The Canadian Persian Gulf Cohort Study:
Detailed Report

Prepared by Statistics Canada
For the Gulf War Veterans Cohort Study Advisory Committee

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To enquire about the concepts, methods and data quality please contact Client and Technical Services at 613-951-1746, Health Statistics Division, Statistics Canada. For all other enquiries, please contact the Department of National Defence, Canadian Forces Media Liaison Office at 613-996-2353 or 613-996-2354.

Executive Summary

The Gulf and Kuwait War of 1990/91 officially began with the invasion of Kuwait by Iraq on August 2, 1990. The Canadian military participated actively in the subsequent blockade and war initially contributing three ships committed on August 24, 1990. Between this date and February 28, 1991 that marked the end of the war, Canada deployed 5,100 military personnel (soldiers, sailors and airmen). Canada's contribution consisted of one headquarters, a naval task force, an air task group, a field hospital, two infantry companies and a platoon that provided security for the group of airmen, the hospital and the headquarters.

Since the end of the war, concerns have been expressed about the health of veterans who were deployed to the Persian Gulf. These concerns related partly to the general circumstances of deployment to a war zone and partly to the unique factors to which these veterans may have been exposed, including anti-chemical warfare substances, various immunizations and the possibility of exposure to low-level chemical and biological warfare agents. In this study, the term "veterans" refers to retired and currently serving members of the Canadian military.

In 1997, the Department of National Defence (DND) commissioned a survey on the health status of Canadian Gulf and Kuwait War veterans (Gilroy, 1998). Results from the survey indicated that, when compared to the active Canadian Forces (CF) members who were not deployed to the Gulf, Gulf and Kuwait War veterans had a higher prevalence of self-reported health problems including diseases of bones and joints, digestive system, skin, and respiratory system. They also had a higher prevalence of chronic fatigue symptoms, cognitive dysfunction, major depression, Post Traumatic Stress Disorder (PTSD), anxiety and fibromyalgia.

The long-term health ramifications of deployment to a war zone have yet to be studied among Canadian Gulf and Kuwait War veterans. Results from an American study (Kang & Bullman, 1996) indicated that United States (US) Gulf War veterans had higher death rates from motor vehicle accidents, particularly in the first 2 to 3 years after they returned from the Persian Gulf. However, there was no evidence of an increased risk of diseases. Similar mortality patterns were found in a mortality study of United Kingdom (UK) Gulf War Veterans (MacFarlane, Thomas & Cherry, 2000) A recent UK study of cancer incidence reported no evidence of an increase in cancer incidence in UK military personnel deployed to the Persian Gulf (MacFarlane, Biggs, Maconochie et al., 2003).

In 2000, the Gulf and Kuwait War Illness Advisory Committee commissioned a report to explore the feasibility of undertaking a study on the mortality and cancer incidence of military personnel posted to the Persian Gulf based on record-linkage methodology (Birkett, 2000). It was concluded, in the feasibility report, that a cohort study using this methodological approach was feasible and warranted and that the statistical power of study was deemed sufficient to detect differences between military groups in the "overall" risk of death and "overall" risk of developing cancer over the proposed 9-year follow-up. The proposed study had an 80% power to detect around a 60% increase in overall mortality (RR=1.63) and a 75% increase in overall cancer incidence (RR=1.75). The lower power for cancer outcomes reflects the shorter follow-up of 7 years instead of 9 years.

The main objective of this study, as was proposed in the feasibility report, was to determine if military personnel deployed to the Persian Gulf between August 24, 1990 and September 30, 1991 were at a higher risk of death or of developing cancer after their return to Canada than either other members of the military who were not deployed to the Persian Gulf or the general Canadian public. The availability, in Canada, of a national mortality database as well as a national cancer registry provided a unique opportunity to examine this cohort for higher than expected rates of mortality and cancer incidence using record linkage methodology.

This report describes the results of analyses, based on a nine-year follow-up (1991-1999), on mortality and cancer incidence among Canadian Gulf and Kuwait War veterans. Two cohorts were established. The final Deployed cohort consisted of 5,117 CF members sent to the Gulf between August 1990 and October 1991. The comparison cohort consisted of 6,093 members of the Canadian Forces who were eligible for deployment at the time of the 1990/91 Gulf and Kuwait War but who were not deployed. The age-sex distribution of the Non-deployed cohort was checked to ensure that it matched the distribution of the Deployed cohort. Record linkage methodology was used to identify deaths and incident cases of cancer in the two cohorts. In total,

there were 96 deaths during the nine-year follow-up and 71 new cases of cancer during the seven-year follow-up.

To compare the two cohorts, direct standardization methods were used to compute Mortality Rate Ratios (MRR) and Incidence Density Ratios (IDR). Survival methods (Kaplan-Meier, log-rank and Cox regression) were also applied to the data when a sufficient number of cases were available. Finally, indirect standardization methods were used to compare the cohort mortality and cancer incidence to the general Canadian population using Standardized Mortality Ratios (SMR) and Standardized Incidence Ratios (SIR).

