Dapsone Exposure and Australian Vietnam Service: Mortality and Cancer Incidence.

Department of Veterans' Affairs

Australian Institute of Health and Welfare

Canberra

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The Hon Bruce Billson, MP
Minister for Veterans' Affairs
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Dear Minister

I have pleasure in submitting to you the final report of the *Dapsone Exposure and Australian Vietnam Service: Mortality and Cancer Incidence*. This study investigated the effects of Dapsone on Army veterans who served in Vietnam.

This report is the fourth and final volume to be published in this series on Vietnam veterans. The first volume was a cancer incidence study of Vietnam veterans, and the second volume extended the previous mortality study of Vietnam veterans which was published in 1997. The third report compared the mortality and cancer incidence of National Service Vietnam veterans to those who served in Australia. This fourth volume extends the 1992 Dapsone study. Taken together, these reports present a comprehensive picture of mortality and cancer incidence in Vietnam veterans.

I would like to take this opportunity to thank my predecessor, RADM Simon Harrington, who oversaw the continuation of this study.

I would like to acknowledge the important role played by members of the Vietnam Veterans Study Consultative Forum who provided invaluable assistance during the conduct of the study. A full list of the members representing key ex- Service organisations on the forum is listed in Appendix D of the report.

The report's preparation was supervised by an independent Scientific Advisory Committee, who undertook to ensure the scientific rigour of the study. The membership of the committee is listed in Appendix E of the report.

Finally, I would like to acknowledge the Australian Institute of Health and Welfare and the many Departmental staff who worked on the study.

Yours sincerely

Bill Rolfe
COMMISSIONER

9 May 2007

THE UNIVERSITY OF
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3 May 2007

Brigadier Bill Rolfe (Rtd)
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Dear Brigadier Rolfe

On behalf of my fellow members of the Scientific Advisory Committee, I would be grateful if you could convey to the Minister for Veterans' Affairs the Committee's view that the fourth and final volume of the current series of studies, *Dapsone Exposure and Australian Vietnam Service: Mortality and Cancer Incidence*, has been completed satisfactorily. The Committee is of the opinion that the study has been done with appropriate diligence and rigour, and that the methodology used is appropriate to the task at hand.

As the report notes, the study has found that Army Vietnam veterans who took the Dapsone anti-malarial prophylaxis during their service have not experienced adverse health, as measured by mortality and cancer incidence, compared to those veterans who took anti-malarial treatment without Dapsone.

Given that this second study of Vietnam veterans and Dapsone has shown no evidence of adverse health effects attributed to the drug, there would seem to be little value in any further investigations. However, as this series of studies have developed a well defined nominal roll of Vietnam veterans, it could be beneficial to undertake a further data matching analysis of mortality and cancer incidence of Vietnam veterans at some point in the future.

On behalf of the Committee I would like to extend our thanks to the Department for the opportunity to be part of this comprehensive study of Vietnam veterans. If we can be of any additional assistance to the Minister of the Commission, the Committee would be happy to provide such assistance.

Yours sincerely

Professor Peter Smith RFD
Chair
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Abbreviations

AATTV	Australian Army Training Team Vietnam
AEC	Australian Electoral Commission
AIHW	Australian Institute of Health and Welfare
ARVN	Army of the Republic of Vietnam
CARO	Central Army Records Office
CI	Confidence Interval
CMF	Civilian Military Force
CNS	Central nervous system
COD	Cause of Death
COPD	Chronic obstructive pulmonary disease
DIMIA	Department of Immigration, Migration and Indigenous Affairs
DOD	Department of Defence
DVA	Australian Government Department of Veterans' Affairs
HWE	Healthy worker effect
HIC	Health Insurance Commission
ICD	International Classification of Disease
MVA	Motor vehicle accident
NAA	National Archives of Australia
NAS	National Academy of Science
NCSCH	National Cancer Statistics Clearing House
NDI	National Death Index
NHL	Non-Hodgkin's lymphoma
NRVV	Nominal Roll of Vietnam Veterans
NYSIIS	New York State Intelligence Information System
PTSD	Post-traumatic stress disorder
RAAF	Royal Australian Air Force
RAN	Royal Australian Navy
RAR	Royal Australian Regiment
RBDM	Registrars of Birth Deaths and Marriage
RN	Royal Navy (British)
RNZN	Royal New Zealand Navy
RR	Relative Rate
SD	Standard deviation
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
VEA	*Veterans' Entitlements Act 1986*

Definitions

Australian Vietnam veteran study cohort: All male Australian members of the defence forces and the Citizen Military Forces (CMF) who were allotted or deemed allotted for service in Vietnam; all Australian members of the defence forces who landed in Vietnam including those who were seconded to the Army of the Republic of Vietnam (ARVN), the United States Air Force (USAF), the United States Navy (USN) and any other allied service; all members of the Australian Army Training Teams Vietnam (AATTV); who saw service in Vietnam during the period between 23 May 1962 and 1 July 1973.

Allotted for Duty means a person or unit of the Defence Force that was allotted for duty in an operational area. Allotment may be retrospective or prospective, and occurs via a written instrument issued by the Defence Force;

Operational Service is rendered where a person is allotted for duty and serves in an operational area. Current use of this term is not the same as normal posting procedures used in the Defence Force to move members from one unit to another.

National Service veteran: For the purposes of this study a National Service veteran is a man who was conscripted for Army service under the National Service scheme between January 1965 and December 1972 and who had service in Vietnam.

National Service non-veteran: For the purposes of this study a National Service non-veteran is a man who was conscripted for Army service under the National Service scheme between January 1965 and December 1972 and served in the Army but did not have service in Vietnam.

Executive Summary

Study initiation

A key recommendation of the 1997 *Mortality of Vietnam Veterans: The Veteran Cohort Study* was to monitor the mortality of Vietnam veterans and repeat the study after 2000. In 2002, the then Minister for Veterans' Affairs agreed that the Repatriation Commission should undertake the *Third Vietnam Veterans Mortality Study* and *Cancer Incidence in Vietnam Veterans Study*. The Commission asked the Australian Government Department of Veterans' Affairs (DVA) to conduct these studies which were undertaken with assistance from the Australian Institute of Health and Welfare (AIHW).

This report is the last of four volumes published in this third series of studies on Vietnam veterans. The other volumes are:

- *Cancer Incidence in Australian Vietnam Veterans Study 2005;*
- *The Third Australian Vietnam Veteran Mortality Study 2005;* and
- *Australian National Service Vietnam Veterans: Mortality and Cancer Incidence*.

Study objectives

The objective of this study was to analyse the effects of Dapsone, an anti-malarial drug used during the Vietnam War on the mortality and cancer incidence of Vietnam Veterans. This investigation adds to the study completed in 1992 by the Australian Institute of Health and Welfare entitled *Dapsone exposure, Vietnam service and cancer incidence*.[1]

Study design

This study was a retrospective cohort study of male Army personnel who served in Vietnam between 1962 and July 1973. The study examined all deaths identified from the end of service to 31 December 2001 and all cancers diagnosed from 1982 to 31 December 2000. Relative mortality and cancer incidence rates were calculated for Army personnel who served in Vietnam and consumed Dapsone as part of the malarial prophylaxis treatment compared to Army personnel who did not consume Dapsone during their Vietnam service. Standardised ratios comparing the two treatment groups to the Australian population were also calculated. In addition,

models were developed to assess the effect of the total cumulative Dapsone dose received during Vietnam service on mortality and cancer incidence.

Report structure

Chapter One of the report provides a brief background to Australia's involvement in the Vietnam War and an overview of the drug Dapsone and its use in malaria prevention during that conflict. **Chapter Two** details the methods used for data matching and characteristics of the Army cohort. In brief, the study roll of Army personnel was matched to a number of databases to determine vital status, the number of deaths and their causes and the number and types of cancers diagnosed. Characteristics of the cohort include age and some service details by Dapsone exposure. **Chapter Three** describes the statistical methods used to analyse the mortality and cancer incidence data. Three methods were used. A direct comparison between the dapsone exposed veterans and the non-exposed veterans was used to calculate Relative Rate (RR). An indirect comparison was used in which the mortality and cancer incidence of the exposed veterans and the non-exposed veterans was compared to the male Australian population. This is presented as Standardised Mortality or Incidence Ratios (SMR/SIR). Lastly, regression analysis was used to assess whether a dose-response relationship between total cumulative dapsone dose and mortality or cancer incidence exists. The findings are presented and discussed in **Chapter Four**.

Features of the study

This was a large study that examined the long-term health effects amongst more than forty thousand veterans who consumed specific drug courses of therapy and who were followed for more than thirty years following service. This study compares mortality and cancer incidence among those who consumed a Dapsone plus Paludrine anti-malarial prophylactic treatment during their Vietnam service to those who consumed Paludrine only prophylaxis.

The consumption of the Dapsone was strictly monitored and recorded during the Vietnam era. Through these records, total cumulative Dapsone consumption was able to be reconstructed at an individual level. Dapsone consumption information was compiled for the previous study[1] and no further refinement of this data was undertaken for the present study.

The temporal nature of Dapsone use needs to be considered. Dapsone was used from the last quarter of 1968 to 1972. Orders were given as to when Dapsone should be used and with few exceptions all who served during the time these orders were in effect (mainly during the wet seasons of these years) were given the Dapsone/Paludrine treatment. Over 80% of the Army personnel served one tour in Vietnam. The majority of those exposed to Dapsone served after 1968 and the majority of those who were not exposed to Dapsone served prior to 1969. Thus Dapsone exposure in general also correlates with the operational exposures occurring during the two time periods.

The study does not have information for many of the other exposures that would have occurred during service in Vietnam. Although this cohort was exposed to a range of stresses and toxic substances, little is known about the amount of exposure that an individual may have experienced. In addition, any adverse or beneficial health exposures an individual may have experienced following Vietnam service are also not known or quantified.

Statistical power must be considered when interpreting the results. Statistical power is the probability that a study will detect a statistically significant difference between two study groups if the groups truly differ. The size of the group being studied, the magnitude of the effect observed and the rate of occurrence of a health outcome influence statistical power. If a particular health outcome is rare then even a large study may not have sufficient power to detect a true difference, especially if this difference is small.

The role of chance and the concept of multiple comparisons must also be considered when interpreting the results. By convention statistical significance is at the 95% level, which means there is up to a one in twenty probability the result could be due to chance. Over 100 specific cancer diagnoses or causes of death are reported in this study. Thus by definition, apparently statistically significant associations could arise for up to 5 cancers or causes of death by chance alone.

Another feature of this study is that the cancer incidence could only be measured from 1982 (the first year of national cancer registration) to 2000 (the last year that all States and Territories had submitted their registry data to the National Cancer Clearing House at the time when the data matching was completed). Information on mortality from cancer was obtained from the end of Vietnam service to 2001. Any cancers diagnosed prior to 1982 and not resulting in death were not able to be captured in this study.

The healthy worker effect should also be considered. This is a phenomenon observed in occupational health studies in which those who are employed exhibit a lower mortality rate than the general population. This phenomenon is often referred to as the healthy soldier effect for occupational studies of military cohorts. This distinction denotes the fact that military populations are healthier than other employed populations, which in turn are healthier than the general population consisting of those employed and unemployed.

Findings

Indirect comparison

The indirect comparison showed that amongst Dapsone exposed Army veterans overall mortality was 6% lower than in the Australian male population, SMR = 0.94 (95% CI 0.90, 0.98). Two specific causes of death were more common in this group of veterans, alcoholic liver disease and suicide by gas, although suicide rates in total were not different from the Australian population. Mortality from infectious diseases, diabetes, nervous and circulatory system diseases was significantly less common.

Mortality was also lower amongst the Dapsone non-exposed group of Army veterans, SMR = 0.96 (95% CI 0.91, 1.00) compared to the Australian male population. No specific causes of death were significantly more common in this group compared to the Australian population whereas death from diabetes, diseases of the circulatory system and respiratory system were less common than expected.

The overall incidence of cancer was significantly higher among the Army personnel compared to the Australian population for both Dapsone exposed and non-exposed veterans, 7% and 20% higher than expected, respectively. Specifically, both groups had higher than expected incidence for Hodgkin's disease, melanoma and cancer of the head and neck region. Dapsone exposed veterans also had higher than expected incidence for eye cancer whereas those veterans not exposed to Dapsone had higher than expected incidence for cancers of the lung and connective soft tissue.

However, overall mortality due to cancer was not significantly different from the Australian population for either exposure group. Mortality for specific types of cancer was higher than expected for lung and oesophageal cancer amongst the non-exposed veterans. Dapsone exposed veterans had higher than expected mortality due to cancer of the eye and oral cavity and lower than expected mortality from connective soft tissue cancer.

Direct comparison

The all cause mortality did not differ between the two exposure groups, RR = 1.00 (95% CI 0.94, 1.07). Nor were there statistically significant differences in mortality between the groups for any of the causes of death analysed.

When direct comparison between the exposure groups was calculated, overall cancer incidence was 10% lower amongst the Dapsone exposed group compared to the non-exposed veterans, RR = 0.90 (95% CI 0.83, 0.97). All calculations were adjusted for age. There were no cancer types for which the incidence was significantly elevated amongst the Dapsone exposed veterans. The incidence of connective soft tissue cancer, lung cancer and genitourinary cancer was significantly lower amongst those Army veterans exposed to Dapsone.

