Australia prior to April 1967, mainly because of recurrences of disease (Fleming, 1974).

In September 1967 the outgoing Senior Medical Officer issued an instruction advising medical officers to treat falciparum malaria with a combination of quinine, pyrimethamine and dapsone, as was done by US forces. Treatment involved 1.8 g of quinine dihydrochloride per day for three days and 25 mg of dapsone per day for 30 days. A survey in January 1968 of the medical records of fifty patients who had been admitted to 8 Field Ambulance in the previous four months found that without exception they had been treated with all three drugs. Thus it would appear that the SMO's instruction was adhered to thenceforth.

In September 1968 it was the unanimous opinion of the ADMS conference in Vietnam that the three drug combination was superior to chloroquine treatment even in malaria not resistant to chloroquine. A recommendation was made to the Director-General of Medical Services (DGMS) that the US treatment be used as routine in Australian Force Vietnam (Army Component). On 11 October 1968 the DGMS gave approval for use of the drug combination in falciparum malaria to be decided by the specialist physician in charge of the case. In view of the unanimous opinion of the RAAMC medical officers in Vietnam this ensured that the US treatment for falciparum malaria became routine in 1 Australian Field Hospital.

Major illnesses and casualties in the Army, RAN, RAAF were referred to Australian Army or US hospitals throughout the period of the Australian forces' service in Vietnam. Thus dapsone use in the treatment of falciparum malaria by Australian and US hospitals can be presumed as follows:

Australian hospitals:

- prior to August 1966 almost certainly did not use dapsone;
- from August 1966 to the end of September 1967 is a period of unknown dapsone use (FMed11 files of a sample of individuals will be accessed to ascertain treatment given);
- after September 1967 used dapsone in treatment.

United States hospitals:

- used dapsone in treatment from about 1966 to 1970.

I.1.2 Use of dapsone in prevention of malaria

Australian Army

The following describes the periods of use of dapsone and those units or locations where dapsone was issued.

Trial of dapsone in 1RAR 4RAR and 12 Field Regiment from 23 October 1968 to 16 November 1968

In response to a significant rise in the incidence of falciparum malaria in the latter part of 1968, the Australian Army introduced dapsone on a trial basis to be used in conjunction with paludrine as a malarial prophylactic. Personnel in defined platoons were given dapsone while the rest of the battalions remained on paludrine alone. Members of 102 and 104 Field Batteries were divided alphabetically into halves with one half of each battery on dapsone. Each of the 536 soldiers in the selected platoons or half-batteries took a 25 mg tablet of dapsone each day in addition to his daily 200 mg of paludrine. The remaining 504 soldiers in 1RAR, 4RAR and 12 Field Regiment continued to take their daily paludrine only.

Dapsone issued to 3RAR from 26 October 1968 until departure to Australia

This battalion of 500 personnel had not been included in the trial as it was due to return to Australia at the end of November 1968. However to protect members of 3RAR against falciparum malaria in its few remaining operations, the greater part of the Battalion was placed on daily dapsone on 26 October 1968. B Company and some members of Battalion HQ which were not embarking on operations at this time were not given dapsone.

The cessation date is presumed to be the departure date to Australia for each individual.

Dapsone issued to all AFV troops from 17 November 1968 to 10 February 1970

The trial of dapsone continued until 16 November 1968. From 17 November 1968, 25 mg dapsone and 2000 mg paludrine per day became the standard anti-malarial chemoprophylactic in the Army component of the Australian Forces Vietnam. This regimen was discontinued as from 11 February 1970.

Dapsone issued to personnel posted for duty with 1 Australian Task Force (1ATF) and Australian Army Training Team Vietnam (AATTV) in Phuoc Tuy Province . From 5 August 1970 to 28 February 1971 and from 3 August 1971 to departure of 1ATF to Australia

On 5 August 1970 the daily routine of 25 mg dapsone and 200 mg paludrine was again instituted for all members of 1 ATF and AATTV members stationed in Phuoc Tuy Province. However early in the new year it was decided that soldiers arriving in Vietnam after 31 January 1971 would not be given dapsone.

On 3 August 1971 the dapsone/paludrine routine was again introduced for 1ATF troops and AATTV troops stationed in Phuoc Tuy Province. Although there was

some difficulty in distributing the tablets at this time, with the result that some troops did not receive and start taking them until 6 August, it will be assumed that all dosages commenced on 3 August. The regimen appears to have continued until the withdrawal of 1ATF.

In these last two periods of dapsone use, dapsone was not given to troops based in Saigon or to 1 Australian logistic Support Group units in Vung Tau. However some units based in Saigon and Vung Tau also had detachments or elements with 1ATF at Nui Dat and some members of Saigon and Vung Tau based units were required by their duties to visit Nui Dat from time to time. The feasibility of ascertaining dapsone use for these groups will be examined further.

Royal Australian Navy

RAN Helicopter Flight Vietnam land based personnel (members of the 1st, 2nd and 3rd contingents) were provided with health support almost entirely by the US military. They may have been issued with dapsone from arrival on 15 October 1967 until late 1969 when US forces ceased use of dapsone for prevention of malaria. Other land based RAN units appear to have been issued in accordance with the Australian Force Vietnam. The personnel concerned were all Royal Australian Navy members of Clearance Diving Team 3 (4th, 5th and 6th contingents), miscellaneous land based RAN personnel attached to Headquarters of Australian Force Vietnam, Sea Transport Officers and detached medical officers and chaplains.

Royal Australian Air Force

RAAF personnel were issued with a single dose of 300 mg of chloroquine on the same day of each week as a malarial prophylactic. They were not subject to either US or Australian Army prophylactic regimens. However a small number of RAAF personnel who served in remote areas of South Vietnam or with other forces may have taken dapsone. It would appear that such use would have been between 16 July 1966 and early 1970 when the US forces ceased to use dapsone as a prophylactic.

I.1.3 Sources

The information in this Appendix is based on summaries supplied by Dr Brendan O'Keefe of the Official History Unit of the Australian War Memorial and by the Department of Veterans' Affairs. Some of the source documents of these summaries have also been consulted.

I.2 Imputation of dapsone consumption

This section describes how the quantity of dapsone consumed is proposed to be imputed from information available in machine readable form. The limitations of this process are also discussed.

I.2.1 Prophylactic use

The data items to be used are Unit and what CARO refers to as dates of emplanement and deplanement (to and from Vietnam). These latter dates are in fact dates of departure from Australia for Special Overseas Service and of return to Australia from Special Overseas Service. For travel by aeroplane these dates accurately reflect service in Vietnam, but adjustment needs to be made for sea travel. Where Unit departure or return dates coincide with the movements of HMAS Sydney, these dates will be utilised to allow for sea travel in the calculation of dates in Vietnam.

Malaria discipline in the force was generally good. In November 1968 the Commander AFV wrote to all members of the force explaining the introduction of the drug and urging them to use it. Similarly, in August 1970 and July 1971 the Commanders of 1ATF wrote to all troops in Phuoc Tuy urging them to use the drug.