Key findings

Mortality: Deployed versus Non-deployed comparisons

- There was no significant difference in the overall risk of death between the Deployed and Non-deployed cohorts; the total number of deaths amounted to 96, 42 in the Deployed cohort and 54 in the Non-deployed cohort.

- Over the full follow-up period, there was no significant difference in the rate of suicide between the two groups (nine events in each group). While the suicide rate in the first half (1991-1995) of the follow-up period was higher among the Deployed group, this was compensated by a lower rate in the latter half (1996-1999) of the follow-up period. Due to the small number of events, this finding was not statistically significant and could be due to chance.

- There was a statistically significant increased risk of death from airspace crashes in the Deployed group. This result may be explained by the fact that there were three times as many members in flying occupations, such as pilots, navigators, flight engineers, in the Deployed cohort as there were in the Non-deployed cohort.

- In contrast to the US and UK studies, during the early and full follow-up periods, there was no increased risk of death due to motor vehicle crashes in the Deployed cohort compared to the Non-deployed cohort.

Mortality: Canadian Forces compared with the general population

- For both the Deployed and the Non-deployed cohort, there was a statistically significant lower risk of death from all causes of about 50% compared to the general population.

- For each study group, the risk of dying from coronary heart was not different from the risk for the general population.

- The overall risk of suicide in each cohort was not different from the risk for the general population.

- The death rate from airspace crashes was higher in the Deployed cohort. These differences are likely due to a higher number of individuals in flying-related occupations relative to the general population, as well as the higher risk associated with military aviation activities.

Cancer comparisons

- There was no significant difference in the risk of being diagnosed with cancer in the two military cohorts. In total, there were 71 cancer cases, 29 in the Deployed cohort and 42 in the Non-deployed cohort.

- The rate of cancer in both the Deployed and Non-deployed cohorts was not significantly different from the rate in the general population.

The lack of observed differences between the two cohorts, in some cases, may be related to the small number of events. A longer follow-up may permit the examination of long-term outcomes such as cause-specific mortality and cancer incidence provided there is sufficient time for the accumulation of events.

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Introduction

The Gulf and Kuwait War of 1990-91 officially began with the invasion of Kuwait by Iraq on August 2, 1990. This event was the culmination of increasing tension in the region over a period of several months. The initial response of the international community to the invasion was the establishment of a naval blockade to which Canada contributed three vessels which were committed on August 24, 1990. The crisis culminated with an armed conflict during the months of January and February 1991. This conflict largely involved aerial bombardment. There was limited involvement of infantry or ground forces. At the end of the conflict, the Iraqi military ignited over 600 oil well fires which required months to extinguish and which produced extensive local air pollution.

Upon the return of the deployed military personnel to their host countries, concern gradually developed about potential after-effects of the war on their health. In 1997, the Department of National Defence (DND) commissioned a survey on the health status of Canadian Gulf and Kuwait War veterans (Gilroy, 1998). This survey was conducted by Goss Gilroy Inc. According to the 1998 GG report, which was based on data from the survey, approximately 4,600 Canadian Forces members served in the Gulf and Kuwait War with only 2,200 being present in the Gulf during the time of the actual conflict, January and February 1991. The two largest CF contingents participated in the Naval Blockade and in the Air War segment. The latter involved a combination of air support for the naval blockade, fighter escort of bombers and bombing missions. In addition, Canadians operated a field hospital about 80 km south of the Iraqi border. After the conflict ended, Canadians were also involved in various post-war peace-keeping and clean-up operations, particularly in the Kurdish area of Iraq and with managing the Kurdish refugee problem in Southern Turkey and Northern Iraq. There were no reports of involvement by members of the Canadian military with any of the ground forces or with extinguishing the oil well fires with the exception of 52 Canadians who served with Coalitions units. Some of these Canadians were reported to have been involved in combat.

A master list of approximately 4,600 CF members deployed to the Gulf and Kuwait War of 1990/91 and 6,223 controls not deployed but eligible to be was compiled for the GG survey from Department of National Defence (DND) records. A self-completed questionnaire which focused on a range of health conditions was mailed to 4,262 Gulf and Kuwait War veterans and 5,699 controls and responses were received from 3,113 Gulf and Kuwait War veterans and 3,439 controls. Results from the survey indicated that, when compared to the active CF members who were not deployed to the Gulf, Gulf and Kuwait War veterans had a higher prevalence of self-reported health problems including diseases of bones and joints, digestive system, skin, and respiratory system. They also had a higher prevalence of chronic fatigue symptoms, cognitive dysfunction, major depression, Post Traumatic Stress Disorder (PTSD), anxiety and fibromyalgia. These self-reported illnesses were also found among Gulf War veterans from the UK and the US and were witnessed in veterans from World War 1, World War II (Hyams, Wignall, & Roswell, 1996) and the Vietnam War (Tegan, Boehmer, Flanders et al., 2004).