Dose response

There was no significant relationship between increasing Dapsone dose and all cause mortality or cancer mortality. There was a borderline significant inverse relationship between Dapsone dose and cancer incidence. That is, with increasing total cumulative Dapsone dose there was a small decrease in the incidence of cancer.

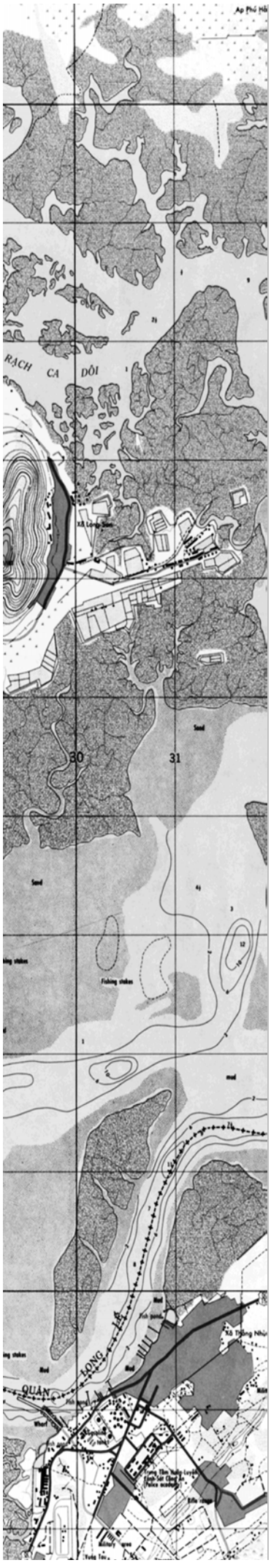
Summary and conclusion

In this study assessing long term health effects from exposure to Dapsone during Vietnam service, mortality was assessed for over 30 years since exposure and cancer incidence follow-up was for 19 years. There was no statistically significant difference in non-cancer mortality between those who consumed Dapsone and those who did not. There was a modest but statistically significant lower than expected overall cancer incidence, and for some specific cancers, a lower than expected mortality for the Dapsone exposed group.

This study concludes that those who took the anti-malarial Dapsone/Paludrine prophylaxis have not experienced adverse health, as measured by mortality and cancer incidence, compared to those veterans who took anti-malarial treatment without Dapsone.

References

1 AIHW. Dapsone exposure, Vietnam service and cancer incidence. Canberra: Australian Institute of Health and Welfare, 1992:149.



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Introduction

Chapter 1 Introduction

1.1 Background

The health and wellbeing of Vietnam veterans and their families has been an important issue for the Department of Veterans' Affairs which has conducted three extensive health studies between 1983 and 2006 on the military personnel deployed to Vietnam. The aim of these studies has been to increase the understanding of the impact of military service and to further support Vietnam veterans through targeted programs of care, compensation, rehabilitation and commemoration.

The impact of possible chemical exposure has been a key issue in the study of the health of Vietnam veterans. The initial focus was on herbicides such as Agent Orange. This focus was extended by the Royal Commission established in 1983 investigating the Use and Effects of Chemical Agents on Australian Personnel in Vietnam (the Evatt Royal Commission)[1].

Dapsone was one of the drugs investigated by the Evatt Royal Commission. During the Vietnam conflict, Australian forces used Dapsone for the treatment and prevention of falciparum malaria. The Evatt Royal Commission recommended the study of the carcinogenicity of Dapsone. This recommendation was supported by the assessment and recommendation report to the Evatt Royal Commission (the Hogg report) in 1987 that urged the immediate establishment of an epidemiological study into the effects of Dapsone on deployed military personnel[2].

In 1992, the Australian Institute of Health and Welfare published the results of the study *Dapsone Exposure, Vietnam Service and Cancer Incidence* commissioned by the Department of Veterans' Affairs[3]. This study found no evidence that Dapsone exposure was associated with an increase in total cancer incidence.

The purpose of the present study is to examine the rates of mortality and cancer incidence among veterans who were given Dapsone while serving in Vietnam. It repeats some of the analysis done by AIHW previously. This report extends the previous report with an additional 11 years of follow-up and therefore potentially captures details of types of cancer that occur in an older population.

This chapter gives the history of the use of Dapsone by the Australian Army in the Vietnam conflict. A general description of Australia's involvement in Vietnam is also given and this is followed by the history of the use of Dapsone by those forces. The aim of this chapter is to provide some background information for those unfamiliar with Australia's involvement in Vietnam, and to allow the reader to understand who received Dapsone and why. A more detailed history of the Vietnam conflict is provided in *Cancer Incidence in Australian Vietnam Veterans Study 2005*[4].

1.2 History of Australian involvement in Vietnam

1.2.1 Location

Vietnam is located on the eastern rim of the Indo-Chinese peninsula, stretching from the Chinese border to its southern tip. Following the French defeat at Dien Bien Phu, the Geneva Conference of 1954 was established to settle the political future of Indo-China and Korea. One of the outcomes was the establishment of the Republic of Vietnam. The Geneva Accords of July 1954 fixed a provisional Demarcation Line at 17 degrees north. The region south of this line formed the Republic of Vietnam, while the northern region became the Democratic Republic of Vietnam. Despite their official titles, the countries became more commonly known as 'South' and 'North' Vietnam respectively.

1.2.2 Geography and climate

Most of the country, north and south, consists of a rugged highland region, the Annamite Chain, a jungle covered mountain range interspersed in its southern portion with fertile plateaux. These plateaux slope gradually to the valley of the Mekong River in the west, but rise sharply in the east, leaving a narrow coastal plain cut by spurs of the mountain chain. This region extends down from the northern borders to just north of Ho Chi Minh City (formerly known as Saigon).

The second important region in southern Vietnam is the Mekong Delta, a low level plain covering some 68,000 square kilometres which at no point is more than three metres above sea-level. The Delta is crisscrossed with streams, ditches and canals, which both irrigate the paddy fields and drain the seasonal floodwaters.

The third region is the Central Lowlands which extend along the coast from Phuoc Tuy province, east of Ho Chi Minh City, north to the Demarcation Line. In general, this region is fertile and extensively cultivated, although the immediate 160 kilometres north from Vung Tau receives less rainfall than any other part of Vietnam and is somewhat infertile.

Rainfall and temperature in South Vietnam is determined by the seasonal alternation of the monsoons. During the summer monsoon, moist air flows inland from the sea, depositing heavy rainfall in its passage. The monsoon normally arrives in Vietnam by June each year. During the winter monsoon, cool air flows outward towards the sea, producing the country's dry season. In most parts of Vietnam the season is 'dry' only in comparison with the southwest summer monsoon. The winter monsoon normally reaches the Central Lowlands by early October and the Mekong Delta area by November and continues to blow until April.

Except in a few mountainous areas, high temperatures prevail throughout the year and the humidity is generally high. The annual rainfall is heavy in all regions and torrential in many. In addition, typhoons off the South China Sea strike somewhere in Vietnam on average about ten times per year, usually between June and November.

1.2.3 Chronological overview

The following chronological overview relates specifically to Australian Defence Force involvement in the Vietnam conflict. The period of coverage under the *Veterans' Entitlement Act 1986* (*VEA*) for the Vietnam War has been established as 31 July 1962 to 29 April 1975. This section briefly outlines events that occurred during this period.

The departure from Australia in July 1962 of the first contingent of the Australian Army Training Team Vietnam (AATTV) began the Australian Army's commitment to the Vietnam War.

In 1965, the Australian involvement in Vietnam expanded. The Australian Army dispatched the 1st Battalion, The Royal Australian Regiment, and supporting units to Bien Hoa in South Vietnam. HMAS *Sydney* transported the bulk of the ground forces, and this voyage in May 1965 was the first of 25 voyages into the Vietnam War operational area. Other Navy vessels escorted the troop carrier on these occasions.

The period 1966 to 1967 has been described as a period of consolidation.[5, p217] Australian involvement was increased with the establishment of the 1st Australian Task Force that would contain two battalions, a Special Air Service squadron, and combat and logistical support units based at Nui Dat and the 1st Australian Logistic Support Group at Vung Tau.

The next phase of the war occurred from 1968 to mid 1969, when the task force was expanded with the addition of a third battalion. This period represents the peak strength of Australia's involvement.[5, p217-218]

The task force reverted to a two-battalion structure in November 1970. This marked the beginning of a gradual withdrawal with the remaining two battalions returning to Australian in 1971 and the last of the support units and AATTV personnel departing in 1972. The last Australian troops, the Australian Embassy Guard Platoon, Saigon, were withdrawn in June 1973.

The aim of this section has been to provide some background information to readers unfamiliar with Australia's involvement in the Vietnam War. Australian involvement was formally announced in May 1962. There was a gradual build up of numbers, peaking in 1968, followed by a gradual decline until the bulk of the troops had departed by the end of 1972. The last of the Australian troops left in June 1973.

1.3 History of Dapsone use

To understand the reasons behind the use of Dapsone in Vietnam, and the particular manner in which the drug was used, it is necessary to understand some of the history of malaria and the Australian Defence Force.

1.3.1 Malaria and its control

Malaria was a considerable problem to the Australian military in World War One.[6, p10] During World War Two, malaria control moved from being the responsibility of the medical staff to being a command responsibility. In particular, it was a command responsibility to ensure that appropriate malaria prophylaxis was taken everyday. This responsibility fell to the commanding officer of each unit.

By use of appropriate prophylaxis and discipline, the Australian Army was able to reduce the incidence of malaria in the South West Pacific to less than 1 per 1,000, 'the lowest figure in military history'.[6, p244]

This culture continued in the Australian Army during the time of the Vietnam War. Malaria control was viewed very seriously. In the early to mid 1960s, the standard malaria prophylaxis with the Army was Paludrine. In December 1966, forty-six cases of falciparum malaria occurred, mainly in 6 Battalion, Royal Australian Regiment (6RAR). There had been a breakdown in mosquito control measures in the area of operation and once the use of repellents and nets were given stricter observance the incidence of disease decreased.

However following another severe outbreak in 1968, there was emerging evidence that the malaria strains in the area that the Australian Army were serving (Phuoc Tuy Province) were resistant to Paludrine and additional prophylactic treatment regiments would be needed. Dapsone was considered a prime candidate for the additional drug regimen.

1.3.2 Pharmacology and uses of Dapsone

Dapsone is a sulfone drug (4,4-sulfonylbisbenzenamine or 4,4-diaminodiphenyl sulfone) that acts by inhibiting folate synthesis. Folate synthesis is an essential metabolic step in unicellular organisms, such as the malaria parasite, that cannot use preformed folates. As well as an anti-infective activity due to folate synthesis inhibition, Dapsone also has an anti-inflammatory action.

At the time of the Vietnam conflict, Dapsone had been in widespread clinical use for many years in the treatment of leprosy. In the early 1960s, promising results against chloroquine-resistant *P. falciparum* using Dapsone as a prophylactic agent were reported in field trials in Asia and Africa.[7-11]

1.3.3 Dapsone use by Defence Forces in Vietnam

In 1966, the US Army began field trials in Vietnam using a triple-drug regimen consisting of quinine, pyrimethamine and Dapsone. In September 1967, its use was recommended by the Senior Medical Officer in an instruction advising medical officers to treat falciparum malaria with a combination of quinine, pyrimethamine and Dapsone. Quinine dihydrochloide (1.8g per day) was given for three days and Dapsone (25mg per day) for 30 days.[3, p119]

Australians used a different drug combination to the Americans for anti-malarial prophylaxis. The basic treatment was 200mg Paludrine (Proguanil) per day administered as one 100 mg tablet in the morning and one in the evening. Debate continued within the Australian Army medical hierarchy whether the addition of Dapsone was necessary, and eventually it was agreed to undertake their own field trial of Dapsone in October 1968.[12, p154] The trial was not a clinical trial of Dapsone. Dapsone was a well established drug that had been used for many years, and had been shown to have anti-malarial properties. The point of the trial was to ascertain if the drug would work in the particular province (Phuoc Tuy) of Vietnam that Australians were operating in, and against the particular malarial parasites that were present in Phuoc Tuy province.

The trial supplemented the Paludrine regimen with 25mg Dapsone given with the morning Paludrine tablet. The trial proved successful.[13] Rates of malaria infection dropped close to zero. Dapsone was added to the daily anti-malarial treatment in November 1968. During the dry season in the Phuoc Tuy province Dapsone supplementation was discontinued as the risk of malaria was much lower and it was felt Paludrine only treatment was sufficient.

As outlined above, malaria prophylaxis was a very high priority in the Australian Army and excellent records were kept of the changes in malaria prophylactic regimens. The exact start and end dates of Dapsone supplementation to the treatment regimens was recorded. In addition, records are kept of who within the task force was given Dapsone.

Considerable effort was placed on ensuring that each person did receive their antimalarial prophylaxis. For example, in each infantry platoon, a non-commissioned officer would check that the tablets had been consumed. Thus the available documents provide an accurate retrospective exposure record of the consumption of this drug.