It will be imputed that each individual took 25 mg of dapsone on each day his Unit was in an area where dapsone was used except -

- personnel whose Units took part in the dapsone trial (1RAR, 4RAR, 12 Fd Rgt) in October and November 1968 will be assumed to have taken 25 mg daily for two weeks during that period unless further research indicates that individual participants can be identified. (It appears that servicemen in 12 Fd Rgt who took dapsone as part of the trial can be identified.)
- for personnel who developed falciparum malaria at a time when dapsone was administered to their Unit it is difficult to assume that dapsone was or was not taken. Some statements of malaria sufferers regarding their compliance have been collected. The analysis will be conducted:

  A. assuming that these servicemen did not take dapsone from the beginning of the current period of administration until the date of onset of malaria but did take it thereafter, and

  B. assuming that these servicemen did take dapsone from the beginning to the end of the current period of administration.

  This method has the following limitations:

- the accuracy of the data is only partially known;
- personnel were transferred between Units or attached to Units with different malaria prophylaxis policies;
- data on sub-Unit membership to identify dapsone use during the trial may not be available; and
- there was poor compliance in use of dapsone by a few individuals.

A sample of records will be drawn from CARO of veterans who served in Vietnam after 5 August 1970, the first date on which some Australians took dapsone and some did not. Transfers between Units which would have affected dapsone usage will be noted and taken into account in the analysis. Accuracy of recording of Unit in the CARO tapes will also be examined.

I.2.2 Therapeutic use

The treatment for falciparum malaria included 25 mg of dapsone daily for 30 days i.e. 750 mg of the drug.

This total dose will be imputed to each patient with an episode of 'definite' or 'probable' (these terms are defined in Section A.3.5 of the protocol) falciparum malaria with onset after September 1967. Extension of this to those identified as 'possible' malaria cases will be examined.

Medical records for samples of 25 falciparum malaria sufferers from each of October 1966 and February 1967 will be examined to determine what drug therapy was used before September 1967. If necessary the date of onset chosen will be amended.

I.2.3 Group in which dapsone use will not be imputed

AATTV (AAAG): These advisers, approximately 1000 in number, 'ranged far and wide over many provinces and military regions' (Department of Defence, 1984). Those stationed outside Phuoc Tuy Province and in US controlled units may have taken dapsone from 16 July 1966 to early 1970, the period of dapsone administration for malaria prophylaxis in the US forces. Those stationed in Phuoc Tuy Province are believed to have been issued with dapsone in accordance with the Australian usage, but these individuals cannot be identified by any systematic allocation.

Attachment II—Sources of data on malaria cases

The Official History Unit of the Australian War Memorial will supply details of cases of malaria. Dr Brendan O'Keefe of the Official History Unit of the Australian War Memorial has access to most of the surviving records of RAAMC (medical corps) Units in Vietnam and a variety of miscellaneous sources. He can identify many cases of malaria treated in these Units. The rest of the RAAMC records are currently being examined by Lt Col John Flynn. He has made photocopies of them available to the study. In addition Dr O'Keefe has access to notifications of infectious diseases; these notifications have survived from early 1968 and include malaria cases.

To date nearly 1100 episodes of malaria have been identified, including recurrences. For each case the following data are available:

- surname,
- initials,
- Army number,
- admission and/or discharge diagnosis,
- date of diagnosis and/or date of admission to RAAMC Unit,
- medical facility,
- details of treatment (occasionally), and
- source of information.

The number exceeds the 907 known to Black (1972), but may include some New Zealand veterans who will be excluded.

Prior to April 1967, an unknown number of veterans were evacuated to Australia because of malaria. Fleming (1974) refers to 12 such cases although it is believed that there were many others. Some veterans are known to have developed malaria after return to Australia. Many of both groups will have been treated in the Department of Veterans' Affairs or military hospitals. At this time, it appears that only DVA treated cases can be identified.

Another possible source is the malaria registry kept from 1969 by the late Professor R H Black, then Professor of Tropical Medicine at the University of Sydney. Professor Black's Department also examined slides earlier in the campaign and Dr O'Keefe has at least some of these reports. There may be others at the University. Professor Black's records are now held by Professor Moodie, who has been contacted and has agreed to assess their potential usefulness for the study.

Attachment III—Soundex codes for surnames

The following are the rules followed by the Soundex program used by the Cancer Registry of NSW:

Retain first letter of surname
Drop vowels and H, W, Y after first letter
Assign number codes to other consonants
Drop any repeated number
Drop any more than three numbers
Right fill to three numbers with zero
Number Assignments:

1 B F P V
2 C G J K Q S X Z
3 D T
4 L
5 M N
6 R

e.g. Mapremarora = M165
Mathews = M320
Matthews = M320
Schmidt = S253
Smith = S530

This framework may be extended to code all letters of the surname and to the coding of forenames as the development of the matching procedure is developed.

Appendix B: Matching of service and cancer registration records

B.1 Procedure for determining which servicemen had had cancer

To determine which servicemen had had cancer, it was necessary to match records in the service file to cancer incidence registrations from the six State cancer registries. The service file contained surname, first and second forenames, and day, month and year of birth. Most cancer registry records contained surname, first and second forenames, and day, month and year of birth, as well as the site of cancer and the date the cancer was diagnosed. The records from the South Australian registry had the name abbreviated as a HASAC identifier (first four letters of surname, first two letters of first forename, second initial, gender and date of birth).

Inevitably, some service and some cancer registration records had missing or incorrect information. Consequently, criteria were developed to determine which records matched.

Surnames were standardised by capitalising the surname, changing 'MC' to 'MAC', removing any hyphen, apostrophe or space and by replacing common misspellings of common surnames with standard spellings (e.g. 'NAUGHTON' becomes 'NORTON'). Forenames were standardised by capitalising the forenames and replacing common familiar forms of names with standard names (e.g. 'BILL' becomes 'WILLIAM'). A Soundex version of the forenames (see Attachment III to Appendix A) and a HASAC version of the surname and forenames were also created.

An exact match between a service record and a cancer registration record required agreement for the date of birth and for the standardised surname (or HASAC version for matching to South Australian cancer registrations). It also required close agreement for the forenames. This could be exact agreement for the standardised forenames or their Soundex versions. Experience with New South Wales registry records showed that a second forename was often missing or abbreviated to its initial, and that the forenames were often transposed. Accordingly, these minor discrepancies in the forenames did not preclude an exact match being declared.

Records which matched for surname but not for one or more components of the forenames and date of birth were regarded as partial matches. Mismatched components were assigned scores as follows: score of 1 for each of missing first forename, missing or incorrect day of birth, missing month of birth, missing year of birth, year of birth difference of one year. Putative matches whose cumulative scores were greater than 10 were discarded as mismatches.

The records for putative matches with cumulative scores between 1 and 10 were referred to Central Army Records Organisation and the appropriate cancer registry for confirmation of their data. If the putative match remained a partial match, the

data were scrutinised by a team of three people. This team discarded putative matches that they regarded as equivocal or unlikely.