It has been documented since at least the time of the American Civil War in the 1860's that military personnel returning from a combat zone are at higher risk of death due to accidental causes, particularly in the first five-years upon their return home (Hyams, Wignall & Roswell, 1996;). It is generally believed that this reflects a psychological process rather than specific physical exposures. One theory postulates that military personnel become immune or desensitised to the signals of a high-risk situation and thus unintentionally engage in high-risk behaviour which leads to increased mortality. A second theory suggests that military personnel effectively become addicted to the high from being in high risk situations and crave that same effect upon their return home. Other psychological problems, such as flash-backs and similar events widely discussed following the Vietnam War, may contribute as well. Military personnel might be more likely to engage in risky exposure to toxic chemicals or negative health-related behaviours such as abuse of alcohol, drug use and smoking. It has been documented that Canadian military personnel with multiple deployments were much more likely to have symptoms of PTSD (Statistics Canada, 2003). PTSD was 2.8 times more common in members who had served on 3 or more deployments (4.7%) compared to those who had never been deployed (1.7%). Members with 1 or 2 deployments had an intermediate prevalence (2.7%). No difference in depression prevalence among the various deployment groups was found.

Much attention has focussed on a set of diffuse symptoms or illnesses that are sometimes referred to as the Gulf War Syndrome. These illnesses, which are not unique to military personnel who have served in the Persian Gulf or elsewhere as they have been diagnosed in civilian as well, involve a range of physical, neurological and psychological effects that cannot be linked to an identifiable cause. Some groups have expressed concern that these symptoms among Gulf and Kuwait War veterans might stem from exposure to various agents including chemical or biological weapons from Iraq, uncommon immunizations (e.g. Anthrax), depleted uranium (from spent munitions) or prophylactic drugs (such as pyridostigmine bromide) designed to counter the potential effects of exposure to chemical weapons. Extensive research on this syndrome has been completed and has been the subject of large-scale formal government enquiries. The present report does not contain an examination of this syndrome but focuses on mortality and cancer incidence as health outcomes.

In addition to concerns about the Gulf War Syndrome, there were also concerns that the various exposures associated with the Gulf and Kuwait War, either from chemical warfare agents or more routine exposures such as solvents, might have led to other illnesses (e.g. cancer) or to increased mortality. In particular, concerns were expressed about potentially increased rates of cancer, birth defects, accidental death and overall mortality.

According to the GG report (1998), Canadian Forces personnel had very limited opportunities for exposure to the most putative risks such as depleted uranium, oil well smoke, Chemical Agent Resistant Compound (CARC), paint and organo-phosphate pesticides. This conclusion is based on deployment patterns for the Canadian military personnel. However, some military personnel would have been exposed to a variety of immunizations (e.g. plague, anthrax), anti-malarial prophylaxis, and pyridostigmine. Plague vaccine was given to all persons at the field hospital, the second crew of the HMCS Protecteur and some aircrew who were present in the Gulf for long periods. The administration of anthrax was restricted to the field hospital staff. Chloroquine was given only to the Naval Task group during their passage through the Suez Canal and pridostigmine bromide was administered to about 85% of CF members in the Persian Gulf, but not to the first crew of the Protecteur. Exposure to biological and chemical warfare agents is uncertain but some military personnel may have had low-level exposure. The types of agents and their sources to which the Canadian military personnel may have been exposed are listed in Table 01.

Table 01. Potential exposures of CF military personnel and their sources
Smoke and Combustion Products
- Oil well fires - Heaters/generators - Burning of trash, diesel or other fuels
Solvents/Petrochemicals
- Fuel fumes or fuel on skin - Paints or Solvents - Contaminated food or water
Pesticides Chemical warfare agents Infectious disease agents (e.g. contact with dead animals) Psychological stressors Physical trauma Radiation (including depleted uranium exposure) Lead Non-routine immunizations Pyridostigmine
Source: Gilroy, 1998

In 1999, upon completion of the GG study, the Gulf and Kuwait War Illness Advisory Committee[1] commissioned a report (Birkett, 2000) to explore the feasibility of undertaking a record linkage study that would provide information on the health of Canadians Forces members who had been deployed to the Persian Gulf. The Committee proposed the study of two categories of health effects: mortality and cancer incidence. It was concluded, in the feasibility report, that a follow-up study using a record-linkage methodology was feasible and warranted. The number of events which would be expected during the follow-up would be small due to the young age of the deployed military personnel, the relatively small size of the cohort and the short follow-up time. However, the importance of detecting adverse health effects justified proceeding with the study. The feasibility report contained two recommended study designs to be carried out on data obtained from a computer-based record linkage to the Canadian Mortality and Canadian Cancer databases. The two designs were:

1. A historical cohort study comparing mortality and cancer incidence rates between deployed military personnel and members of the military in 1990/91 who were not deployed to the Persian Gulf;
2. A comparison of mortality and incidence rates between each military cohort and the general Canadian population.