In this study cohort, a total of 23,262 members of the Australian Army who served in Vietnam were exposed to Dapsone, while a total of 16,945 Army veterans who served in Vietnam while Dapsone prophylaxis was not in use received no Dapsone. Thus this is a large population exposed to Dapsone, with a large and appropriately matched control group.

1.3.4 Adverse reactions to Dapsone

During the use of Dapsone in Vietnam, several cases of adverse reactions attributed to the drug were reported. In its use for leprosy, some very rare blood disease conditions such as aplastic or haemolytic anaemia and mononucleosis syndrome had been reported but these occurred at doses much higher than were being used in anti-malarial prophylaxis.[14] The first reported case of agranulocytosis (a decrease in the number of a type of white blood cell that is important in fighting infection) attributed to Dapsone was in 1958 in a patient treated with 100mg daily for dermatitis herpetiformis (a skin disease). The agranulocytosis was found to be reversible with the cessation of the drug.[15]

In 1969, the Americans reported 16 cases of agranulocytosis in soldiers receiving daily Dapsone prophylaxis in conjunction with chloroquine-primaquine tablets. Eight

of these soldiers died from overwhelming sepsis.[16] Three cases of agranulocytosis occurring amongst Australian troops between June 1969 and February 1970 and presenting as septicaemia were reported in the medical literature. All recovered with the withdrawal of Dapsone and antibiotic treatment.[17 18]

Subsequent research on the toxicity of Dapsone has shown that the risk of agranulocytosis in the treatment of leprosy is virtually zero whereas when taken in combination with antimalarial treatment, the risk at one in 10 – 20,000. The greatest toxicity risk for agranulocytosis occurs in patients taking Dapsone for the treatment of dermatitis herpetiformis whose risk is 25-35 times higher compared with patients without this condition.[19]

The mechanism by which Dapsone causes agranulocytosis is unknown. Several theories have been proposed. The hydroxylamine metabolic by-product could cause bone marrow toxicity but reversibility of the adverse affects following drug withdrawal suggests interference with specific mechanisms of cell control rather than basic toxicity.[19]

Other conditions associated with Dapsone have been investigated. Briton *et al* [20] assessed cancer mortality among patients with leprosy. Although they observed a slight elevation in overall cancer mortality and increase of cancer deaths for cancer of the oral cavity, bladder and kidney, no clear trends with Dapsone dose were seen. Hironaka[21] presented a case study of 12 leprosy patients with urinary tract carcinoma who had been taking high dose Dapsone and analgesics for many years. Although Dapsone has been implicated as a carcinogen in laboratory animals,[22] no clear association has been found in humans. Conversely the anti-infective and anti-inflammatory properties of malarial drugs have been suggested as playing a role in lower rates of Crohn's disease (an inflammatory intestinal disease) amongst Vietnam veterans.[23 24]

1.4 Summary

This chapter has provided some background information about Australia's involvement in the Vietnam War. Australian involvement was formally announced in May 1962. There was a gradual build up of numbers, peaking in 1968, followed by a gradual decline until the bulk of the troops had departed by the end of 1972. The last of the Australian troops left in June 1973. Air Force personnel participated in humanitarian flights and the final evacuation of Australian and Vietnamese civilians in 1975.

Malaria was endemic in Vietnam and the Australian Army went to great lengths to ensure the best possible prophylaxis was followed. In augmenting the drug regimen with Dapsone some adverse drug reactions were experienced, most notably among American troops. This lead to concerns that ingestion of Dapsone could have some long term adverse health effects for Australian Vietnam veterans.

This report is the second investigation into the effects of Dapsone amongst Vietnam veterans. It details the mortality and cancer incidence over more than 30 years since Dapsone ingestion and correlates these outcomes with total Dapsone dose.

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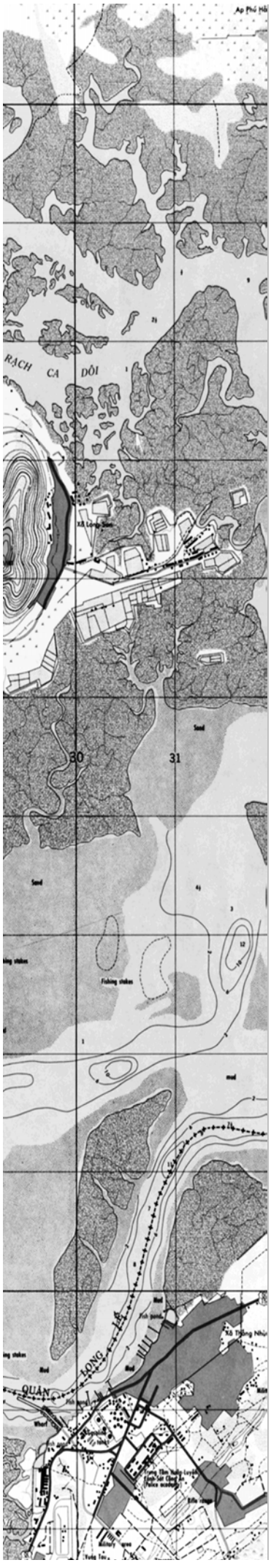

2

Record Linkage Methods and Cohort Characteristics

Chapter 2 Record Linkage Methods and Cohort Characteristics

In the conduct of a mortality and cancer incidence study such as this one, five tasks are needed: compiling the study roll, determining the vital status (those who are alive and those who have died) of as many participants as possible, investigating the cancer incidence and cause of death of all participants and determining the amount of Dapsone each participant received.

This chapter will discuss data sources and linkage methods used for determining the vital status, cause of death, cancer incidence and Dapsone exposure, and describe the characteristics of the study cohort.

The following chapter will describe the methods for statistical analysis of the information obtained from the data linkage. The results of the investigations into cause of death and cancer incidence among Dapsone exposed and nonexposed veterans are presented in Chapter 4.

2.1 Study roll

The study roll for Army Vietnam veterans was compiled from data used in previous studies.[1, 2, 3] The present study roll includes a total of 40,207 Army Vietnam veterans including 16,945 veterans who were not exposed to Dapsone and 23,262 veterans who were exposed. In this study there were 67 fewer veterans than in the previous Dapsone study.[3] These veterans had very poor name and/or date of birth information, making data matching with mortality and cancer incidence databases too problematic. A further 877 Army veterans were excluded because their exposure to Dapsone was unknown.

2.1.1 Quality of the study roll

Missing or incomplete data items reduced the chances of matching the Study Roll records with the National Death Index (NDI) and other databases. Failure to match with the NDI may falsely indicate that the veteran is alive or, conversely, an incorrect match may give the false impression that the veteran is dead.

Table 2-1 shows that missing and incomplete data were a minor concern for the Study Roll. All first names were recorded. Most second names were recorded in full but for 10 per cent of cases this data item was missing although the percentage of missing

second names compared with those who had no second names to record is unknown. In all, the quality of the study roll was considered good for matching purposes.

Table 2-1: Frequencies of incomplete and missing data on the study roll

Veterans	Total on Study roll	Initial only for first name	No second name	Missing date of birth
Exposed	23,262	0	2,329 (10.0%)	0
Non-exposed	16,945	0	1,665 (9.8%)	0

2.2 Vital status and sources of data

Determining vital status was carried out in part using computerised matching of veterans' records with information in large national databases, such as the NDI, the electoral roll, Veterans' Affairs databases and other registers. Primarily, the study roll was matched against the DVA databases, as this contained information about both living and deceased veterans.

Registration of deaths in Australia is compulsory and is the responsibility of the State and Territory Registrars of Births, Deaths and Marriages (RBDM). All veterans who died in Australia should be registered with the RBDM but the quality of information (eg. the lack of computerised records in the early years, changing names of veterans, incomplete date of birth) does not always allow for precise confirmation of death. Therefore, multiple sources of information are needed to maximise coverage regarding the vital status of each veteran.

Tables 2-2 and 2-3 summarise the different sources of vital status data used in this study. Table 2-2 shows the period covered for death information and Table 2-3 shows the sources used to determine events indicating whether a person is alive and on what date.

Table 2-2: Summary of sources of vital status — dead

Date of death	Source
On active service in Vietnam	Department of Defence
In service, post-Vietnam	Department of Defence
Between 1963 and 1980	Australian State and Territory Registries of Births, Deaths and Marriages
After 1980	National Death Index
Since Vietnam service	Veterans' Affairs Client Data Base
After 1999	Health Insurance Commission Medicare database

Table 2-3: Summary of sources of vital status — alive

Action indicating the subject is alive	Assumed alive on the date of	Source
Receiving a Veterans' Affairs pension	their last payment	Veterans' Affairs Client Data Base
Made a Medicare claim	their last claim	Health Insurance Commission Medicare database
Contracting cancer	date of registration	National Cancer Statistics Clearing House
Enrolled to vote	extraction of the roll	Electoral Commission rolls
Departed or arrived in Australia	departure/arrival	Department of Immigration, Multicultural and Indigenous Affairs

2.2.1 Department of Veterans' Affairs client data base

The Department of Veterans' Affairs (DVA) maintains its Client Data Base, which provides a central source of information about servicemen who have registered for any benefit provided by DVA. The Client Data Base record contains information on surname, given name, other initials, date of birth, date of death and some information on military service. It also includes reliable information about the military service on which a claim was determined but other service is recorded inconsistently.

Data quality

Because the personal data, names and pension details on the Client Data Base are regularly used and referred to in correspondence with veterans, these details are believed to be current and accurate. However, details of military service are less

reliable and often incomplete as this database was originally intended for payment management, not military service tracking. Such details were obtained from the Army service records office. It should be noted that pension related details were not accessed for the purposes of this study.

The Department of Veterans' Affairs has no information on the vital status of veterans who have not registered for any benefit provided by the Department.

2.2.2 The National Death Index and the National Mortality Database

The NDI is a database located at the Australian Institute of Health and Welfare. It contains identified records of all deaths in Australia registered after 1980. In excess of 2.5 million records are contained in the database. The Registrars of Births, Deaths and Marriages in each Australian State and Territory supply the information for this database. As registration of death is a legal requirement, the database is virtually complete for deaths in Australia. The data available for matching in the NDI covered the period from 1980 to 2003 for all States and Territories, and some 2004 data. For identification of deaths prior to 1980 the individual registers were searched.

Although the NDI identifies each person who dies, it does not record the cause of death in a standardised manner. This standardised cause of death information is available in the National Mortality Database, also located at the Australian Institute of Health and Welfare.

The National Mortality Database contains de-identified information on each person's *underlying* cause of death, coded using the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD). [4] An NDI record can be linked to its corresponding record in the National Mortality Database, via a common registration number to obtain cause of death information, under Ethics Committee approval.

Data quality

The data quality of the NDI varies considerably between States and Territories and over time within each State and Territory. Data quality and completeness affected the matching strategy and the results of data matching for this study. The NDI does not have full dates of birth for:

- Queensland for the period 1980–1996 inclusive;
- New South Wales for the period 1980–1992 inclusive; and
- Victoria for the period 1980–1989, inclusive.

In these situations, a year of birth is derived from the date of death and the age at death.

Within the NDI there are inconsistencies in the way names are recorded. Data standardising procedures were therefore applied to the NDI in order to reduce inconsistencies. Examples are provided in Section 2.3.1.

While personal information is usually provided about the deceased by the next of kin, an acquaintance or official of the institution where the death occurred, information on the cause of death is variously supplied by family doctors, hospital residents,

pathologists, or coronial staff. This large range of information sources contributes to the variable quality of cause of death data and a degree of inaccuracy overall. This situation also applies to the data held by the State and Territory Registries of Births, Deaths and Marriages.

2.2.3 The electoral roll

The electoral roll was supplied by the Australian Electoral Commission (AEC). It was extracted as at August 2003 for all States and Territories. The roll contains over six million records of male Australians. Most living Australian citizens over the age of 18 will appear on the roll.

Enrolment on the electoral roll is compulsory for all Australian citizens who have attained 18 years of age. However, some citizens, such as a person of unsound mind or a person serving a sentence of 5 years or longer for an offence against the law of the Commonwealth or of a State or Territory, are not included in the roll. [5]

Data quality

There are known to be multiple registrations on the electoral roll of persons across States and Territories. This occurs if a person moved between States and Territories of Australia and their previous entry had not been removed from the electoral roll.

Recorded names may not necessarily be legal names and there are persons who have died but their deaths are not known to the AEC.

2.2.4 Medicare Australia

Medicare Australia (formerly known as the Health Insurance Commission) has administered Medicare, Australia's national health insurance scheme, since its introduction on 1 February 1984. The scheme provides free access to hospital services for all Australian residents and subsidises the costs of a range of other medical services. [6]

Two databases are maintained by Medicare Australia: one of persons enrolled in the Medicare scheme; and one for claims processing. As at 30 June 2003 there were 10,282,188 males enrolled with Medicare, which is 104% of the estimated resident male population of Australia. [6] The excess is because those enrolled in Medicare include some persons who are not Australian residents (e.g. long-term visitors, greater than 6 months, and eligible short-term visitors).

Data quality

When notified, Medicare Australia records the date of death and the date of departure from Australia of persons on its database, but more commonly the record just becomes inactive.