Manual matching scores were assigned as follows to the putative matches that were regarded as likely matches: one difference, usually in the day of birth (score of 1); two differences, usually the day of birth and a one-year difference in the year of birth (score of 2); transposition of day and month of birth (score of 3); transposition of forenames or initials of forenames (score of 4); different month of birth or year of birth differing in only one digit (score of 5); other partial matches considered to be matches (score of 10). The manual matching also took account of the rarity of the names and completeness of the data. When evaluating mismatches in the year of birth, the age distribution of the site of cancer was also taken into account.

B.2 Effect of exact and partial matching on estimated relative cancer incidence rates

The incident cases analysed in Chapters 4 and 5 of this study report were obtained by matching Army personnel records with cancer registration records (see Section B.1). Where full name and date of birth agreed, it is reasonable to presume that the serviceman was the person whose cancer was registered.

However, full name and date of birth were not always available. Moreover, minor errors are likely to occur in the recording of this information. This means that identification of some servicemen with cancer requires accepting partially, not exactly, matching information. The algorithm for doing this is discussed in detail in Section B.1.

Accepting partially matching records increases the chance that the serviceman was not the person with cancer. Incorrectly matched records will lead to biased estimates of relative cancer incidence rates. Such records probably occur at random with respect to the subgroups being analysed; for example, dapsone exposure and Vietnam service. On average, such records add cancer cases to both subgroups in proportion to their size, usually resulting in a relative cancer incidence rate for these records close to unity. Accordingly, inclusion of these records will probably bias the estimated relative cancer incidence rate toward unity.

There were 1,266 exact matches and 372 partial matches. The partial matches are a substantial percentage—23 per cent—of the 1,638 partial and exact matches. However, Section B.1 makes clear that almost all partial matches will have correctly identified a serviceman with cancer. Therefore, exclusion of the partial matches would needlessly lower the power of the study, and their inclusion should not greatly bias the estimated relative cancer incidence rates.

Giles et al. (1987) give gender- and age-specific cancer incidence rates for 1982. These rates allow the expected number of incident cancers in the study cohort to be calculated for the period 1982 to 1984 (see Section 4.7). For all cancers, there were 588.7 cancers expected and 616 observed exact and partial matches. The relative rate of 1.05 is not statistically significantly different from unity. By contrast, the relative rate for exact matches would be 0.81, with a 95 per cent confidence interval of 0.75 to 0.88. These data suggest that the exact matches substantially underestimate the

number of servicemen with cancer, and that combining the partial and exact matches gives approximately the correct number.

The analyses in Chapter 4 can be repeated using only the exact matches. For the comparison of dapsone-exposed and -unexposed Vietnam veterans, the only 95 per cent confidence interval that excludes unity for the relative cancer incidence rate is for testis cancer. With the partial matches included, skin melanoma also has a relative cancer incidence rate statistically significantly lower than unity (see Table 4.6). This result suggests that combining the exact and partial matches has increased the power of the analysis compared with an analysis of the exact matches only.

For both testis cancer and skin melanoma, the relative rate among the partial matches is further from unity than that among the exact matches. Inclusion of the partial matches increases the statistical significance both by increasing the difference between the relative rate and unity and by increasing the number of cancers on which the relative rate is based. The increase in the difference between the relative rate and unity means that inclusion of the partial matches has not biased the relative rate toward unity. This is consistent with the partial matches having correctly identified servicemen with cancer.

For the exact and partial matches combined, no cancer site shows a statistically significant difference in cancer incidence between the Vietnam veterans and non-veterans (Table 4.17). This is also the case for service type restricted to Australian Regular Army servicemen (Table 4.19). However, among National Servicemen, Vietnam veterans had statistically significantly higher incidence rates for cancers of the pancreas, lung and brain. For lung and brain cancers, the estimated relative rate for partial matches was more extreme than that for exact matches. For cancer of the pancreas, the estimated rate for partial matches was between unity and the rate for exact matches. For each of these three sites of cancer, the 95 per cent confidence interval calculated using only the exact matches includes unity, while the 95 per cent confidence interval calculated using the exact and partial matches combined excludes unity. Thus, inclusion of partial matches appears to increase power and not to bias these estimated relative risks toward unity.

Restriction of the analysis to only exact matches would suggest additional statistically significant results for two sites of cancer. Both are for comparisons of Vietnam veterans with non-veterans. For brain cancer, the estimated relative incidence rate would be 2.2 among the 32 exact matches, while it is only 0.3 among the six partial matches. The relative incidence rate is 1.6 for the exact and partial matches combined. For lung cancer, the opposite pattern is seen for Australian Regular Army servicemen: an estimated relative incidence rate of 0.6 among the exact matches, 1.7 among the partial matches, and 0.8 for the exact and partial matches combined.

If many of the partial matches were of servicemen incorrectly identified as having cancer, the percentage of matches that are partial matches would be inflated. However, in both cases the percentage is less than the average (23 per cent—see above). It also happens in both cases that the estimated relative rate among the partial matches is not intermediate between that for the exact matches and unity. Instead, it is in the opposite direction and more extreme.

Taken together, the most likely explanation for these differences is chance. This means that the estimate among the combined exact and partial matches is unbiased, and that this estimate is the best estimate of the relative cancer incidence rate.

Conclusion

Estimation of relative cancer incidence rates among the exact and partial matches combined is unlikely to be biased and will have greater precision than an analysis using the exact matches only.

Appendix C: Statistical information

C.1 Calculation of 'expected' numbers of incident cases

The standard statistical argument for assessing whether an exposure of interest (such as dapsone exposure) is associated with differential cancer incidence requires calculating the expected number of cancer cases assuming equal cancer incidence. For these calculations, cancer incidence rates were assumed to vary by age group and calendar year but not by the exposure of interest.

In Sections 4.2 to 4.6 the following algorithm was used to calculate the expected number of cancer cases:

1. The site of cancer, the age at diagnosis and the calendar year of diagnosis were available for each incident case.
2. The study population was defined for the particular analysis. For example, for Section 4.2 the study population was Vietnam veterans only, and it was further restricted to National Service Vietnam veterans for some analyses in this section. (The study population is shown in a note at the end of each table, preceded by the annotation 'Population:'.)
3. The number of observed cases in the study population was tabulated by five-year age group and single calendar year.
4. The corresponding table of the person-years at risk was also calculated. Each person in the study population was counted in the age group they were in for each calendar year.
5. The ratio of the observed number of incident cases and the person-years at risk, for each age group and calendar year, gave the age-group- and calendar-year-specific incidence rate for the study population.
6. The number of person-years at risk, classified by five-year age group and single calendar year, was tabulated for each subgroup of interest within the study population. An example of a subgroup is dapsone-exposed Vietnam veterans.
7. The expected number of incident cancer cases was calculated by multiplying the person-years at risk for the subgroup by the corresponding age- and calendar-year-specific incidence rate.
8. The expected number of incident cancer cases was summed for all age groups and calendar years for the subgroup of interest. This gives the expected number of cancers for the subgroup.