The 2000 feasibility report recommended, as well, that individual level information be obtained about exposures to factors of interest (e.g. depleted uranium, solvents), confounders (e.g. smoking status), medical history and work experience post-1991. This personal information was not available for the linkage. The most readily available source for such information, the GG survey (Gilroy, 1998) could not be used since the letter of invitation from the Surgeon General to potential GG participants stated that it would not be possible to link participants to their survey responses and that all identifying information would be destroyed by the consultant after a six-month period. In addition, it was not feasible to re-interview the military personnel to obtain exposure information since many of them had left the CF and would be very difficult to find.

A follow-up report was prepared (Birkett & Brodksy, 2001) containing the detailed methodology which could be used to complete the two studies proposed in the initial report. This proposal was accepted by the Canadian Gulf War Veterans Cohort Study Advisory Committee. It formed the basis for the present report on the Canadian Gulf and Kuwait War veterans cohort study.

The current report presents the results of the analyses as proposed (Birkett & Brodksy, 2001). A nine year computerized record linkage identified deaths and new cases of cancer. The deployed veterans were compared to a matched group of CF members eligible for deployment but who were not sent overseas. In addition, the study reports on a comparison of the mortality and cancer incidence in the two cohorts to that of the general Canadian population. As well, the results of the Canadian study are compared to those of other countries, mainly the United States (US) and the United Kingdom (UK).

Previous studies from other countries on the health of veterans of the Gulf and Kuwait War of 1990/91

This section primarily focuses on published studies on the mortality and cancer incidence of veterans from the Gulf and Kuwait War of 1990/91. They are from the US, the UK and Australia. The section also examines hospitalization and other health outcomes in published reports from these countries.

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[1]This Advisory Committee included representatives from Veterans Affairs Canada, Defense and Civil Institute of Environmental Medicine (DND), Defense Medical Services in the United Kingdom, the Department of Veterans Affairs in the United States, Health Canada, Canadian Forces Medical Group and medical experts from the University of Alberta, Faculty of Medicine, the Ottawa General Hospital and the Royal Ottawa Hospital.

The US has produced three reports that have examined mortality in the 695,516 US military personnel who were deployed to the Persian Gulf in 1990/91. The initial report looked at mortality within a year of the initial deployment and included the period of active hostilities (Writer, DeFraites & Brundage, 1996). A follow-up report explored the 2-year mortality in that group and compared it to the mortality of 746,248 veterans selected as a comparison cohort (Kang & Bullman, 1996). The third report examined the 7-year mortality in the two cohorts of the previous study (Kang & Bullman, 2001). In addition to studies on mortality and cancer, hospitalization patterns in the first two years after the end of the war have been examined in the deployed cohort (Cherry, Creed, Silman, et al., 2001a). Finally, a report on the risk of testicular cancer in servicemen from the US in the five-years following the end of the Persian Gulf War (Knoke, Gray & Garland, 1998) and a case-study of a veteran with multiple giant cell tumours of the hand (Cannova, 1998) have been published.

The UK has published a study on the eight-year mortality (Macfarlane, Thomas, Cherry, 2000) and cancer incidence (Macfarlane et al., 2003) of 53,462 UK Gulf War veterans and 53,450 members of a comparison cohort. 'Ill health' was also studied in the UK cohort (Cherry et al., 2001a; Cherry, Creed, Silman, et al., 2001b; Hotopf, David, Hull, et al., 2003).

A report was prepared for the Australian government (Sim, Abramson, Forbes, et al., 2003). It examined mortality and cancer incidence in 1,833 deployed military personnel and 2,847 members of a comparison cohort. 'Ill health' was also studied in the Australian cohort (Sim et al., 2003).

The US Mortality studies

The US mortality study, operational mortality risks

Writer, DeFraotes & Brundage (1996) published a paper that examined mortality in a one-year period between August 1, 1990 and July 31, 1991. This period includes the time of the active conflict (roughly August 1990 to March, 1991). The authors compared total mortality and cause-specific mortality rates of military personnel deployed to the Persian Gulf to the mortality rates of military personnel not posted to that area. Battle related deaths were excluded from the comparison.

Overall, military personnel deployed to the Persian Gulf had an 11% higher mortality rate for non-battle related deaths (Standardized Mortality Ratio (SMR=111, 95% C.I. = 96.5, 125.5). Most of this non-statistically significant excess was due to injury-related deaths, with 'deaths due to unintentional injury' being 54% higher in military personnel deployed to the Persian Gulf (SMR=154, 95% C.I. = 132, 177). There was no difference in non-injury related deaths.