Medicare Australia only keeps records of claims made in the last five years. Older claims are deleted from the database. As only recent and active records are kept, matching with Medicare data can reliably ascertain that a person in this age group is

alive provided they have made a claim in the last five years. Conversely, as information on deaths and departures from Australia is only gathered if the information is proffered, the finding of this type of information is less reliable than other sources.

2.2.5 National Cancer Statistics Clearing House

Cancer is a notifiable disease in all States and Territories. The data are collected by cancer registries and include clinical and demographic information about people with newly diagnosed cancer. This information is obtained from hospitals, pathologists, radiation oncologists, cancer treatment centres, nursing homes and the RBDMs.

The AIHW is responsible for the national collection of cancer incidence statistics through the National Cancer Statistics Clearing House (NCSCH). The NCSCH receives data from individual State and Territory cancer registries on cancer diagnosed in residents of Australia. National statistics are available for all years from 1982 to 2000. The database is updated annually.

Data quality

The NCSCH was used as an additional check to determine the vital status of the study participants. The important data items for this purpose are names, date of birth and date of diagnosis. Surname was available for all records in the NCSCH, first name for 99.9% of the records, second name for 52%, date of birth for 99.9% and date of diagnosis for 99.9%.

2.2.6 Other data sources

The directorate of Honours and Awards in the Department of Defence maintains a database of those servicemen and women who have applied for a service medal or award. The database contains service number, surname, given names, date of birth and some dates of death for service personnel who have applied for a service medal or award or in the case of a deceased serviceman, their family members have applied for a posthumous award. The Department of Defence also administers the Central Army Records Office (CARO), which maintains the personnel service records for all Army personnel.

The Department of Immigration, Multicultural and Indigenous Affairs (DIMIA) maintain an electronic Movement Reconstruction database of all persons arriving in and leaving Australia from 1980 to the present. DIMIA were able to provide information on date of death, if known, and date of last movement, that is the last known date alive.

2.3 Record linkage between the study roll and selected data sources

The study incorporated a wide range of data matching techniques to accommodate the various data holdings. Some matching involved manual searches of paper or microfiche records. Electronic matching was used whenever possible, using both ‘deterministic’ and ‘probabilistic’ techniques. ‘Deterministic matching’ involves the use of registration

numbers or a specific combination of data elements to match two records. 'Probabilistic matching' involves linking records that are believed to relate to the same individual. The process is described as 'probabilistic' because for each linkage there is an associated degree of certainty that the records are correctly paired, the same as if the process were carried out manually. [7]

The software package[8] used for 'probabilistic matching' calculates the likelihood of a correct linkage, i.e. that the records represent the same individual. The higher the likelihood of a correct linkage, the higher the weight accorded the match. Below a designated cut-off value, the weight of the match is too low to be considered a correct linkage and the records linked are considered to be different individuals.

2.3.1 Matching by DVA

DVA was responsible for matching the Study Roll of Army veterans of the Vietnam War with information indicative of vital status of servicemen available within DVA and with the electoral roll.

Matching with the DVA Client Data Base

For the matches with the DVA databases, only an exact match of surname, forenames and day, month and year of birth or an exact match of surname and service number were permitted. These criteria were more stringent than those for matching with the NDI and the electoral roll, where a probabilistic approach was taken, and were thus given precedence.

The Study Roll was matched with the Client Data Base, which contains records of servicemen receiving payment of a pension or allowance from the DVA and records of client deaths. If there was a match, the veteran was recorded as being alive at the date of last payment or if a death was recorded, the veterans' date of death, was entered onto the Study Roll.

Matching with the electoral roll

The Study Roll and the electoral roll were standardised to improve the likelihood of successfully matching veteran's details. This meant that apostrophes, hyphens and other miscellaneous characters were removed from surnames, and dates of birth and dates of death, where available, were presented within valid ranges. Soundex and New York State Intelligence Information System (NYSIIS) coded versions of the standardised surnames were created which allows for variations in spelling of names (e.g. Smith, Smithe, Smythe). Standard versions of first names were added to all files (e.g. Robert for Bob and Rob). If there was a match, the veteran was recorded as being alive.

2.3.2 Matching by AIHW

The Australian Institute of Health and Welfare was responsible for:

- identification of potential duplicate records in the Study Roll;
- matching with the NDI;
- matching with the NCSCH for all States and Territories except Victoria;
- supervising the matching with the Victorian cancer registry; and
- supervising the matching with the State and Territory RBDMs.

Identification of potential duplicate records and matching with the NDI and the NCSCH were undertaken using 'probabilistic' matching techniques.

Matching with the NDI and NCSCH and Victorian cancer registry

The Study Roll, the NDI and the NCSCH files were standardised, as above, to improve the likelihood of successfully matching veterans' details.

The identification of the cause of death (COD) amongst veterans was determined by matching the Study Roll against the deaths registrations at the RBDM. This was achieved by matching with the NDI, which holds all the RBDM deaths from 1980, or by directly searching at the individual registries for deaths prior to 1980.

As well as vital status information, matching to the NCSCH and the Victorian cancer registry provided information on cancer diagnosis and date of diagnosis. This identified all cases of cancer diagnosed between 1982 and 2000, apart from non-melanocytic skin cancers, which are not routinely reported to the cancer registries. An individual may experience more than one type of cancer, and each of those was recorded on the NCSCH, and was included in the analysis.

The matching with the Victorian cases of the NCSCH could not be done by the AIHW for privacy reasons, but the matching strategy used by the Victorian cancer registry was similar to that used for matching the other NCSCH cases.

Matching with the State and Territory BDM

It was considered likely that a significant proportion of the 'unknown' group (i.e. those veterans who were not found on any of the above mentioned databases) may have been missed because they had died during the period from 1966, when the first veterans returned from Vietnam to 1980, immediately prior to the establishment of the NDI. In order to capture these deaths, the 'unknown' group was matched against State and Territory death records for the period. Records from all States and Territories were accessed, except for the Northern Territory where the possible returns were deemed too low. NSW, Victorian and Tasmanian records were matched in part by electronic means. All other records were matched manually. In some circumstances this meant searching nearly 20 yearbooks for approximately 4,500 names.

The data quality of the Registries' mortality information varies between States and Territories and over time within each State and Territory. Varying storage and indexing methods also influence the results of the data matching carried out for this study. Personnel carrying out the matching were provided with guidelines and encouraged to include doubtful matches, which could then be further examined by the AIHW to maximise consistency across States and Territories. The relatively conservative matching criteria adopted for the NDI and NCSCH matching were then applied to the State and Territory RBDMs.

2.3.3 Matching by Medicare Australia

Medicare Australia was responsible for the following tasks:

- matching of veterans whose vital status was previously unknown (i.e. there had been no match with the DVA Client Data Base, NDI or electoral roll) with their Medicare enrolment database record; and then
- retrieving the date of the most recent claim from the claim database.

For matching with Medicare enrolment database, an exact match of surname, given names and the day, month and year of birth was used. Each matched record was linked to the claim database to determine the date on which the subject last received a medical service. That is, the date they were last known alive, unless there was a more recent date of death or departure from Australia was recorded.

2.3.4 Other matching

Those study participants not identified through other sources were matched against databases from DIMIA and the Directorate of Honours and Awards. For matching with the Movement Reconstruction database maintained by DIMIA, an exact match of surname, given names and date of birth was used. A match indicated the last movement date in or out of Australia and thus the last known date alive.

The database maintained by the Directorate of Honours and Awards includes the service number of the veterans as a unique identifier. This database was useful in identifying changes of names since Vietnam service and alternative dates of birth for those study participants not identified on other databases.

2.4 Determination of cumulative Dapsone consumption

For the original Dapsone study, 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 amount of Dapsone taken prophylactically by each Vietnam veteran was inferred from these data and from information from the postings file.[3] In some cases, a veterans' total cumulative dose was expressed as a range: the study classified those veterans at the mid point of their ranges. The assignment of Dapsone consumption has been taken from the previous

study and no refinement of the exposure data was undertaken for the present study. Table 2-4 shows the distribution of the cumulative Dapsone exposure.

Table 2-4: Vietnam Army veterans and their total cumulative Dapsone exposure (g) based on daily dose of 25mg

Total dosage	0	0.01–1.99g (up to 80 doses)	2–3.99g (80-159 doses)	4.00–5.99g (160-239 doses)	6+g (240+ doses)
Veterans	16,945	5,592	5,362	6,681	5,627
Per cent	42.1	13.9	13.3	16.6	14.0

2.5 Results of matching process

The summary results of matching are presented in Table 2-5. It shows that vital status was determined for 97.5% of the cohort and 2.5% were lost to follow-up. Of the 2.5% lost to follow-up, 1.5% were partially unknown, that is, they were known to be alive until a specific time point during the study period but were lost to follow-up by the end of the study on 31 December 2001. In this study, the veterans who were exposed and not exposed to Dapsone had a similar proportion of subjects lost to follow-up, 2.6% and 2.3%, respectively.

Table 2-5: Summary of vital status from the matching process

Army veterans	Alive		Dead		Unknown		Total
Exposed	20,665	88.8%	1,988	8.5%	609	2.6%	23,262
Non-exposed	14,516	85.7%	2,037	12.0%	392	2.3%	16,945
All Army veterans*	35,181	87.5%	4,025	10.0%	1,001	2.5%	40,207

*The Dapsone exposure of 877 Army veterans was unknown and these veterans were excluded from the analysis

2.6 Summary and discussion on data matching

The objective of the matching was to determine the vital status and record the mortality and cancer incidence information of as many members of the cohort as possible. To achieve this, the study used a variety of data sources. Some of these are specific to Vietnam War veterans while others are general to the whole Australian population.

The cohort was first matched with data held by the Department of Veterans' Affairs. This included data on deaths obtained from the Department of Defence and data on deaths and those alive, obtained from the Veterans' Affairs Client Data Base. These

sources were not mutually exclusive. Some deaths that occurred before 1980 (including deaths during service) were identified from these sources.

All members of the cohort were then matched with the NDI to identify deaths in the period 1980–2003 not previously known to DVA. The whole cohort was concurrently matched with the electoral roll to identify those who were alive. The statutory requirements that underpin compulsory registration on the electoral roll and the NDI are indicative of each database's completeness for Australia as a whole.

The names of those veterans who failed to match any of the above-mentioned sources were then matched with the Medicare database, immigration records and pre 1980 deaths held at the State & Territory RBDMs.

Overall, 87.5 % of the cohort was determined to be alive and 10.0 % were accepted as having died. This left 2.5 % of the veteran cohort for whom vital status remained unknown at the end of the study period.

The 1,001 veterans with an unknown vital status were not in contact with DVA after 31 December 2001, and were not found on the Australian Electoral Roll, the NDI or other databases accessed. For these veterans, it was therefore not possible to determine whether they were still alive and residing in Australia on 31 December 2001 or if they had died or moved permanently overseas.

This group is referred to as the 'veterans whose vital status is unknown' or 'veterans lost to follow-up' for the purposes of this study. However, some of these unknowns were found on databases with entries prior to 31 December 2001, indicating that they were alive for at least some time of the study period.

2.6.1 Potential reasons for unknown status

The group of 1,001 veterans lost to follow-up will possibly contain subjects who died, most likely before 1 January 1980, the first date for data for the NDI, and who were not captured by any of the DVA registers or the manual searches by the various RBDMs. Another proportion of the lost to follow-up group may have emigrated from Australia since the end of the Vietnam War.

Other reasons for lost to follow-up include:

- change of name since the end of the Vietnam War;
- living in certain types of institutional care;
- living in Australia but have never been or are no longer on the electoral roll; and
- typographical or other errors in data records in the Study Roll and/or databases used as sources of vital status information.

In summary, from a total cohort of 40,207 Army veterans followed up after approximately 30 years, the vital status of 2.5 % remained unknown.

2.7 Cohort characteristics

The following section provides some age and service characteristics of the study cohort. Cohort characteristics were calculated using SPSS[9] statistical software.

As detailed in Tables 2-4 and 2-5, there were 40,207 Army personnel who served in Vietnam and whose Dapsone exposure is known. Of these 23,262 received some Dapsone as part of their anti-malarial treatment and 16,945 veterans did not receive Dapsone. The amount of total Dapsone consumed during Vietnam service was generally evenly distributed across those who were exposed with between 23% – 29% of the exposed population in each of the four categories of cumulative Dapsone exposure.

2.7.1 Age of Army personnel by exposure

The mean year of birth of Army personnel who did not receive Dapsone was 1942 (range 1907 – 1954) whereas the mean year of birth for those exposed to Dapsone was 1945 (range 1911 – 1952), in part reflecting the time of use of Dapsone during the Vietnam conflict (Figure 2-1). The mean age of those determined to be alive at the end of the study period, 2001, was 56 years (range 47 – 90); 58 years for non-exposed veterans and 55 years for those exposed.