Each expected number of cancer cases in the tables in Sections 4.2 to 4.6 was separately calculated in this way. The values have been rounded to the nearest tenth of a case for display in the tables, but approximately eight decimal digits of precision were retained for use in subsequent calculations. These calculations were performed using the GLIM computer package (NAG 1987).

For Section 4.7, the 1982 Australian male age-specific cancer incidence rates were taken from Giles et al. (1987), instead of being calculated as in steps 1 to 5 above. For step 6, the calendar years were restricted to 1982 to 1984, the period for which all cancer registries supplied data and had nominally complete coverage.

Calculation of expected numbers of cancers is a standard method in epidemiology. Given the form of the data, it is convenient to assume that the cancer incidence rate is uniform for each age group and calendar year. An alternative analysis, which would yield similar results, would assume that the cancer incidence rate is uniform for each age group and birth year of the persons in the study.

Section C.2 shows that the expected number of cancers is similar regardless of the age grouping (for example, using 10-year age groups instead of five-year age groups) or calendar period (for example, using two or five calendar years instead of a single calendar year) for the classification of incident cases.

C.2 Different methods of calculation of the expected number of cancers

In Chapters 4 and 5, the expected number of cancers was calculated as described in Section C.1. Cells were defined by five-year age groups and single calendar year (for example, aged 30–34 in 1975). For each cell, the observed cancer incidence rate was obtained by dividing the number of cancers in the cell by the number of person-years at risk for the cohort in that cell. The expected number of cancers for a subgroup within a cell (for example, Vietnam veterans aged 30–34 in 1975) was calculated by multiplying the observed cancer incidence rate for that cell by the number of persons-years at risk for the subgroup. The total expected number of cancers is the quantity displayed in the tables and used for further calculations.

The extent to which the expected number of cancers depends on the 'size' of these cells was examined. If the dependence was great, the choice of the size of the cells could affect the conclusions of the study. The cells were increased in four ways, as shown in the notes to Table C.1. However, even increasing the size of the cells four- or five-fold did not greatly affect the expected number of cancers (see Tables C.1, C.4 and C.7). Tables C.2 and C.5 show that these different cell sizes do not greatly affect the estimated relative cancer incidence rates. Tables C.3 and C.6 show that the test statistics are also little affected, and that the analysis would come to the same conclusions regardless of which size cells were used.

Fewer incident cancer cases have been analysed in this appendix compared with the analyses in Chapters 4 and 5. A total of 1,300 cancers are analysed here, compared with 1,638 in Chapters 4 and 5. The analyses in this appendix use an early version of the data set, for which some cancer registrations were unavailable. However, the conclusions of this appendix are unlikely to be affected by this difference.

These tables also show the effect of calculating the expected number of cancers using a different method. This method used log-linear models of the year and age variation for cancer incidence. These models are computationally intensive, and require some care with respect to computational accuracy. However, it appears that the sophisticated models performed similarly to the straightforward calculations

described above. Where there are differences, they appear to occur in situations where the computational algorithm is stressed. Accordingly, the simpler calculations are preferred.

A potential deficiency in the calculation of the expected number of cancers is that mortality in the cohort has been ignored. Given the method of calculation, the expected numbers of cancers in different subgroups in a cell should be almost unaffected by mortality in the cohort, provided the mortality is either small or depends only on age or year of birth, or both. In this predominantly young cohort, mortality will have been small, with the control for age group and calendar year further ensuring that the proportion of servicemen in a particular subgroup within a cell is similar whether mortality is or is not taken account of.

Conclusion

This appendix shows that the conclusions of the analysis are similar regardless of the coarseness of classification of age group and calendar year.

C.3 Conformation of the data set

The data set was organised in two parts: for each category of servicemen classified by calendar year, age group, service type, Vietnam service, total dapsone dose and treatment for malaria, there was a single record giving the corresponding person-years at risk; and for each cancer case there was also a single record. The expected number of cancers (see Section C.1) was calculated for each record and then summed within each subgroup of interest. The summary observed and expected numbers of cancers were analysed using Poisson regression modelling (Breslow & Day 1987).

The form of the data set gave considerable flexibility. For example, the same data set was suitable for analyses involving any combination of the categories of serviceman and any site of cancer or matching score. Summing the expected number of cancers is important because it dramatically reduces the computational resources required to fit the Poisson regression models.

The data set was created using the SAS program (SAS 1988). SAS was also used to calculate the expected number of cancers assuming the 1982 Australian male age-specific incidence rates (Section 4.7). All other calculations, including the Poisson regression modelling, were carried out using the GLIM statistical package (NAG 1987). The exact binomial confidence intervals were programmed as a GLIM macro using an iterative algorithm.

C.4 Statistical issues

Statistical tests or confidence intervals?

The confidence interval for an estimated relative cancer incidence rate shows the range of values for the relative rate that are not contradicted by the data. A confidence interval that excludes a relative rate of 1 corresponds to a statistically

significant statistical test, and conversely. Therefore a confidence interval and its corresponding statistical test give identical conclusions on whether a relative rate is statistically significantly different from unity.

However, the confidence interval gives additional information on the power of the test. A narrow range of values for the confidence interval suggests that there are sufficient data for high power. Conversely, a wide confidence interval characterises low power.

The confidence interval also gives the range of values for the relative rate that the data set supports. For example, if the upper limit of the confidence interval is, say, 1.5, the data are clearly inconsistent with elevated relative rates of 2, 3 or more. Therefore the confidence interval can provide evidence that excludes the possibility of extreme relative rates.

The analyses in this study report make extensive use of 95 per cent confidence intervals. Statistical tests at the 5 per cent, 1 per cent and 0.1 per cent levels are also tabulated.

Asymptotic or exact statistical calculations?

Conclusions from the confidence interval and the statistical test are asymptotically equivalent. In data sets with a finite number of cancer cases, the method of calculation ensures that the results must be close, but not that they are identical. For example, it could happen that the confidence interval just excludes a relative rate of 1, but that the statistical test statistic is just short of the corresponding significance level. Such minor anomalies should not affect the conclusions from the analysis.

The maximum likelihood test statistic is close to being chi-square distributed only when the observed number of cancers is large. Statistical research suggests that five or more cancers in each subgroup is adequately large for tests based on a chi-square distribution to be reliable.

Unfortunately, many of the analyses involve smaller numbers of cancers than five per subgroup. In these circumstances the test statistic should be regarded with caution. This is particularly the case when there are no cancers for one of the subgroups.

Choice of a different asymptotic test statistic, such as the Pearson chi-square test statistic, cannot resolve this problem. However, it is possible to calculate the exact confidence intervals.

Standard statistical theory shows that the distribution of a Poisson-distributed variable is binomial when conditioned on its sum with another Poisson variable. This is precisely the situation when there are two subgroups. Exact confidence intervals, based on the binomial distribution, are computationally feasible, and these have been calculated whenever there are four or fewer cancer cases observed for a subgroup.

Typically, the exact confidence intervals are wider than the asymptotic confidence intervals. When a confidence interval includes a relative rate of 1, the conclusion is that the observed number of cancers in the two subgroups is not inconsistent with equal cancer incidence rates in the subgroups. The conclusion based on exact

confidence intervals should be preferred to a nominally statistically significant asymptotic test statistic.