The US veterans cohort mortality study, the 2-year follow-up results

In this study, the US cohort included all military personnel who had served in the Desert Storm campaign (n=695,516), and a US military-based comparison group (n=746,291) including a large number of reserve and National Guard members who were deployed to other theatres of operation (Kang & Bullman, 1996). These groups were compared using Cox proportional hazards modelling. A second comparison was made to the total US population using SMR methods, adjusting for age, sex, race and year of death. The primary outcome was cause-specific mortality between 1991 and Sept. 30, 1993 (approximately two years of follow-up). Information on mortality was obtained from death certificates. Male military personnel deployed to the Persian Gulf had slightly higher all cause mortality than non-deployed military personnel (RR=1.09, 95% C.I. = 1.01, 1.16). There was higher mortality from 'external causes' (RR=1.17, 95% C.I. = 1.08, 1.27) with most of the excess mortality attributable to accidental deaths, including motor vehicle accidents. In contrast, disease-related mortality was similar in the two cohorts (RR=0.88; 95% C.I. = 0.77, 1.02). As well, rates of all cancers mortality were similar (RR=0.83; 95% C.I. = 0.66, 1.05). Deaths due to infectious diseases were significantly lower in the deployed veterans (RR=0.21; 95% C.I. = 0.11, 0.43). The results were generally similar for women military personnel although the point estimates for each of the cause-specific mortality rates tended to be higher in women. Compared to the overall US population, both the deployed and non-deployed veterans had all-cause mortality rates that were under 50% of what was

expected. However, for women Gulf War veterans, accidental death was comparable to the rate found in the general population.

Bell, Amoroso, Wegman & Senier (2001) offered several explanations for the higher mortality from injury which had been observed in the US cohort deployed to the Gulf. The development of depression, post-traumatic stress disorder or other anxiety disorders may be a contributing factor. Physical and psychological trauma experienced during the war may foster the adoption of high risk coping strategies (e.g. heavy drinking) after returning home. An indirect consequence of ill-defined diseases and symptoms reported by returning veterans, poor survivability to crashes, leading to mortality rather than morbidity and selection bias in identifying the deployed cohort (e.g. risk takers may be more likely to be selected for deployment) were also suggested as possible explanations for the phenomenon.

The major limitation of this study is the short follow-up time. A study with a 2-year follow-up should be able to detect short-term causes of mortality such as infectious diseases, respiratory disease due to exposure to chemical toxins and accidental deaths. However, it would be unable to detect mortality from diseases with a long natural history such as cancer and cardiovascular disease. In this study, a lack of information on potential confounder variables such as smoking is another limitation, especially if the confounder might be expected to differ according to exposure to a highly stressful environment.

The comparability of the two cohorts may be limited in some aspects. It was suggested that the comparison cohort might have suffered from the healthy warrior effect (Haley, 1998) although a subsequent paper (Kang & Bullman, 1998) suggests that this bias would not be large. However, an article on the hospitalization experience of Gulf War veterans (Gray, Coate, Anderson, et al., 1996) indicated that the healthy warrior hypothesis might have some validity. In the eighteen months prior to deployment, the veterans in the deployed cohort had significantly lower hospitalization rate than the non-deployed cohort (Campion, 1996).

The US veterans cohort mortality study, the 7-year follow-up results

This study reports on a 7-year follow-up of the cohorts established for the 2-year mortality study (Kang & Bullman, 2001). It also examined the potential impact of exposure to nerve gas at Khamisiyah, Iraq. The methods and objectives were essentially the same as those of the 2-year follow-up. Overall mortality in the deployed cohort was similar to the mortality in the comparison cohort (MRR=0.95 (95% C.I. = 0.92, 0.99) in men and 1.16 ((95% C.I. = 0.97, 1.38) in women). Mortality from natural causes was lower in men of the deployed cohort (MRR=0.83, 95% C.I. = 0.78, 0.89) and similar between women of the two cohorts (MRR=1.02, 95% C.I. = 0.79, 1.33). In contrast, mortality from external causes was similar between men of the two cohorts (MRR=1.04, 95% C.I. = 0.99, 1.10) but was significantly higher for women (MRR=1.39, 95% C.I. = 1.08, 1.80). The lower mortality from natural causes in men appeared to be related mainly to a markedly lower mortality from HIV (MRR=0.21, 95% C.I. = 0.15, 0.30). The higher mortality from external causes in women in the deployed cohort was mainly related to higher mortality from motor vehicle accidents (MRR=1.63, 95% C.I. = 1.09, 2.45). No excess mortality from suicide was noted in the deployed cohort (MRR=0.92, 95% C.I. = 0.83, 1.02 in men and 1.29, 95% C.I. = 0.78, 2.31 in women). The study did not report separately on the mortality from air/space crashes.