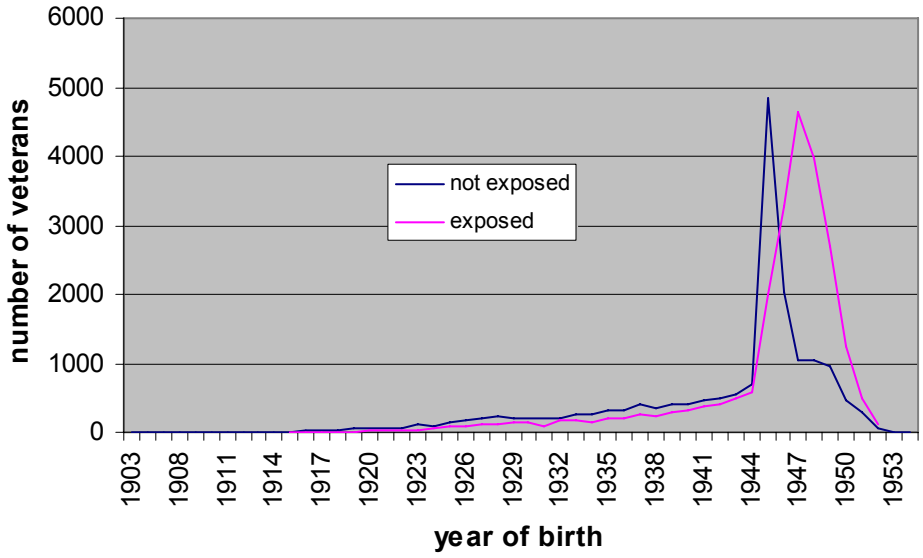

Figure 2-1: Year of birth for Dapsone exposed and non-exposed veterans

2.7.2 Characteristics of Vietnam service by exposure

Table 2-6 summarises the characteristics of service for the two exposure groups. The differences between the groups for the service characteristics available were modest but statistically significant. Those Army personnel who were exposed to Dapsone tended to be younger at the time of their first service, had served in more units, undergone more tours of service and had longer service in Vietnam.

Table 2-6 Service characteristics for Dapsone exposed and non-exposed Army personnel

Characteristic	Dapsone Exposed (N = 23,262)	Dapsone non-exposed (N = 16,945)	Total Cohort (N = 40,207)
Age at 1st service (years)			
Mean ± SD	23 ± 5.0	25 ± 6.4	24 ± 5.7
Median	21	22	21
Range	(17 – 58)	(17 – 59)	(17 – 59)
90th percentile	30	35	32
Number of units served			
Mean ± SD	1.4 ± 0.7	1.2 ± 0.5	1.3 ± 0.6
Range	(1 - 6)	(1 – 5)	(1 – 6)
Number of Tours			
Mean ± SD	1.5 ± 0.9	1.3 ± 0.6	1.4 ± 0.8
Range	(1 – 14)	(1 – 17)	(1 – 17)
Days in Vietnam			
Mean ± SD	337 ± 133	278 ± 134	316 ± 1.33
Range	(2 – 1,571)	(1 – 2,149)	(1 – 2,149)
90th percentile	418	380	390

Table 2-7 shows a selection of units by exposure group for which approximately 2% or more of the exposure group served. Data are for the first unit in which an individual served in Vietnam. Many of those who were initially assigned to the 1 Australian Reinforcement Unit were then assigned to other units after arrival in Vietnam. The differences in units served between the exposure groups reflect the correlation of the period of Dapsone use and the time period that specific units served in Vietnam.

Table 2-7: Selected units first served in Vietnam by Dapsone Exposure

Unit	Dapsone Exposed (N = 23,262)	Dapsone non-exposed (N = 16,945)
A Squadron 3 Cavalry Regiment	586 (2.5%)	245 (1.4%)
Australian Army Training Team	< 0.8%	755 (4.5%)
HQ Australian Force Vietnam	639 (2.8%)	664 (3.9%)
HQ 1 Australian Logistics Support Group	475 (2.0%)	289 (1.7%)
HQ 1 Australian Task Force	831 (3.6%)	358 (2.1%)
1 Australian Reinforcement Unit	2,666 (11.5%)	754 (4.4%)
1 Field Regiment	546 (2.3%)	426 (2.5%)
1 Field Squadron	1,030 (4.4%)	440 (2.6%)
2 Advanced Ordnance Depot	433 (1.9%)	486 (2.9%)
32 Small Ships Squadron	< 0.9%	347 (2.0%)
4 Field Regiment	366 (1.6%)	367 (2.2%)
12 Field Regiment	692 (3.0%)	< 0.5%
104 Signals Squadron	603 (2.6%)	< 1.1%
110 Signals Squadron	560 (2.4%)	590 (3.5%)
17 Construction Squadron	711 (3.1%)	986 (5.8%)
1 Battalion, Royal Australian Regiment	605 (2.6%)	894 (5.3%)
2 Battalion, Royal Australian Regiment	611 (2.6%)	717 (4.2%)
3 Battalion, Royal Australian Regiment	984 (4.2%)	411 (2.4%)
4 Battalion, Royal Australian Regiment	1,083 (4.7%)	< 0.6%
5 Battalion, Royal Australian Regiment	625 (2.7%)	640 (3.8%)
6 Battalion, Royal Australian Regiment	615 (2.6%)	529 (3.1%)
7 Battalion, Royal Australian Regiment	522 (2.2%)	784 (4.6%)
8 Battalion, Royal Australian Regiment	637 (2.7%)	< 0.1%
9 Battalion, Royal Australian Regiment	590 (2.5%)	< 0.1%
Other units	6,501 (2.8%)	5,928 (3.5%)

2.8 Summary of cohort characteristics

There were some differences in the age and service characteristics between the Dapsone exposed and non-exposed Army veterans. This reflects the temporal nature of Dapsone use during the Vietnam War era. Dapsone was first used as an anti-malarial medication in the Australian Army in October 1968. Thus those exposed to Dapsone would have had service between October 1968 and the end of the Australian involvement in 1972.

Twelve per cent of the exposed group had more than one tour and also may have served at times prior to the initiation of Dapsone prophylaxis. However for the vast majority of the Dapsone exposed group, the characteristics of their service represent the operational conditions in the later part of the Vietnam War. Possible implications of this are discussed in Chapter 4.

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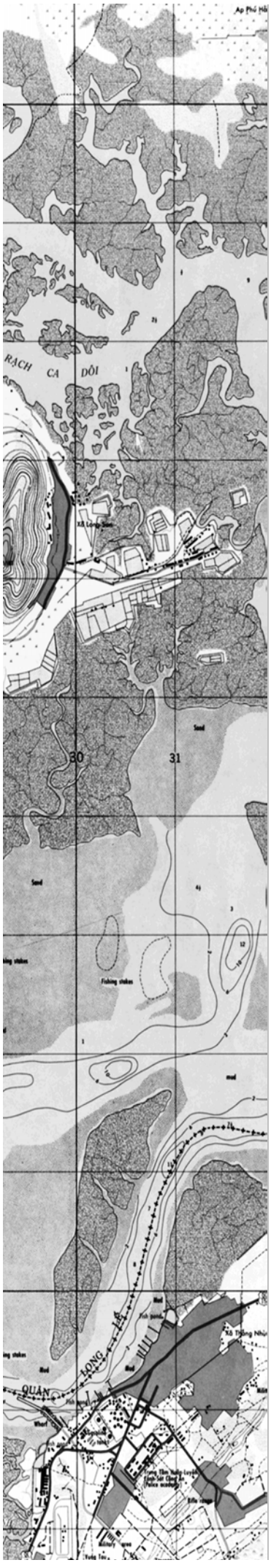

3

Statistical Methods

Chapter 3 Statistical Methods

This chapter describes the statistical methods used in calculating the results of the mortality and cancer incidence of Australian Army Vietnam veterans in regard to exposure to Dapsone, the antimalarial medication given during their Vietnam service.

3.1 Statistical methods

This study used three methods to analyse the mortality and cancer incidence experience of the Army veterans. A direct comparison between the Dapsone exposed veterans and the non-exposed veterans was used to calculate Relative Rate (RR). An indirect comparison was also used in which the mortality and cancer incidence of the exposed veterans and the non-exposed veterans was compared to the male Australian population and is presented as Standardised Mortality or Incidence Ratios (SMR/SIR). The indirect comparison was the method used in the first two volumes of this series on Vietnam veteran health. Lastly, regression analysis was used to assess whether a dose-response relationship between total cumulative Dapsone dose and mortality or cancer incidence exists.

3.1.1 Population at risk

Veterans became part of the population at risk if they were alive at the beginning of the study period (1 January 1982 for the cancer incidence study, the end of their time in Vietnam for the mortality study). They contributed person-time until the study end date (31 December 2000 for the cancer incidence study, 31 December 2001 for the mortality study) or the date they died, if this occurred during the study period. For example, a 23-year-old soldier departing Vietnam in 1972 and dying in 1993 aged 44 would contribute 12 person years to the population at risk for the cancer incidence study, and 22 years to the mortality study.

The length of time each cohort member was alive during the period of observation was estimated and the person-years method was used to calculate the total number of person years at risk for each calendar year and five-year age group.

The size of the unknown vital status group (n = 1,001) was too large to ignore and therefore needed to be accounted for in the analysis where the veterans' cancer incidence and mortality rates were compared to the Australian population. This was managed by treating the unknown vital status of veterans using two scenarios for the population at risk:

- Scenario 1 excludes veterans whose status is unknown from the at-risk population. These veterans are effectively treated as average compared to the other veterans. If the mortality/cancer incidence rate among those lost to follow-up is substantially different, then the SMR/SIR calculated using this scenario may be an over or under-estimate of the true situation.
- Scenario 2 includes veterans whose status is unknown in the at-risk population, and assumes that they are still alive and residing in Australia at the end of the follow-up period. The effect of including veterans whose status is unknown is that the expected number of cancers/deaths may be over-estimated and thus the estimate of the SIR/SMR may be lower than the true situation. This is because the veteran population under Scenario 2 is not adjusted for the possible death or emigration from Australia of those lost to follow-up.

In presenting the findings from the analysis in this report Scenario 1 is shown except where the two scenarios gave different results when both sets of results are presented.

3.1.2 Direct comparison of Vietnam Army veterans

The direct comparison compares the sub-group of Dapsone exposed veterans to the sub-group of non-exposed veterans. In this analysis the null hypothesis is that there is no difference between the two sub-groups, that is, that Dapsone exposure had no effect on mortality or cancer incidence rates and consequently the rates should be the same in the two sub-groups.

The mortality/cancer incidence rates for the whole Army veteran group were used to determine the expected numbers of deaths/cancers in the sub-group that was exposed to Dapsone and the sub-group that was not exposed. These were then compared to the observed numbers of deaths/cancer cases in the two sub-groups.

It should be noted that the observed and expected numbers for particular cancers can be aggregated to whatever group of cancers required. For example, the observed and expected numbers for head and neck cancers can be added to the observed and expected numbers for larynx cancer to obtain the observed and expected cases of oropharynx and larynx cancer. Commonly used groupings and selected subsets of interest have been included in the tables.

The direct comparison between the Dapsone exposed and the non-exposed was carried out by dividing the ratio of (observed/expected) numbers of deaths/cases for the Dapsone exposed veterans by that for the non-exposed veterans. This value is called the Relative Rate (RR).

A RR of 1.00 means that the mortality/cancer incidence rates are equal in the two subgroups. A RR of, say, 0.88 means that the rate in the first subgroup (in this study the Dapsone exposed veterans) is 0.88 times, or 12% less than that in the second subgroup (in this study the non-exposed veterans), while a RR of 1.12 indicates an elevation of 12% in the incidence or death rate.

The relative rates are displayed in tables and visually in figures in this publication (see for example Figure 4-1). These figures have a vertical line showing the location of a

RR of 1.0 indicating no difference in mortality or cancer incidence. Horizontal lines for individual cancers consist of a central dot showing the point estimate of the RR and a horizontal error bar showing the 95% confidence interval (CI). Small error bars indicate good precision. A result is statistically significant if the error bar does not cross the vertical 1.0 line. Error bars which are wholly to the right of the vertical line indicate causes of death/cancers that are significantly more common than expected and those wholly to the left of the vertical line indicate causes of death/cancers that are significantly less common than expected.

3.1.3 Indirect comparison with the male Australian population

The expected number of deaths/cases of cancer by cause of death/type of cancer was calculated for each year by applying five-year age-specific mortality/cancer incidence rates for the Australian male population to the corresponding age-specific number of living veterans in each year.

The steps involved in these calculations were:

- Calculate incidence/mortality rates for the Australian male population for each cancer/cause of death being studied, by five-year age groups, for each year of the study period.
- Derive the population of living veterans (population at risk) by 5-year age groups for the study period, from the Army Veteran Study Roll.
- Calculate the expected number of cases/deaths being studied for both groups of veterans, had veterans experienced the cancer incidence/mortality rates of the general Australian population for each year of the study period. This was done by multiplying the age-specific incidence rates for the Australian population by the corresponding veteran population in that age group, for that year.

The yearly expected numbers of cases are added to derive the total expected number of cases for the study period. The actual number of cancers/deaths experienced by the veterans (observed cases) was compared to the expected number, by dividing the former figure by the latter. The resulting ratio, the standardised incidence ratio (SIR) or the standardised mortality ratio (SMR), is above one if the number of observed cases among veterans is higher than the expected number. The ratio is below one if the number of observed cases amongst veterans is lower than the expected number.