Extra-Poisson variation

Another statistical issue is whether the Poisson assumption holds. Some epidemiological studies have shown variation that is greater than that implicit in a Poisson regression analysis (see Breslow & Day 1987). Extra-Poisson variation would not affect the relative cancer incidence rate: analyses assuming Poisson variation would give the same relative rates as analyses taking account of extra-Poisson variation.

However, extra-Poisson variation will lead to widened confidence intervals and to the need to deflate test statistics before they can be validly compared with chi-square distributions. Therefore analyses assuming Poisson variation may erroneously suggest statistically significant differences in cancer incidence rates but will correctly identify situations where the cancer incidence rates are not statistically significantly different.

The confidence intervals and statistical tests in this study report retain the Poisson assumption. Therefore some nominally statistically significant results may occur where there are no underlying differences.

Multiplicity of statistical tests

With so many sites of cancer being analysed, it is likely that chance will lead to nominally statistically significant differences in incidence rates for some sites of cancers between some subgroups of servicemen. In particular, the definition of performing tests at the 5 per cent significance level asserts that 5 per cent of tests where there is no underlying difference will be nominally statistically significant.

The problem with this is that it may be difficult to distinguish between a difference in cancer incidence rates caused by, say, dapsone exposure and a difference that is coincidental. This is a standard issue in statistics. It necessarily arises when many statistical tests are performed.

Several strategies can be employed in this situation: restrict the number of tests; perform tests at a smaller significance level; emphasise confidence intervals rather than statistical tests.

Restrict the number of tests

The number of tests has been restricted here by analysing only those sites of cancers that previous research suggests may be of interest. For example, multiple myeloma (ICD 203) was not identified as a cancer of interest in previous research and so is not analysed in this study, except that it is part of the 'All cancers' (ICD 140–208) category.

It is tempting to review critically the list of cancers to eliminate those sites for which differential cancer incidence is fanciful or implausible. While this would deal with the multiple-testing problem, it might result in the analysis missing a possible

relationship in the data. (Some readers of this report may wish to exclude from consideration the sites of cancer they consider irrelevant.)

Another way to limit the number of statistical tests is to restrict the sites of cancers to those sites with appreciable numbers of incident cancer cases in the data set. This also would reduce the number of tests with a low power; that is, those with only a small chance of detecting a statistically significant difference.

Unfortunately, if there were an underlying difference between different groups of servicemen in their cancer incidence, the biological mechanism of the difference probably would mean that the difference must be confined to specific sites of cancer. Indeed, the specificity of the difference would be important evidence that the biological mechanism was operating. This means that the analysis would be incomplete if it did not include these specific sites of cancer, even if these sites have few cancer cases in the data set.

Perform tests at a smaller significance level

For example, if there is a known number of independent tests, the significance level for each test can be set so that the overall significance level for all tests combined is 5 per cent. The drawback with this approach is that it results in individual tests of very low power. This approach has not been followed.

Emphasise confidence intervals rather than statistical tests

Confidence intervals have been emphasised in this report.

Correlated statistical tests

A related problem is that some cancer sites are subsets of other sites. (This is shown in the tables by indenting subsites.) This means that the statistical tests for the some sites of cancers are correlated. For example, any difference found for leukemia (ICD 204–208) is likely to be repeated for myelocytic leukemia (ICD 205). Yet, restricting the analysis to mutually exclusive sites of cancers almost certainly dooms the analysis to be mainly of cancer sites with few incident cases and so to have low power. Accordingly, the analysis in this report includes some cancer sites that are subsets of others.

Table C.1 *Observed and expected cancers for National Service and Australian Regular Army Vietnam veterans, by dapsone exposure, using six different algorithms*

Site of cancer	Observed cancers		Expected cancers for dapsone-exposed Vietnam veterans, calculated using algorithm					
	Exposed	Not exposed	(1)	(2)	(3)	(4)	(5)	(6)
All	210	193	206.4	207.8	209.1	209.3	205.9	205.8
Oral	25	13	18.8	18.9	19.1	19.1	18.5	18.8
Lip	12	7	10.7	10.8	10.4	10.4	10.1	10.4
Nasopharyngeal	1	2	1.6	1.7	1.6	1.6	1.5	-
Stomach	6	6	6.1	6.2	6.1	6.1	6.0	5.6
Colon	10	13	10.6	10.7	10.7	10.7	10.6	10.6
Rectum	12	11	10.7	10.9	11.0	11.1	10.9	10.8
Primary liver	1	1	0.9	0.9	0.9	0.8	0.9	-
Pancreas	5	6	4.6	4.9	5.5	5.5	5.3	5.1
Larynx	5	0	2.2	2.4	2.4	2.4	2.2	-
Lung	25	23	21.9	21.8	22.4	22.5	21.8	21.6
Soft-tissue	3	6	5.8	5.8	5.7	5.7	5.6	5.4
Skin melanoma	42	35	43.5	43.6	43.4	43.3	43.1	43.4
Prostate	2	6	3.5	3.5	3.6	3.6	3.5	3.6
Testis	13	8	12.6	12.7	12.5	12.6	12.6	12.7
Bladder	12	11	11.4	11.5	11.3	11.3	10.9	11.0
Kidney	3	5	3.5	3.6	3.8	3.8	3.6	3.6
Brain	5	7	6.3	6.4	6.4	6.4	6.5	6.3
Non-H lymphoma	5	13	9.8	10.0	10.1	10.2	10.3	9.9
Lympho- & reticulo-	4	11	8.1	8.2	8.3	8.4	8.5	8.1
Other lymphoid	1	2	1.7	1.7	1.8	1.8	1.8	-
Hodgkin's disease	4	6	6.0	6.0	5.9	5.9	6.1	5.8
Leukemia	13	3	8.1	8.3	8.3	8.3	8.1	7.9
Myelocytic leukemia	9	2	5.9	6.0	6.1	6.1	5.8	5.6

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

Expected cancers calculations assume equal incidence for both groups in cells defined by

(1) five-year age groups and one-year calendar year groups

(2) five-year age groups and two-year calendar year groups

(3) 10-year age groups and one-year calendar year groups

(4) 10-year age groups and two-year calendar year groups

(5) five-year age groups and five-year calendar year groups

(6) log-linear modelling of calendar year variation (as seen for all cancers) together with polynomial terms for age (- when not calculated).