There was no excess mortality found for military personnel potentially exposed to nerve gas. All mortality rates in the deployed cohort were well below the rates in the general US population, with SMRs around 0.50.

The study also examined trends in mortality within four time frames following return from the Gulf. It had been previously noted that mortality from motor vehicle accidents was elevated in the deployed cohort (Kang & Bullman, 1996). This effect was noted in the first two time frames (entry to December 31, 1992 and January1, 1993 to August 31, 1994). However, in the last two time windows (September 1, 1994 to April 3, 1996 and May 1, 1996 to December 31, 1997), the excess mortality was no longer present. The MRRs displayed a linear trend over the four follow-up time frames. There was some suggestion that HIV mortality in the deployed cohort had increased in the most recent time window. However, the MRR was still low (MRR=0.34; 95% CI: 0.20, 0.57). This raised the issue of a possible selection bias in the identification of military personnel to be deployed to the Gulf.

The US hospitalization study

This study on hospitalization (Gray et al., 1996) was a companion study to the mortality study described above. It compared rates of hospitalization occurring between January 1, 1992 and September 30, 1993 to those in the period prior to the Gulf War. Only hospitalizations within the military health care system were captured. No differences were found between the deployed and non-deployed veterans.

The UK Gulf War veterans cohort study

The UK veterans cohort mortality study

The UK mortality study (Macfarlane, Thomas & Cherry, 2000) followed a cohort of 53,462 UK Gulf War veterans for eight years, from April 1, 1991 to March 31, 1999. The underlying cause of death was obtained from death certificates using a record-linkage methodology. A comparison group of the same size was formed from the military personnel not posted to the Gulf and was matched on age, sex, service and rank. For most of the Gulf War cohort, the control group was also matched on their level of fitness for service in an attempt to control for a potential healthy warrior effect. There were 395 deaths in the Gulf cohort and 378 deaths in the comparison cohort giving a relative risk (RR) of 1.05 (95% C.I. = 0.91, 1.21). Although the estimates were unadjusted as they were in the US study, the use of matching renders the estimates comparable. Mortality from external causes and mortality from diseases were not statistically different between the two cohorts (RR = 1.18; 95% C.I. = 0.98, 1.42 and RR = 0.87; 95% C.I. = 0.67, 1.11, respectively). However, the authors report an excess of deaths form external causes principally due to higher mortality rates from accidents despite the lack of statistical significance. As well, the UK study observed no excess cancer mortality (RR = 1.11, 95% C.I. = 0.73, 1.67). This study did not report on mortality within specific time windows during the follow-up.

The UK veterans cohort cancer incidence study

The UK Gulf War veteran cohorts were examined for cancer incidence between April 1, 1991 and July 31, 2002 (Macfarlane et al., 2003). The cohorts for this analysis were the ones that had been used in their mortality study (Macfarlane, Thomas & Cherry, 2000). A record linkage approach was used to identify cancers listed in the National Health System (NHS) central registry. Cox proportional hazards methods were used to estimate incidence rate ratios. The analysis was conducted separately for the first six years and the last five-years of follow-up. A total of 270 incident cancers were identified in the deployed cohort for a crude incidence rate of about 5.1 per 10,000, and 269 cases in the non-deployed cohort for a crude incidence rate of about 5.2/10,000. No evidence of a higher overall or specific cancer incidence in the deployed cohort was found (IRR=0.99 for all cancers). Information about lifestyle cancer risk factors was available on a sub-set of the cohorts. Including this information in the analysis did not change the results. There was no increased risk in veterans exposed while in the Gulf to a range of putative risk factors. Finally, the incidence rate ratios were similar in the early and late follow-up periods.

The UK veterans cohort ill health study #1

Cherry et al., (2001a; 2001b) examined two randomly chosen groups of veterans from the deployed and non-deployed cohorts identified for the mortality and cancer follow-up studies (Macfarlane et al., 2003; Sim et al., 2003). They found evidence of a higher prevalence of a variety of self-reported symptoms in the deployed cohort. There was also evidence of a greater concern about ill health in the deployed veterans. However, there were no clear associations between symptoms and specific exposures in the Gulf. Handling pesticides and the number of vaccinations received were suggested as factors associated with a worse health state but these observations were preliminary.

The UK veterans cohort ill health study #2

A longitudinal follow-up of about 8,000 veterans who were either deployed to the Gulf, to Bosnia or formed a comparison group has been done (Hotopf et al, 2003). The initial survey was done in 1997 and a follow-up was conducted in 2001. Self-completed standardized scales to estimate

fatigue, psychological distress, health perception and related issues were the main focus of the follow-up.