Australian age-specific mortality rates for some causes of death (CODs) were not available for the whole study period. In these instances, study periods were reduced by advancing the starting year to when Australian mortality rates became available for the indirect comparisons only. (The calculation of relative rates for the direct exposed/non-exposed comparison did not involve Australian mortality rates and the whole study period between 1963 and 2001 was used for all tabulated CODs.)

3.1.4 Dose-response relationship

The study analysed the possible ordered relationship between mortality or cancer incidence on the one hand, and Dapsone dose on the other. This analysis, based on the Cox proportional hazards model, controlled for age and the time spent in Vietnam.

The regression model excludes the subgroup of veterans not exposed to Dapsone. This is a standard issue in bio-assay, where the response (here, mortality and 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.

3.1.5 Confidence intervals

On their own, the RR/SIR/SMR are not sufficient to say whether the veterans experienced significantly higher or lower rates of cancer/mortality than might be expected because differences may arise by chance. The RR is the best estimate of the difference between the Dapsone exposed and the non-exposed and the 95% CI gives an indication of the precision of that estimate. The SIR/SMR is the best estimate of the difference between the veterans and the Australian population and the 95% confidence interval (CI) around the SIR/SMR gives an indication of the precision of that estimate. A narrow 95% CI indicates good precision, the true RR/SIR/SMR is likely to lie within a narrow range of values, while a wide 95% CI indicates poor precision.

A RR/SIR/SMR of 1.0 means that there is no difference between the two groups being compared. A 95% CI which does not include the value 1.0 indicates that the calculated RR/SIR/SMR is significantly different from 1.0 and, therefore, unlikely to be due to chance. In other words, there may be a real difference between the groups. For example, a RR of 1.2 with a CI of 1.1 to 1.4 is statistically significant because the interval does not include 1.0. If the CI were 0.9 to 1.5, the difference would not be statistically significant because the CI includes 1.0.

A standard statistical assumption is that the observed number of cases has a Poisson distribution the mean of which is the expected number of cases. The Poisson assumption allows the closeness of the observed and expected numbers of cases to be assessed statistically. This study has calculated exact confidence levels[1] for the relative rates. Confidence intervals for the SIR/SMR were calculated using the asymptotic method, except where the number of cancers diagnosed was small (<= 20), when the exact method was used.

3.1.6 Statistical Power

In addition to RR/SIR/SMR and 95% CIs, a third factor, statistical power, is important in assessing the results of a study. The power of a study is the probability that the study will detect a statistically significant difference between two study groups if the groups truly differ. This probability depends on the size of the effect, the incidence of the outcome and the number of observations or participants in the study. If an outcome of interest (ie. a specific cause of cancer incidence or mortality) is rare then even a large study may not have sufficient power to detect a true difference, especially if this

difference is small. Conversely, if an event is very common or the difference between the groups is very large, then a smaller study will give a statistically significant result.

A study of this size, comprising more than 41,000 Vietnam Army veterans, has 80% power to detect a statistically significant 20% difference between groups where the risk of cancer/mortality is approximately 2% or greater. This means that this study had good power to detect a 20% difference (RR = 1.2) for conditions such as all cause mortality or mortality due to cancer, but it had less power to detect a difference of this size for some other causes of death such as, for example, diseases of the respiratory or nervous system.

3.1.7 Adjustment for missing causes of death

Eighty veterans (2.0 % of all Army veteran deaths) were known to have died but their cause of death was not recorded. This had no bearing on the all cause mortality analysis, but posed a problem for the cause-specific analysis. As there was no indication that these deaths were in any way different from those deaths with a known cause where documentation was available, these deaths were assigned a cause of death according to the distribution of causes of death among the other Army veterans, adjusting for the year of death.

An additional 32 veterans had poorly defined external causes of death. These deaths were allocated a more precise cause of death based on the distribution of the external causes of death among other veterans, adjusting for the year of death. For example, most of these deaths involved major head trauma and the study estimated that 80% of these deaths were due to motor vehicle accidents.

These adjustments were only done for the comparison with the Australian male population; the direct comparison between the veterans and the non-veterans was based only on known causes of death.

3.2 Statistical software used

Several statistical packages were used for data management and analysis. Initial processing, such as the calculation of person-years, and regression analysis was performed in SAS[2] Release 8.2. Tables of observed and expected cases of cancer and the standardised incidence ratio were compiled in EXCEL[3] 2003 and DeltaGraph[4] Version 5.0.0 was used to produce the graphs.

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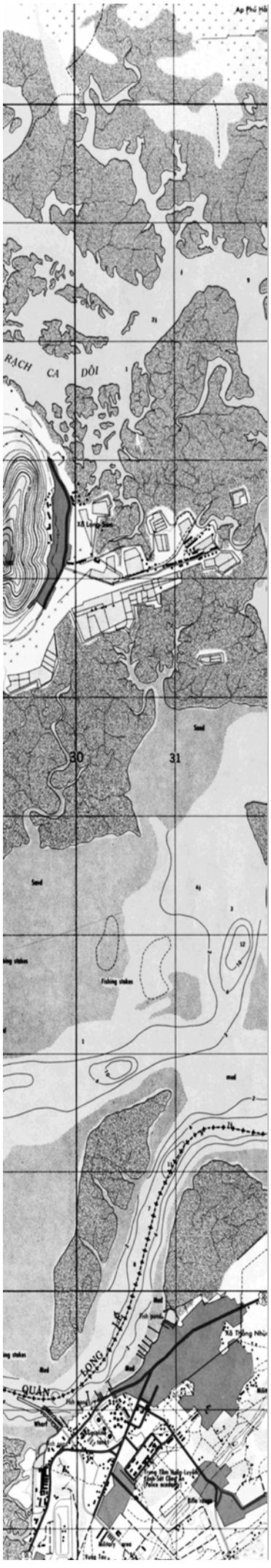

4

Results and Discussion

Chapter 4 Results and Discussion

This chapter presents the results of the analysis of the mortality and the incidence of cancer observed amongst the Army veterans who were treated with dapsone and the Army veterans who were not treated with dapsone. This analysis was carried out for a range of specific causes and groupings of causes of death and for the most common cancers in the Australian population.

The first of the three analyses presented is the indirect method which compares the mortality and cancer incidence amongst Army veterans who did or did not take Dapsone to that expected for Australian males of the same age. These results are presented as Standardised Mortality Ratios (SMR) and Standardised Incidence Ratios (SIR).

The second method, the direct method, compares mortality and cancer incidence of the Army veterans who took Dapsone during their service to that of the Army veterans who did not take Dapsone and these are presented as Relative Rates (RR). All calculations were adjusted for age.

Lastly, the results of the regression analysis investigating the effect of individual total cumulative dose of Dapsone on mortality and cancer incidence are presented.

The results are then discussed in the context of the literature and previous studies.

4.1 Mortality rates for exposed and non-exposed Army veterans

This section reports the mortality rates of Army veterans who were exposed to Dapsone compared to those Army veterans who were exposed to other anti-malarial treatment while serving in Vietnam.

During the study period from completion of Vietnam service to 31 December 2001, there were 1,929 deaths observed amongst the veterans exposed to Dapsone and 1,966 deaths observed amongst the veterans who did not take Dapsone.

4.1.1 Indirect comparison of mortality to the Australian population

Standardised mortality ratios (SMR), comparing mortality to the age standardised male Australian population, were calculated for Army personnel who had any exposure to Dapsone and for those with no exposure to Dapsone. The complete results of the SMR analysis are presented in Appendix C, Tables C1 and C2.

Dapsone exposed

Amongst Dapsone exposed Army veterans overall mortality was 6% lower than in the Australian male population, SMR = 0.94 (95% CI 0.90, 0.98). Two specific causes of death were statistically significantly more common in this group of veterans, alcoholic liver disease and suicide by gas (although overall suicide rates did not differ from the Australian population. Mortality from infectious diseases, diabetes, nervous and circulatory system diseases was significantly less common.

Dapsone non-exposed

Mortality was also lower amongst the Dapsone non-exposed group of Army veterans, SMR = 0.96 (95% CI 0.91, 1.00) compared to the Australian male population. No specific causes of death were significantly more common in this group compared to the Australian population whereas death from diabetes, diseases of the circulatory system and respiratory system were less common than expected.

4.1.2 Direct comparison of exposed to non-exposed Army veterans

Relative rates (RR) were calculated which directly compare mortality amongst Army veterans who were exposed to Dapsone to those who were not exposed.

The all cause mortality did not differ between the two exposure groups, RR = 1.00 (95% CI 0.94, 1.07). Nor were there statistically significant differences in mortality between the groups for any of the causes of death analysed. Figure 4-1 and Table 4-1 present the results of the mortality analysis.

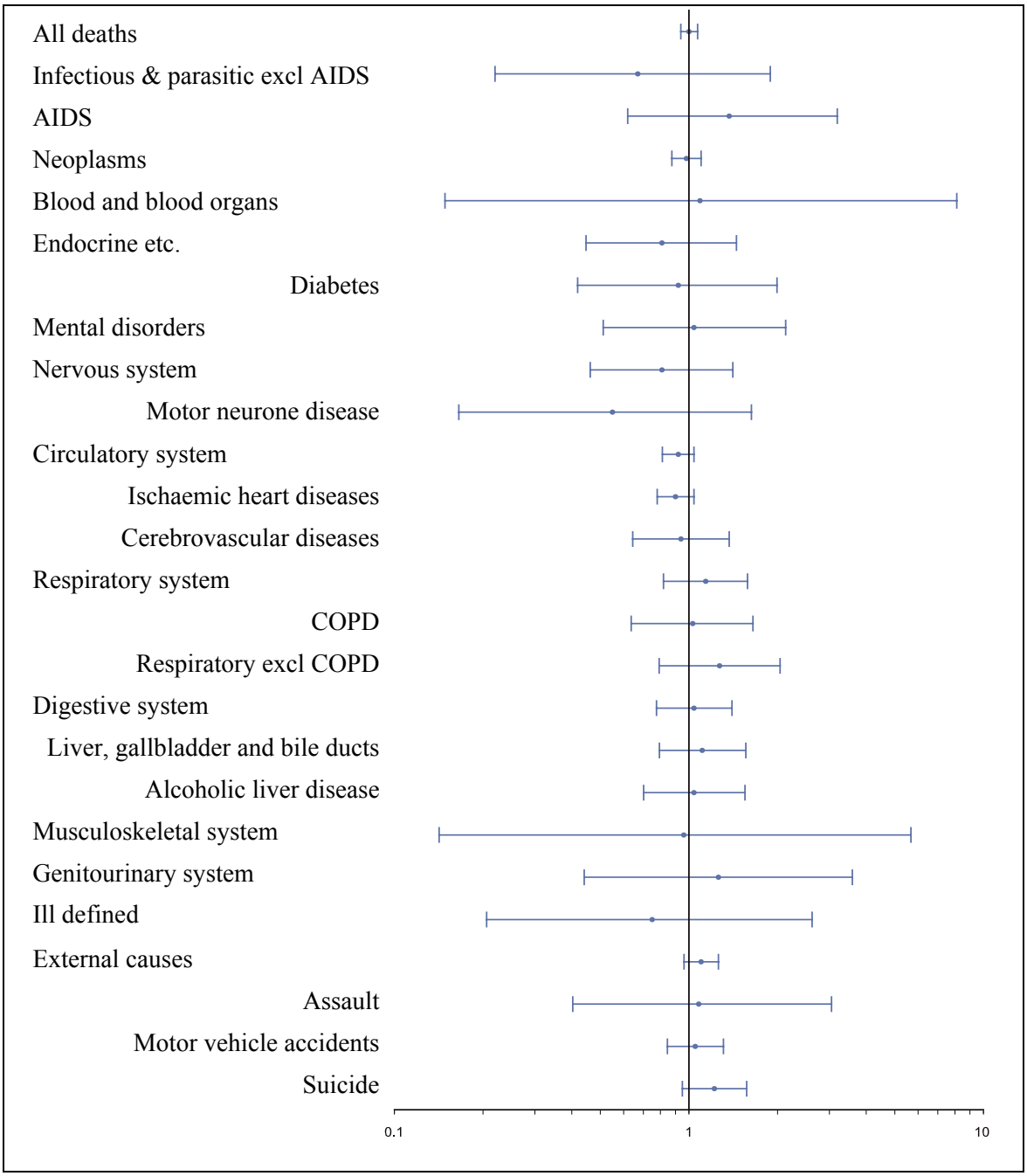

Figure 4-1: Relative rates and 95%CI for mortality in Dapsone exposed compared to non-exposed Army veterans, 1963-2001

Table 4-1: Observed and expected number of deaths and the relative rate (RR) for dapsone exposed and non-exposed Army veterans.