Table C.2 *Relative cancer incidence rates of dapsone-exposed Vietnam veterans compared with other Vietnam veterans, using six different algorithms*

	Algorithm for calculation of expected number of cancers					
Site of cancer	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
All	0.9	0.9	0.9	0.9	0.9	0.9
Oral	0.5	0.5	0.5	0.5	0.5	0.5
Lip	0.5	0.4	0.5	0.5	0.5	0.5
Nasopharyngeal	1.7	1.6	1.8	1.8	2.0	-
Stomach	1.0	0.9	1.0	1.0	1.0	1.1
Colon	1.5	1.5	1.5	1.5	1.5	1.5
Rectum	1.1	1.0	1.0	1.0	1.0	1.0
Primary liver	1.3	1.3	1.4	1.4	1.3	-
Pancreas	1.6	1.5	1.2	1.2	1.3	1.4
Larynx	0.0	0.0	0.0	0.0	0.0	0.0
Lung	1.1	1.1	1.0	1.0	1.1	1.1
Soft tissue	1.1	1.1	1.2	1.2	1.2	1.3
Skin melanoma	0.6	0.6	0.6	0.6	0.7	0.6
Prostate	3.9	3.9	3.7	3.6	3.9	3.7
Testis	0.4	0.4	0.4	0.4	0.4	0.4
Bladder	0.9	0.9	1.0	1.0	1.0	1.0
Kidney	2.1	2.1	1.9	1.9	2.1	2.0
Brain	1.3	1.2	1.2	1.2	1.2	1.3
Non-H lymphoma	2.2	2.1	2.0	2.0	1.9	2.1
Lympho- & reticulo-	2.3	2.3	2.2	2.2	2.1	2.3
Other lymphoid	1.5	1.5	1.3	1.4	1.3	-
Hodgkin's disease	1.0	1.0	1.0	1.0	1.0	1.1
Leukemia	0.2	0.2	0.2	0.2	0.2	0.2
Myelocytic leukemia	0.2	0.2	0.2	0.2	0.2	0.2

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

Expected cancers calculations assume equal incidence for both groups in cells defined by

(1) five-year age groups and one-year calendar year groups

(2) five-year age groups and two-year calendar year groups

(3) 10-year age groups and one-year calendar year groups

(4) 10-year age groups and two-year calendar year groups

(5) five-year age groups and five-year calendar year groups

(6) log-linear modelling of calendar year variation (as seen for all cancers) together with polynomial terms for age (- when not calculated).

Table C.3 *Test statistics for difference between cancer incidence in dapsone-exposed Vietnam veterans compared with other Vietnam veterans, using six different algorithms*

Site of cancer	Algorithm for calculation of expected number of cancers					
	(1)	(2)	(3)	(4)	(5)	(6)
All	1.8	2.2	2.6	2.6	1.7	1.6
Oral	3.7	3.8	4.0*	4.0*	3.2	3.6
Lip	2.8	3.0	2.4	2.4	2.0	2.5
Nasopharyngeal	0.2	0.1	0.2	0.2	0.3	-
Stomach	0.0	0.0	0.0	0.0	0.0	0.0
Colon	1.0	0.9	0.9	0.9	1.0	1.0
Rectum	0.0	0.0	0.0	0.0	0.0	0.0
Primary liver	0.0	0.0	0.0	0.0	0.0	-
Pancreas	0.7	0.5	0.1	0.1	0.2	0.3
Larynx	5.9*	6.4*	6.4*	6.6*	5.9*	-
Lung	0.1	0.1	0.0	0.0	0.1	0.2
Soft tissue	0.0	0.0	0.0	0.1	0.1	0.2
Skin melanoma	3.7	3.9*	3.7	3.6	3.5	3.7
Prostate	3.3	3.2	3.0	2.9	3.3	3.0
Testis	4.1*	4.2*	3.9*	4.0*	4.1*	4.3*
Bladder	0.0	0.1	0.0	0.0	0.0	0.0
Kidney	1.1	1.0	0.8	0.8	1.0	1.0
Brain	0.2	0.1	0.1	0.1	0.1	0.2
Non-H lymphoma	2.4	2.2	1.9	1.9	1.7	2.2
Lympho- & reticulo-	2.4	2.2	2.0	1.9	1.8	2.3
Other lymphoid	0.1	0.1	0.0	0.1	0.0	-
Hodgkin's disease	0.0	0.0	0.0	0.0	0.0	0.0
Leukemia	7.0**	7.4**	7.4**	7.5**	6.9**	6.5*
Myelocytic leukemia	5.8*	6.2*	6.4*	6.4*	5.7*	5.2*

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

Expected cancers calculations assume equal incidence for both groups in cells defined by

(1) five-year age groups and one-year calendar year groups

(2) five-year age groups and two-year calendar year groups

(3) 10-year age groups and one-year calendar year groups

(4) 10-year age groups and two-year calendar year groups

(5) five-year age groups and five-year calendar year groups

(6) log-linear modelling of calendar year variation (as seen for all cancers) together with polynomial terms for age (-when not calculated).

All give $p > 0.05$, except those marked * ($0.01 < p < 0.05$) and ** ($0.001 < p < 0.01$).

Table C.4 *Observed and expected cancers for National Service and Australian Regular Army personnel, by Vietnam service, using six different algorithms*

Site of cancer	Observed cancers		Expected cancers for Vietnam veterans calculated using algorithm					
	Non-veteran	Vietnam veteran	(1)	(2)	(3)	(4)	(5)	(6)
All	897	403	399.6	401.1	405.5	404.5	402.5	401.2
Oral	72	38	37.9	37.8	38.3	38.2	38.0	37.9
Lip	38	19	20.6	20.5	20.3	20.4	20.8	21.0
Nasopharyngeal	1	3	1.6	1.6	1.6	1.6	1.6	(1.4)
Stomach	29	12	11.9	12.0	12.5	12.5	12.3	12.1
Colon	63	23	23.5	23.5	23.5	23.5	23.6	23.1
Rectum	53	23	22.7	23.0	22.3	22.2	22.6	23.5
Primary liver	1	2	0.8	0.8	1.0	1.0	0.9	(1.0)
Pancreas	16	11	6.9	6.9	6.9	7.0	7.1	7.4
Nasal	2	0	0.9	0.9	0.9	0.9	0.9	(0.7)
Larynx	24	5	7.9	7.9	8.0	8.0	7.8	8.1
Lung	137	48	52.0	52.0	52.1	52.2	51.8	51.1
Soft tissue	15	9	7.8	8.0	8.1	8.0	8.1	7.6
Skin melanoma	134	77	72.4	73.3	73.6	72.9	74.0	73.5
Prostate	49	8	8.3	8.3	9.3	9.3	8.6	8.2
Testis	49	21	26.1	26.4	25.7	25.5	26.2	25.2
Bladder	46	23	20.8	21.0	20.7	20.6	20.6	20.6
Kidney	23	8	8.6	8.7	9.1	9.0	9.1	9.1
Brain	18	12	9.6	9.5	10.2	10.2	9.8	10.2
Non-H lymphoma	35	18	19.0	18.8	19.6	19.7	18.8	18.7
Lympho- & reticulo-	20	15	12.9	12.8	13.3	13.3	12.9	12.9
Other lymphoid	15	3	6.1	6.0	6.3	6.4	5.9	6.0
Hodgkin's disease	12	10	7.4	7.4	7.8	7.8	7.2	6.5
Leukemia	25	16	14.2	14.4	14.8	14.7	14.4	14.1
Myelocytic leukemia	14	11	8.8	9.0	9.4	9.3	9.0	8.6

Population: National Service and Australian Regular Army servicemen.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

Expected cancers calculations assume equal incidence for both groups in cells defined by

(1) five-year age groups and one-year calendar year groups

(2) five-year age groups and two-year calendar year groups

(3) 10-year age groups and one-year calendar year groups

(4) 10-year age groups and two-year calendar year groups

(5) five-year age groups and five-year calendar year groups

(6) log-linear modelling of calendar year variation (as seen for all cancers) together with polynomial terms for age (no age terms for those that are bracketed).