Gulf War veterans displayed more self-reported fatigue, higher levels of psychological distress and worse physical functioning than the non-deployed comparison group. Improvement in the Gulf War veterans on many of the scales between the initial examination and the follow-up (four years later) were noted but the degree of improvement was relatively minor. Physical functioning declined slightly between the two interview dates. The group of military personnel who were deployed to Bosnia also displayed a reduction in their physical functioning between the two interview dates.

The Australian Gulf War veterans cohort study

The Australian study (Sim et al., 2002) was much smaller than the US and UK studies, including only 1,833 deployed military personnel. The only publication of the results that could be found was a very large report to the Australian Minister of Veterans Affairs. This report is available from a web site maintained by Morash University, the contractors who produced the report. As with the US and UK studies, a record-linkage methodology was used to identify deaths and incident cases of cancer in the deployed and comparison cohorts.

Due to the small sample size, the number of events identified was low (43 deaths and 19 cancers) and no differences in mortality (MRR=1.4, 95% C.I. = 0.8, 2.7), in disease-related mortality (MRR=2.2, 95% C.I. = 0.8, 5.6) or mortality due to external causes (MRR=1.1, 95% C.I. = 0.5, 2.9) were found between the deployed and comparison cohorts. As expected, the 95% confidence intervals were wide. As well, the authors noted no statistically significant increase in cancer risk (IDR=1.5, 95% C.I. = 0.6, 3.9).

Other studies

The US testicular cancer incidence study

Testicular cancer is a cancer that more commonly affects young men. As such, it is a relevant cancer to consider in the Persian Gulf War cohort. Knoke, Gray & Garland, (1998) studied US regular, active-duty servicemen who had been deployed to the Persian Gulf in 1990/91. The method of obtaining the cancer information is not specified in the abstract. Cancer cases were detected between August, 1991 and March 31, 1996. Analysis was done using Cox proportional hazards regression.

This study reported no evidence of an increased rate of cancer in the deployed military personnel (RR=1.05, 95% C.I. = 0.86, 1.29). Military personnel engaged in electronic equipment repair (RR=1.56, 95% C.I. = 1.23, 2.00) and electrical/mechanical repair (RR=1.26, 95% C.I. = 1.01, 1.58) showed higher risk irrespective of their deployment status. There was an increased incidence (C.I. = 2.12, 95% C.I. = 1.11, 4.02) in deployed military personnel in the last five months of 1991, which would be immediately after return to the US following the end of the Gulf War. This likely reflects delayed diagnosis during deployment and perhaps is a sign of the healthy warrior effect (Haley, 1998). The very short time lag between the war and the diagnosis makes it very unlikely that the cancers were etiologically related to exposures occurring during the war. The rates were not different for the four years following the initial five months after the end of the Gulf and Kuwait War 1990/91.

Miscellaneous Studies

Cannova (1998) presents a case report of a US Gulf War veteran with multiple giant cell tumours of the hand. This patient had previously been diagnosed with Gulf War Syndrome. As noted by Cannova, the significance of this isolated case report is unclear.

Summary

The published literature based on two large Gulf War veteran cohorts is consistent. Only a small increase in mortality was observed, mostly due to an increase in accidental deaths. Mortality due to disease appears to be lower in the deployed than in non-deployed cohort. This might reflect a healthy warrior effect. However, there is little evidence to support a major increase in mortality as

a consequence of deployment to the Persian Gulf and participation in the Gulf and Kuwait War. The only study of cancer incidence failed to detect any increased risk in military personnel deployed to the Persian Gulf area.

Objective of the present study

The main objective of this study was to determine if military personnel deployed to the Persian Gulf between August 24, 1990 and September 30, 1991 were at a higher risk of death or of developing cancer after their return to Canada than either other members of the military who were not deployed to the Persian Gulf or the general Canadian public.

The specific research questions to be addressed when deployed and non-deployed military personnel were compared are:

1) Were deployed military personnel more likely to die after the end of hostilities?
2) Does the pattern of cause-specific mortality differ between the two cohorts?
3) Were deployed military personnel more likely to develop cancer after the end of hostilities?
4) Does the pattern of topography-specific cancer incidence differ between the two cohorts?

The specific research questions to be addressed when deployed and non-deployed military personnel and members of the general Canadian population were compared are:

5) Were military personnel more likely to die after the end of the hostilities than the Canadian population?
6) Does the pattern of cause-specific mortality differ between each cohort and the Canadian population?
7) Were military personnel more likely to develop cancer after the end of hostilities?
8) Does the pattern of topography-specific cancer incidence differ between each cohort and the Canadian population?

The comparisons were age and sex adjusted.