Cause of death	Exposed		Non-exposed		RR	95% CI
	Observed	Expected	Observed	Expected		
All deaths	1,929	1,929	1,966	1,966	1.00	0.94–1.07
Infectious and parasitic diseases excluding Aids	7	9	11	9	0.67	0.22–1.90
Aids	19	17	11	13	1.37	0.62–3.19
Tuberculosis	0	1	2	1	0.00	–
Neoplasms	578	584	663	657	0.98	0.88–1.10
Blood & blood organs	3	3	3	3	1.09	0.15–8.12
Endocrine, nutritional and metabolic diseases	23	26	30	27	0.81	0.45–1.45
Diabetes	14	15	17	16	0.92	0.42–1.99
Mental disorders	19	19	17	17	1.04	0.51–2.13
Nervous system	25	28	32	29	0.81	0.46–1.40
Multiple sclerosis	0	1	2	1	0.00	–
Motor neurone	6	8	11	9	0.55	0.17–1.63
Eye diseases	0	0	0	0	–	–
Ear diseases	0	0	0	0	–	–
Circulatory system	471	492	585	564	0.92	0.82–1.04
Ischaemic	347	368	449	428	0.90	0.78–1.03
Cerebrovascular	54	56	66	64	0.94	0.64–1.36
Respiratory system	73	68	82	87	1.14	0.82–1.59
Asbestosis	1	1	1	1	1.78	0.02–139.34
COPD	33	32	45	46	1.03	0.64–1.65
Respiratory excluding COPD	40	35	37	42	1.27	0.79–2.04
Digestive system	101	99	91	93	1.04	0.78–1.40
Liver, gall bladder and bile ducts	83	79	67	71	1.11	0.80–1.56
Alcoholic liver	60	59	50	51	1.04	0.70–1.55
Peptic ulcer	4	3	3	4	1.70	0.29–11.58
Skin and subcutaneous tissue	0	1	1	0	0.00	–
Musculoskeletal system	3	3	4	4	0.96	0.14–5.67
Genitourinary system	9	8	9	10	1.26	0.44–3.59
Congenital malformation	3	2	0	1	–	–
Ill defined	6	7	7	6	0.75	0.21–2.62
External chapter	540	518	378	400	1.10	0.97–1.26
Assault	12	12	8	8	1.08	0.41–3.06
MVA	197	193	151	155	1.05	0.84–1.31
Suicide	170	157	103	116	1.22	0.95–1.57
Firearms	52	48	32	36	1.20	0.76–1.93
Gas and vapours	56	48	28	36	1.49	0.93–2.43
Hanging	31	28	16	19	1.28	0.68–2.50

4.2 Cancer incidence and mortality rates for exposed and non-exposed Army veterans

This section compares the number of cancers diagnosed for the Army veterans for the period 1982 to 2000 and mortality from cancer from the end of Vietnam service to 2001.

There were 1,360 cancers diagnosed amongst the exposed veterans and 1,499 cancers identified amongst the veterans who were not exposed to Dapsone. Among the Dapsone exposed Army personnel 590 deaths due to cancer were observed, and 673 deaths from cancer were observed among the non-exposed veterans

4.2.1 Indirect comparison to the Australian population

The standardised incidence (SIR) and mortality (SMR) rates for cancer were calculated for Dapsone exposed and non-exposed veterans. The complete results of SIR/SMR are presented in Appendix C, Tables C3 and C4 for cancer incidence and Tables C5 and C6 for cancer mortality.

The overall incidence of cancer was significantly higher among the Army personnel compared to the Australian population for both Dapsone exposed and non-exposed veterans, 7% and 20% higher than expected, respectively. Specifically, both groups had higher than expected incidence for Hodgkin's disease, melanoma and cancer head and neck region. Dapsone exposed veterans also had higher than expected incidence for eye cancer whereas those veterans not exposed to Dapsone also had higher than expected incidence for cancers of the lung and connective soft tissue.

However, overall mortality due to cancer was not significantly different from the Australian population for either exposure group. Mortality for specific types of cancer was higher than expected for lung and oesophageal cancer amongst the non-exposed veterans. Dapsone exposed veterans had higher than expected mortality due to cancer of the eye and oral cavity and lower than expected mortality from connective soft tissue cancer.

4.2.2 Direct comparison of exposed to non-exposed Army veterans

When direct comparison between the exposure groups was calculated, overall cancer incidence was 10% lower amongst the Dapsone exposed group compared to the non-exposed veterans, RR = 0.90 (95% CI 0.83, 0.97). There were no cancer types for which the incidence was significantly elevated amongst the Dapsone exposed veterans. The incidence of connective soft tissue cancer, lung cancer and genitourinary cancer was significantly lower amongst those Army veterans exposed to Dapsone.

Figure 4-2 and Table 4-2 present the results of the cancer incidence analysis.

Cancer mortality did not differ between the groups, RR = 0.98 (95% CI 0.88, 1.10). None of the 32 specific cancer types analysed showed higher mortality in the Dapsone exposed group. Mortality from two cancers, connective soft tissue and oesophagus, was significantly less common amongst those who took Dapsone treatment.

The results of the cancer mortality analysis are displayed in Figure 4-3 and Table 4-3.

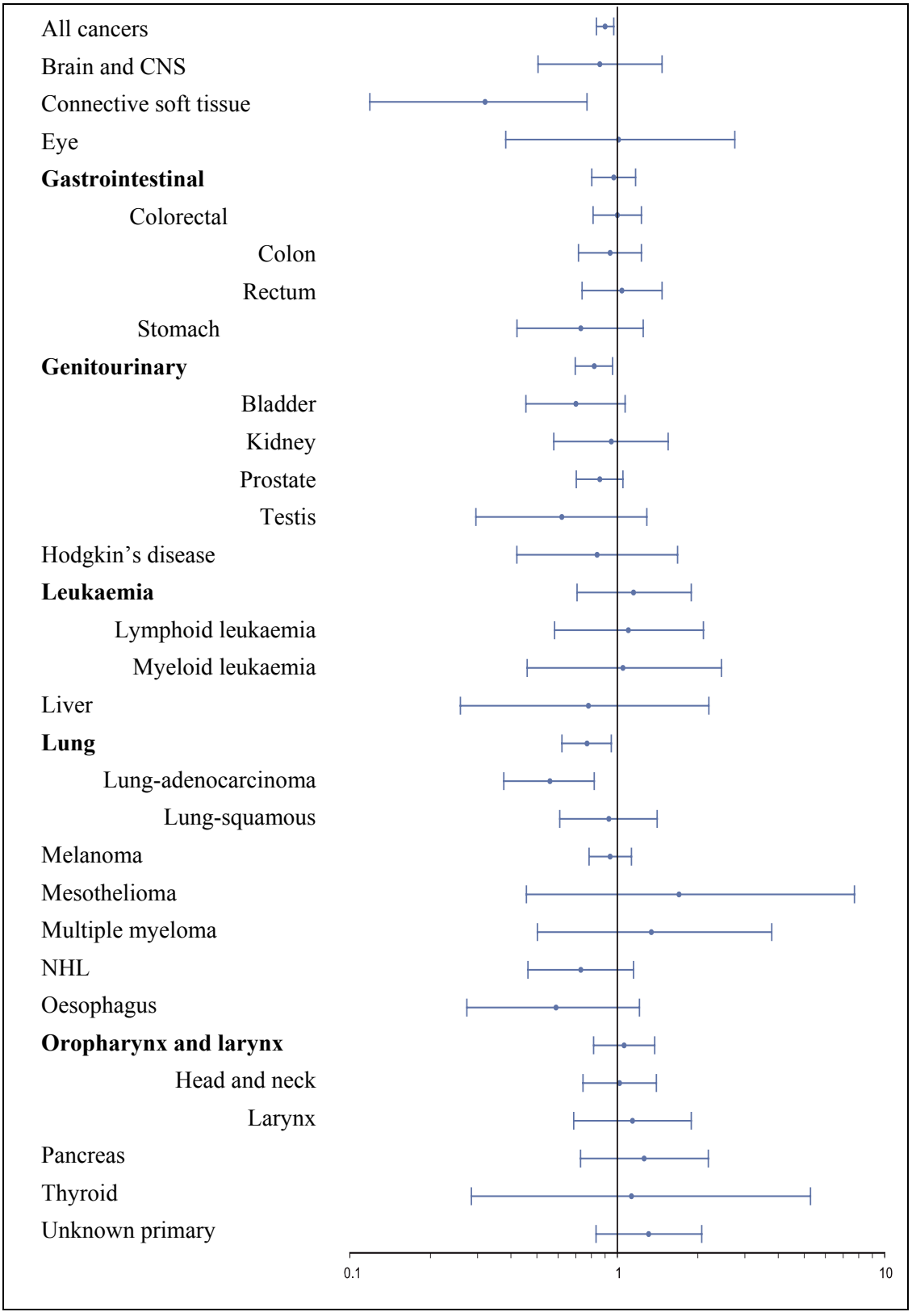

Figure 4-2: Dapsone exposure and cancer incidence (1982 – 2000), relative rates and 95% CI

Table 4-2: Cancer Incidence: Observed and expected number of cancers diagnosed and the relative rate (RR) for dapsone exposed and non-exposed Army veterans.

	Exposed		Non-exposed			
Cancer type	Observed	Expected	Observed	Expected	RR	95% CI
All cancers	1,360	1,436	1,499	1,423	0.90	0.83–0.97
Brain	32	34	29	27	0.86	0.50–1.47
Breast	2	2	3	3	0.81	0.07–7.08
Connective soft tissue	8	15	19	12	0.32	0.12–0.78
Eye	11	11	9	9	1.01	0.38–2.75
Gastrointestinal	217	221	229	225	0.97	0.80–1.17
Colorectal	183	183	188	188	1.00	0.81–1.23
Colon	105	109	117	113	0.94	0.71–1.23
Rectum	72	71	69	70	1.04	0.73–1.46
Stomach	26	31	36	31	0.73	0.43–1.25
Genitourinary	261	291	363	333	0.82	0.70–0.97
Bladder	39	48	59	50	0.70	0.45–1.07
Kidney	33	34	38	37	0.95	0.58–1.55
Prostate	168	183	241	226	0.86	0.70–1.05
Testis	16	20	18	14	0.62	0.30–1.29
Hodgkin's disease	19	21	19	17	0.84	0.42–1.68
Leukaemia	41	38	32	35	1.15	0.71–1.88
Lymphoid leukaemia	24	23	20	21	1.10	0.58–2.10
LL_acute	3	2	2	3	2.03	0.23–24.26
LL_chronic	18	19	18	17	0.91	0.45–1.86
Myeloid leukaemia	15	15	12	12	1.05	0.46–2.45
ML_acute	7	8	8	7	0.76	0.23–2.39
ML_chronic	7	6	3	4	1.85	0.42–11.09
Liver	7	8	11	10	0.78	0.26–2.19
Lung	150	174	215	191	0.77	0.62–0.95
Adenocarcinoma	42	59	78	61	0.56	0.37–0.82
Squamous	45	47	53	51	0.93	0.61–1.42
Small-cell	29	27	31	33	1.16	0.67–1.99
Large-cell	18	21	26	23	0.74	0.38–1.40
Other	16	20	27	23	0.69	0.35–1.33
Melanoma	259	267	229	221	0.94	0.78–1.12
Mesothelioma	8	6	4	6	1.70	0.45–7.71
Multiple myeloma	12	11	8	9	1.34	0.50–3.79
NHL	40	47	44	37	0.73	0.46–1.15
Oesophagus	12	17	26	21	0.59	0.27–1.20
Oropharynx and larynx	120	117	116	119	1.06	0.81–1.38
Head and neck	85	84	83	84	1.02	0.75–1.40
Larynx	35	33	33	35	1.14	0.69–1.90
Pancreas	31	28	27	30	1.26	0.73–2.19
Thyroid	7	7	4	4	1.13	0.29–5.28
Unknown	45	39	38	44	1.31	0.83–2.07