Table C.5 *Relative cancer incidence rates of Vietnam veterans compared with non-veterans, using six different algorithms*

Site of cancer	Algorithm for calculation of expected number of cancers					
	(1)	(2)	(3)	(4)	(5)	(6)
All	1.0	1.0	1.0	1.0	1.0	1.0
Oral	1.0	1.0	1.0	1.0	1.0	1.0
Lip	0.9	0.9	0.9	0.9	0.9	0.9
Nasopharyngeal	4.5	4.6	4.4	4.5	4.4	(5.6)
Stomach	1.0	1.0	0.9	0.9	1.0	1.0
Colon	1.0	1.0	1.0	1.0	1.0	1.0
Rectum	1.0	1.0	1.0	1.1	1.0	1.0
Primary liver	5.1	5.1	3.8	3.7	4.5	3.7
Pancreas	2.0	2.0	2.0	2.0	1.9	1.8
Nasal	0.0	0.0	0.0	0.0	0.0	(0.0)
Larynx	0.6	0.6	0.5	0.5	0.6	0.5
Lung	0.9	0.9	0.9	0.9	0.9	0.9
Soft tissue	1.2	1.2	1.2	1.2	1.2	1.3
Skin melanoma	1.1	1.1	1.1	1.1	1.1	1.1
Prostate	1.0	1.0	0.8	0.8	0.9	1.0
Testis	0.7	0.7	0.7	0.7	0.7	0.8
Bladder	1.1	1.2	1.2	1.2	1.2	1.2
Kidney	0.9	0.9	0.8	0.9	0.8	0.8
Brain	1.4	1.4	1.3	1.3	1.4	1.3
Non-H lymphoma	0.9	0.9	0.9	0.9	0.9	0.9
Lympho- & reticulo-	1.3	1.3	1.2	1.2	1.3	1.3
Other lymphoid	0.4	0.4	0.4	0.4	0.4	0.4
Hodgkin's disease	1.7	1.6	1.5	1.5	1.7	2.0
Leukemia	1.2	1.2	1.1	1.1	1.2	1.2
Myelocytic leukemia	1.4	1.4	1.3	1.3	1.4	1.5

Population: National Service and Australian Regular Army servicemen.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

Expected cancers calculations assume equal incidence for both groups in cells defined by

(1) five-year age groups and one-year calendar year groups

(2) five-year age groups and two-year calendar year groups

(3) 10-year age groups and one-year calendar year groups

(4) 10-year age groups and two-year calendar year groups

(5) five-year age groups and five-year calendar year groups

(6) log-linear modelling of calendar year variation (as seen for all cancers) together with polynomial terms for age (no age terms for those that are bracketed).

Table C.6 *Test statistics for difference between cancer incidence in Vietnam veterans compared with non-veterans, using six different algorithms*

	Algorithm for calculation of expected number of cancers					
Site of cancer	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
All	0.0	0.0	0.0	0.0	0.0	0.0
Oral	0.0	0.0	0.0	0.0	0.0	0.0
Lip	0.2	0.2	0.1	0.2	0.2	0.3
Nasopharyngeal	2.0	2.1	2.0	2.0	1.9	2.7
Stomach	0.0	0.0	0.0	0.0	0.0	0.0
Colon	0.0	0.0	0.0	0.0	0.0	0.0
Rectum	0.0	0.0	0.0	0.0	0.0	0.0
Primary liver	1.9	1.9	1.3	1.3	1.6	1.3
Pancreas	3.0	2.9	2.9	2.9	2.7	2.2
Nasal	2.4	2.4	2.4	2.4	2.4	1.7
Larynx	1.6	1.6	1.7	1.7	1.5	1.8
Lung	0.4	0.4	0.5	0.5	0.4	0.2
Soft tissue	0.2	0.3	0.1	0.2	0.2	0.4
Skin melanoma	0.3	0.4	0.2	0.3	0.2	0.3
Prostate	0.0	0.0	0.2	0.2	0.1	0.0
Testis	1.9	1.6	1.4	1.3	1.7	1.1
Bladder	0.3	0.3	0.4	0.4	0.4	0.4
Kidney	0.1	0.1	0.2	0.2	0.2	0.2
Brain	0.9	0.9	0.5	0.5	0.7	0.5
Non-H lymphoma	0.0	0.1	0.2	0.2	0.0	0.0
Lympho- & reticulo-	0.6	0.5	0.4	0.3	0.5	0.6
Other lymphoid	2.5	2.6	3.1	3.2	2.4	2.5
Hodgkin's disease	1.4	1.3	0.9	0.9	1.5	2.5
Leukemia	0.3	0.4	0.1	0.2	0.3	0.4
Myelocytic leukemia	0.7	0.8	0.4	0.5	0.7	0.9

Population: National Service and Australian Regular Army servicemen.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

Expected cancers calculations assume equal incidence for both groups in cells defined by

(1) five-year age groups and one-year calendar year groups

(2) five-year age groups and two-year calendar year groups

(3) 10-year age groups and one-year calendar year groups

(4) 10-year age groups and two-year calendar year groups

(5) five-year age groups and five-year calendar year groups

(6) log-linear modelling of calendar year variation (as seen for all cancers) together with polynomial terms for age (no age terms for those that are bracketed).

Table C.7 *Observed and expected cancers for National Service and Australian Regular Army Vietnam veterans, by malaria exposure, using six different algorithms*

Site of cancer	Observed cancers		Expected cancers for dapsone-exposed Vietnam veterans, calculated using algorithm					
	Not exposed	Exposed	(1)	(2)	(3)	(4)	(5)	(6)
All	398	5	7.5	7.5	7.5	7.6	7.6	7.7
Oral	38	0	0.7	0.7	0.7	0.7	0.7	0.7
Lip	19	0	0.5	0.5	0.5	0.5	0.5	0.5
Nasopharyngeal	3	0	0.1	0.1	0.1	0.1	0.1	-
Stomach	12	0	0.2	0.2	0.2	0.2	0.2	0.2
Colon	21	2	0.3	0.3	0.3	0.3	0.3	0.3
Rectum	22	1	0.4	0.4	0.4	0.4	0.4	0.4
Primary liver	2	0	0.0	0.0	0.0	0.0	0.0	-
Pancreas	11	0	0.2	0.2	0.2	0.2	0.2	0.2
Nasal	0	0						
Larynx	5	0	0.1	0.1	0.1	0.1	0.1	-
Lung	48	0	0.7	0.7	0.7	0.7	0.7	0.7
Soft tissue	9	0	0.2	0.2	0.2	0.2	0.2	0.2
Skin melanoma	75	2	1.6	1.6	1.7	1.7	1.6	1.7
Prostate	8	0	0.1	0.1	0.1	0.1	0.1	0.1
Testis	21	0	0.5	0.5	0.5	0.5	0.5	0.5
Bladder	23	0	0.4	0.4	0.4	0.4	0.4	0.4
Kidney	8	0	0.1	0.1	0.1	0.1	0.1	0.1
Brain	12	0	0.3	0.3	0.3	0.3	0.3	0.3
Non-H lymphoma	18	0	0.3	0.4	0.4	0.4	0.4	0.4
Lympho- & reticulo-	15	0	0.3	0.3	0.3	0.3	0.3	0.3
Other lymphoid	3	0	0.1	0.1	0.1	0.1	0.1	-
Hodgkin's disease	10	0	0.2	0.2	0.2	0.2	0.2	0.2
Leukemia	16	0	0.3	0.3	0.3	0.3	0.3	0.3
Myelocytic leukemia	11	0	0.2	0.2	0.2	0.2	0.2	0.2