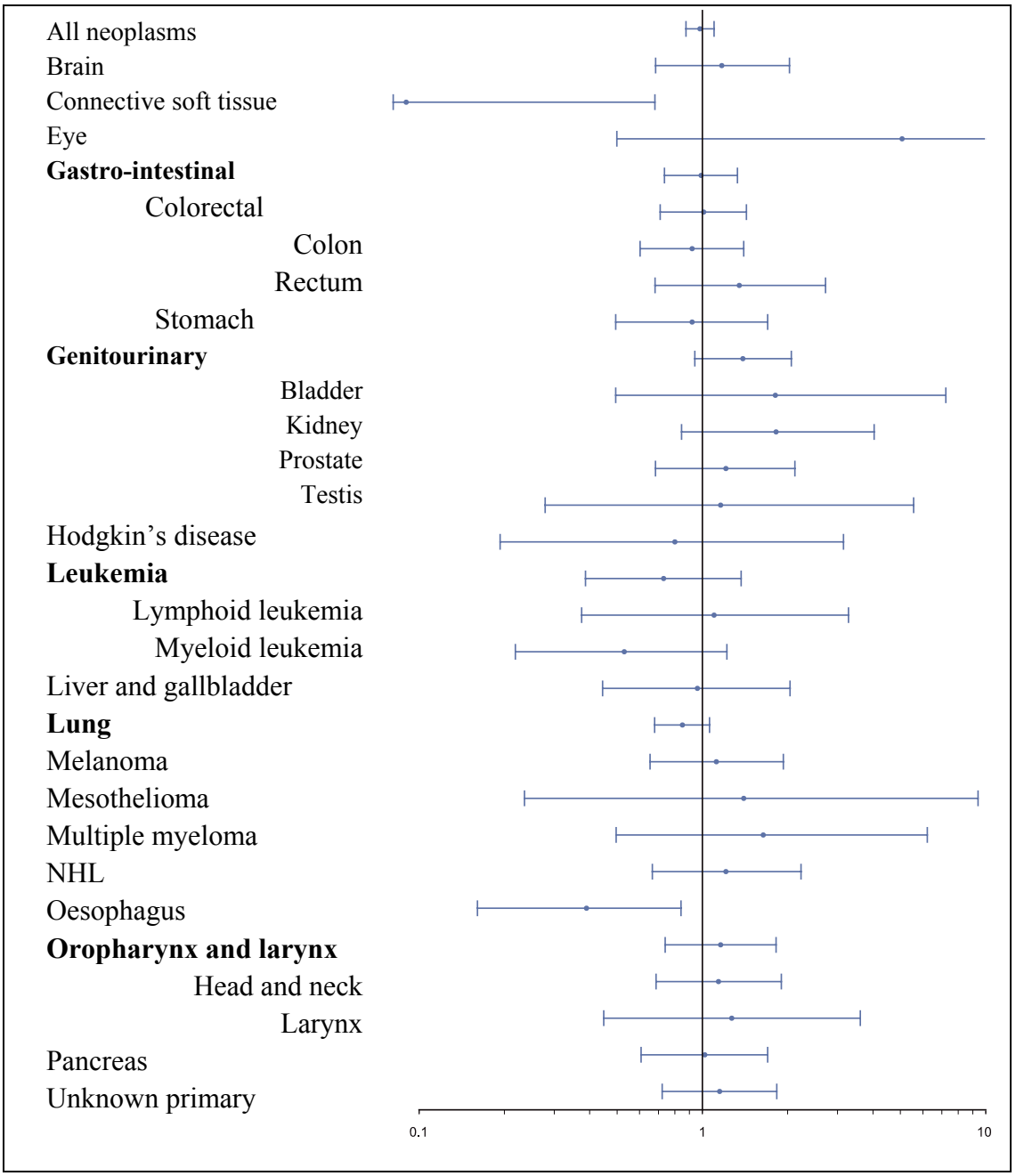

Figure 4-3: Dapsone exposure and cancer mortality (1963 – 2001), relative rates and 95% CI.

Table 4-3: Cancer Mortality: Observed and expected number of cancer deaths and the relative rate (RR) for dapsone exposed and non-exposed Army veterans.

	Exposed		Non-exposed			
Cancer type	Observed	Expected	Observed	Expected	RR	95% CI
All neoplasms	578	584	663	657	0.98	0.88–1.10
Brain and CNS	36	34	25	27	1.17	0.68–2.03
Breast	1	1	2	2	0.79	0.01–15.09
Connective soft tissue	1	5	8	4	0.09	0.00–0.68
Eye	4	2	1	3	5.07	0.50–249.83
Gastrointestinal	87	88	100	99	0.99	0.73–1.33
Colo-rectal	64	64	72	72	1.01	0.71–1.44
Colon	43	45	54	52	0.92	0.60–1.40
Rectum	21	18	17	20	1.35	0.68–2.72
Stomach	21	22	26	25	0.92	0.49–1.69
Genitourinary	56	47	54	63	1.39	0.94–2.05
Bladder	7	5	5	7	1.81	0.49–7.23
Kidney	18	13	13	18	1.82	0.84–4.04
Prostate	25	22	31	34	1.21	0.69–2.12
Testis	6	6	4	4	1.16	0.27–5.57
Hodgkin's	5	6	6	5	0.80	0.19–3.15
Leukemia	20	24	25	21	0.73	0.38–1.36
Lymphoid leukemia	9	9	8	8	1.10	0.38–3.29
Myeloid leukemia	10	14	17	13	0.53	0.22–1.22
Liver and gallbladder	14	14	18	18	0.96	0.44–2.03
Lung	136	150	191	177	0.85	0.67–1.06
Melanoma	31	29	29	31	1.12	0.65–1.92
Mesothelioma	4	3	3	4	1.40	0.24–9.57
Multiple myeloma	9	7	5	7	1.64	0.49–6.22
Nasal	0	0	1	1	0.00	–
NHL	27	25	22	24	1.21	0.66–2.22
Oesophagus	9	17	31	23	0.39	0.17–0.85
Oral cavity, pharynx and larynx	44	41	41	44	1.16	0.74–1.83
Head and neck	35	33	32	34	1.14	0.68–1.90
Larynx	9	8	9	10	1.27	0.45–3.60
Pancreas	30	30	37	37	1.02	0.61–1.70
Thyroid	0	1	1	0	0.00	–
Unknown	39	36	40	43	1.15	0.72–1.83

4.3 Effect of Dapsone dose on mortality and cancer incidence

As described in Chapter 3, several regression models were developed to assess the effect of the total cumulative Dapsone dose received during Vietnam service on mortality and cancer incidence. The analysis controlled for age and time served in Vietnam. Table 4-4 gives the results of the analysis. There was no significant relationship between increasing Dapsone dose and all cause mortality or cancer mortality. There was a borderline significant inverse relationship between Dapsone dose and cancer incidence. That is, with increasing total cumulative Dapsone dose there was a small decrease in the incidence of cancer.

Table 4-4: Dapsone dose response analysis of mortality and cancer incidence

Outcome	Coefficient	Hazard Ratio	95% CI	P value
All cause mortality	-0.03165	0.97	0.93, 1.01	0.139
Cancer mortality	-0.04213	0.96	0.89, 1.03	0.274
Cancer incidence	-0.04989	0.95	0.91, 1.00	0.048

4.4 Summary and conclusion of results

In summary, the Vietnam Army veterans who received Dapsone during their service displayed no difference in overall mortality or mortality from any specific causes of death compared to those Army veterans who did not receive Dapsone. Both groups displayed a healthy worker effect when mortality was compared to the Australian population. Furthermore, the Dapsone exposed group showed a modest but statistically significant reduction in cancer incidence compared to the non-exposed group. However both groups of Army veterans had a higher than expected number of cancers diagnosed compared to the Australian population.

Taken together the results of the Dapsone analysis show that ingestion of this anti-malarial drug during Vietnam service did not have long term adverse health effects in regards to mortality or cancer incidence. The following section discusses these findings in the context of the literature and previous studies.

4.5 Discussion of results

The purpose of this study was to examine any long term health effects of Dapsone exposure during the Vietnam War on cancer incidence and on causes of death. As discussed in Chapter 1, there was concern about potential adverse health effects due to treatment with Dapsone. These included reports of potential for cancer noted in animal studies and some rare cases of blood disorders (reversible agranulocytosis) observed during use particularly when consumed with other antimalarial medications. This study has concluded that use of Dapsone during Vietnam service did not have long term adverse health effects in regards to mortality or cancer incidence.

4.5.1 Features of the study

This was a large study that examined the long-term health effects amongst more than forty thousand veterans who consumed specific drug courses of therapy and who were followed for more than thirty years following service. This study compares mortality and cancer incidence among those who consumed a Dapsone plus Paludrine anti-malarial prophylactic treatment during their Vietnam service to those who consumed Paludrine only prophylaxis.

The consumption of the Dapsone was strictly monitored and recorded during the Vietnam era. Through these records, total cumulative Dapsone consumption was able to be reconstructed at an individual level. Dapsone consumption information was compiled for the previous study[1] and no further refinement of this data was undertaken for the present study.

The temporal nature of Dapsone use needs to be considered. Dapsone was used from the last quarter of 1968 to 1972. Orders were given as to when Dapsone should be used and, with few exceptions, all who served during the time these orders were in effect (mainly during the wet seasons of these years) were given the Dapsone/Paludrine treatment. Over 80% of the Army personnel served one tour in Vietnam.

The study does not have information for many of the other exposures that would have occurred during service in Vietnam. Although this cohort was exposed to a range of stresses and toxicants, little is known about the amount of exposure that an individual may have experienced. In addition any adverse or beneficial health exposures an individual may have experienced following Vietnam service are also not known or quantified.

Statistical power must be considered when interpreting the results. Statistical power is the probability that a study will detect a statistically significant difference between two study groups if the groups truly differ. The size of the group being studied, the magnitude of the effect observed and the rate of occurrence of a health outcome influence statistical power. If a particular health outcome is rare then even a large study

may not have sufficient power to detect a true difference, especially if this difference is small.

The role of chance and the concept of multiple comparisons must also be considered when interpreting the results. By convention statistical significance is at the 95% level, which means there is up to a one in twenty probability the result could be due to chance. Over 100 specific cancer diagnoses or causes of death are reported in this study. Thus by definition, apparently statistically significant associations could arise for up to 5 cancers or causes of death by chance alone.

Another feature of this study is that the cancer incidence could only be measured from 1982 (the first year of national cancer registration) to 2000 (the last year that all States and Territories had submitted their registry data to the National Cancer Clearing House at the time when the data matching was completed. Information on mortality from cancer was obtained from the end of Vietnam service to 2001. Any cancers diagnosed prior to 1982 and not resulting in death were not able to be captured in this study.

The healthy worker effect should also be considered. This is a phenomenon observed in occupational health studies in which those who are employed exhibit a lower mortality rate than the general population. This phenomenon is often referred to as the healthy soldier effect for occupational studies of military cohorts. This distinction denotes the fact that military populations are healthier than other employed populations, which in turn are healthier than the general population consisting of those employed and unemployed.

4.5.2 Overall mortality

In examining the standardised mortality, there were a large number of causes of death for which mortality rates were significantly below expectation, in both the Dapsone-exposed population, and those who did not consume Dapsone compared to the Australian population. This is almost certainly a manifestation of the health worker effect. For example, both the Dapsone exposed group and unexposed cohort showed a marked decrease in the rate of death from the endocrine diseases. As all veterans were screened at entry into the Army to remove those with diabetes mellitus, this is an entirely expected result.

The overall relative mortality analysis, which compares Dapsone exposed to non-exposed veterans, did not identify differences between the groups. There were no causes of death for which the relative risk was significantly higher or lower than expected when the Dapsone exposed veterans were compared to the veterans who did not take Dapsone.

4.5.3 Cancer incidence and mortality

As previously reported, all Army veterans showed a slight increase in cancer incidence relative to the general Australian population.[2] In this study, there was a slight decrease in the incidence of cancer in the group of veterans who received Dapsone compared to those who did not receive Dapsone. A modest and borderline statistically significant decreasing risk of cancer with increasing total cumulative dose of Dapsone was also

observed. In the absence of other exposure information either at the time of Vietnam service or in the more than 30 years following service, it is difficult to explain this observation.

A number of possible explanations to the lower cancer incidence among the Dapsone exposed veterans could be proposed. A finding due to chance must always be considered, especially when the result is modest. The lower cancer incidence could be due to unknown confounding by other exposures occurring during the periods when Dapsone was or was not administered, which could affect rates of cancer. Alternatively, as well as anti-infective properties, Dapsone also has anti-inflammatory action. Long term use of anti-inflammatory drugs has been shown to reduce cancer incidence.[3] While biologically plausible, it would be difficult to attribute a causal relationship of Dapsone given the relatively short time of exposure to this drug more than 30 years ago.

4.5.4 Discussion of specific cancer types

There were four cancer groups or sub-groups in which the relative rate was significantly lower than expected among the Dapsone exposed group. These include soft tissue sarcoma for which both incidence and mortality were lower than expected, lower than expected incidence of genitourinary and lung cancer and lower than expected mortality from oesophageal cancer. There were no specific types of cancer for which there was a higher than expected relative rate for those exposed to Dapsone.

A major risk factor for lung, oesophageal and genitourinary cancers is smoking.[4] Standardised incidence rates for lung and genitourinary cancer and standardised mortality for oesophageal cancer are significantly higher than expected in the Dapsone non-exposed group compared to the Australian population. Different levels of smoking in the two groups may account for the differences observed in cancer incidence or mortality. However this study does not have information on smoking levels of this cohort.

Although based on modest numbers, there was a pronounced decrease in the relative rate for soft-tissue sarcoma when incidence and mortality among those exposed to Dapsone were compared to the rates among those not exposed to Dapsone.

This finding is somewhat surprising as there were several exposures in Vietnam that could contribute to an increased risk of soft-tissue sarcoma. Most notably, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and the phenoxy herbicides have been repeatedly associated with an increased risk of soft-tissue sarcoma.[5,6] The use of herbicides during the Vietnam War was greatest between 1967 to 1969 when more than 15 million litres were sprayed in each of those years.[7] Relatively little herbicide was sprayed prior to 1966. As discussed in the section on features of this study, Dapsone was consumed from the last quarter of 1968 to 1972. This suggests that herbicide exposure does not explain the relatively higher rates of sarcoma in the non-Dapsone exposed group (who generally served prior to peak use of herbicides) nor the lower than expected incidence in the Dapsone exposed group (who generally served during peak herbicide use).

4.6 Conclusion

In this study, mortality was assessed for over 30 years since exposure and cancer incidence follow-up was for 19 years. There was no statistically significant difference in non-cancer mortality between those who consumed Dapsone and those who did not. There was a modest but statistically significant lower than expected overall cancer incidence, and for some specific cancers, a lower than expected mortality for the Dapsone exposed group.

This study concludes that those who took the anti-malarial Dapsone/Paludrine prophylaxis have not experienced adverse health, as measured by mortality and cancer incidence, compared to those veterans who took anti-malarial treatment without Dapsone.

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