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

Expected cancers calculations assume equal incidence for both groups in cells defined by

(1) five-year age groups and one-year calendar year groups

(2) five-year age groups and two-year calendar year groups

(3) 10-year age groups and one-year calendar year groups

(4) 10-year age groups and two-year calendar year groups

(5) five-year age groups and five-year calendar year groups

(6) log-linear modelling of calendar year variation (as seen for all cancers) together with polynomial terms for age (- when not calculated).

Table C.8 *Expected cancers for three subgroups, calculated without (a) and with (b) taking account of mortality in the cohort*

	Vietnam veterans		Dapsone-exposed		Malaria-exposed	
Site of cancer	**(a)**	**(b)**	**(a)**	**(b)**	**(a)**	**(b)**
All	401.1	401.1	206.4	206.5	7.5	7.5
Oral	37.8	37.8	18.8	18.9	0.7	0.7
Lip	20.5	20.5	10.7	10.7	0.5	0.5
Nasopharyngeal	1.6	1.6	1.6	1.6	0.1	0.1
Stomach	12.0	12.0	6.1	6.1	0.2	0.2
Colon	23.5	23.5	10.6	10.6	0.3	0.3
Rectum	23.0	23.0	10.7	10.7	0.4	0.4
Primary liver	0.8	0.8	0.9	0.9	0.0	0.0
Pancreas	6.9	6.9	4.6	4.7	0.2	0.2
Nasal	0.9	0.9				
Larynx	7.9	7.9	2.2	2.2	0.1	0.1
Lung	52.0	52.0	21.9	21.9	0.7	0.7
Soft tissue	8.0	8.0	5.8	5.8	0.2	0.2
Skin melanoma	73.3	73.3	43.5	43.5	1.6	1.6
Prostate	8.3	8.3	3.5	3.5	0.1	0.1
Testis	26.4	26.4	12.6	12.6	0.5	0.5
Bladder	21.0	21.0	11.4	11.4	0.4	0.4
Kidney	8.7	8.7	3.5	3.5	0.1	0.1
Brain	9.5	9.5	6.3	6.3	0.3	0.3
Non-H lymphoma	18.8	18.8	9.8	9.8	0.3	0.3
Lympho- & reticulo-	12.8	12.8	8.1	8.1	0.3	0.3
Other lymphoid	6.0	6.0	1.7	1.7	0.1	0.1
Hodgkin's disease	7.4	7.4	6.0	6.0	0.2	0.2
Leukemia	14.4	14.4	8.1	8.1	0.3	0.3
Myelocytic leukemia	9.0	9.0	5.9	5.9	0.2	0.2

Population: National Service and Australian Regular Army Vietnam veterans.

Notes: Observed cancers from Australian cancer registrations, 1972–89, where available.

The calculation of the expected number of cancers assumes constant incidence rates within each cell defined by five-year age group and single calendar year, with

(a) no account taken of mortality in each cell

(b) Australian male age-specific mortality rates for 1970 (d'Espaignet et al. 1991) applied to each cell.

Appendix D: Membership of the Scientific Advisory Committee

Chairman

Professor Geoffrey Berry MA PhD (Camb), FIS, FACOM (Hon)
(Head, Department of Public Health, University of Sydney)

Members

Professor David Christie MB BS (Qld), MD (Lond), FRACP, FFCM, FACOM
(Head, Discipline of Environmental and Occupational Health, University of Newcastle)

Professor John McNeil MB BS (Adel), MSc (Lond), PhD (Melb), FRACP
(Chair of the Department of Social and Preventive Medicine, Monash University)

Professor Martin Tattersall MA MD (Camb), MSc (Lond), FRCP, FRACP
(Head, Department of Clinical Oncology, Royal Prince Alfred Hospital; Professor of Cancer Medicine, University of Sydney)

Ms Deborah Turnbull BA MPsych (Clin) (Newc)
(Scientific Secretary to 31 December 1991; Department of Public Health, University of Sydney)

Ms Angela Plunkett BA (Syd)
(Scientific Secretary from 1 January 1992; Department of Public Health, University of Sydney)

Appendix E: Project staff

Staff—Australian Institute of Health and Welfare

Leonard R Smith BA (Hons) (Syd), PhD (UNSW), MSc (Dist) (Lond)
Project Director (from December 1990)

Development of study protocol, matching software package, malaria and dapsone data preparation, evaluation of biological plausibility

John W Donovan MB BS PhD (Syd), FFPHM, FRACMA, FAFPHM
Principal Medical Advisor (January 1989–March 1990)

Michael J Fett MB BS (Hons), BMed Sc (Hons), MPH (Harvard), MD (Monash), FACOM
Principal Investigator & Project Director (March 1990–December 1990)

Kathryn Leary BA (Hons) (ANU)
Systems Development (October 1989–October 1990)

Bruce English BA (Hons) (ANU)
Analyst (October 1989–June 1990)

Brendon O'Keefe BDS (Syd), BA (UNE), Dip Archiv Admin (UNSW)
Analyst (October 1990–January 1991)

Development of matching software package, statistical analysis, and report

Krystian R Sadkowsky BA, Grad Dip Info Sc (CCAE)
Principal Investigator (November 1990–March 1992)

Consultants

Systems (Axon Software Pty Ltd)

Peter Flemming—senior software specialist

Simon Wild—senior software specialist

Statistical analysis and report writing (INTSTAT Australia Pty Ltd)

Michael Adena BSc (Hons) (Melb), PhD (ANU)—statistical consultant

Glossary

Australian Regular Army Volunteer component of the Australian Army.

dapsone Drug taken by some Vietnam veterans for either prevention or treatment of falciparum malaria.

ICD-9 Three-digit code for classification of the site of cancer according to the ninth revision of the International Classification of Diseases.

National Service Conscript component of the Australian Army.

non-veteran Serviceman who was never posted to Vietnam.

serviceman Male member of Australian Army for at least one year between 1 January 1965 and 1 March 1972.

Vietnam veteran Serviceman who was posted to Vietnam; excludes servicemen who went to Vietnam only as visitors.

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