Methods

Two cohorts of Canadian Force members were defined. The Deployed cohort consisted of all CF members deployed to the Gulf and Kuwait War of 1990/91. The Non-deployed cohort was a random selection of CF members who were eligible for this deployment but who were not deployed. The mortality and cancer incidence experience of cohorts were determined using record linkage to the Canadian Mortality Database and the Canadian Cancer Database respectively. At the time of the record linkage procedure, national mortality and cancer data were available until December 31, 1999 permitting a nine-year follow-up period. Mortality rates and cancer incidence rates were computed and compared using direct standardization. Kaplan-Meier and Cox regression methods were also used to compare mortality and incidence rates. For mortality, the first half and the second half of the follow-up were analysed separately. A second comparison of mortality and cancer incidence was performed between each cohort and the general Canadian population.

In an earlier feasibility study (Birkett, 2001), it was estimated that the cohort would have 101,000 person-years of follow-up, 97 deaths and 80 incident cancer cases over a ten-year period. In terms of power, the study had an 80% power to detect around a 60% increase in overall mortality (RR=1.63) or a 75% increase in overall cancer incidence (RR=1.75). The lower power for cancer outcomes reflects the shorter follow-up available of 7 years instead of 9 years. In the actual study reported here, the follow-up period was nine years and the number of person-years was 97,557.78. There were 96 deaths leading to a mortality rate of 9.9/10,000 PYs or a 9-year crude mortality risk of 8.56/1,000 compared to the 10-year risk of 8.6/1,000. The number of actual incident cancer cases was 71. The crude cancer incidence density was 7.4/10,000 PYs or a probability of cancer during the follow-up period of 6.33/1,000 compared to the estimate of 7.5/1,000.

The study cohorts

The final deployed cohort

The final Deployed cohort is based on the master cohort list compiled for DND and Statistics Canada by Goss Gilroy and Associates (1998). The list was extended and modified by Statistics Canada and DND to include an additional 511Gulf and Kuwait War veterans identified through other sources of cohort identification such as medals lists. The modification applied to the master cohort list also ensured that people who had died between the reference date and the time of the GG survey were included in the cohort. As well, the cohort was expanded to include 129 members who had originally been assigned to the comparison cohort and members of the Canadian military who had been deployed with the UN or other militaries (Appendix C). The final Deployed cohort comprised a total of 5117 members. Of those, only about 2,200 were present in the Persian Gulf during the period of actual fighting according to the GG survey.

The non-deployed cohort

The comparison (non-deployed) cohort was also based on the master cohort list compiled by Goss Gilroy and Associates for the 1998 survey. Members of the comparison cohort were randomly selected from members of the Canadian Forces who were eligible for deployment to the Persian Gulf but who were never deployed between August 24, 1990 and October 1, 1991. Eligibility for deployment was dependent on a medical code that varied across occupations and a medical pre-screening process. Some persons considered deployable according to their medical category may not have been deployed following the pre-deployment screening process. This means that although the intent was to match groups according to fitness for deployment, there may have been some selection of healthy personnel in the Gulf and Kuwait War veteran cohort. The final cohort included 6,093 military personnel and was frequency matched on sex, age and military duty status (Regular versus Reserve Force) with the deployed cohort. Members of the comparison cohort may have been deployed to the Gulf or other operations at a later time. Additional information on the study cohorts is presented in Appendix A.

Definitions

The following definitions were used throughout this report.

The term *active stations* refers to locations within the Persian Gulf to which military personnel could have been posted. These include naval ships involved in the blockade of Iraq, air force sites which provided air support for the blockade and/or for the bombing of land targets, military hospitals and similar support stations, including those used to give assistance with the Kurdish refugee problem.

The *deployed cohort* is composed of members of the Canadian military who were posted to an active station in the Persian Gulf area between August 24, 1990 and October 1, 1991. This cohort was comprised of all CF members who met the eligibility criteria.

The *non-deployed cohort* is made up of a random sample of people who belonged to the Canadian military between August 24, 1990 and October 1, 1991, who were eligible for posting to active stations in the Persian Gulf but who were not posted to any of them at any time during the period.

The *final deployed cohort* refers to the cohort of military personnel identified as 'deployed' following adjustment through comparison of the Master List to alternative sources of information (Appendix C). This is the list that is used in all analyses.

The *final non-deployed cohort* is composed of the cohort of military personnel identified as 'non-deployed' following adjustment through comparison of the Master List to alternative sources of information (Appendix C). This is the list that is used in all analyses.

The *primary reference date* selected was April 1, 1991, the same reference date used by the UK mortality follow-up study (Macfarlane, Thomas & Cherry, 2000). This date has been chosen as the starting date for mortality follow-up for most members of the cohorts since it excluded deaths occurring during active service in the Gulf and Kuwait War. Time measurements also used this reference date.

The *secondary reference date* selected was October 1, 1991. The original information provided about the deployed cohort indicated that it was appropriate to establish a single reference date for follow-up. However, it was subsequently discovered that some military personnel had been deployed to the various Persian Gulf operations such as Camp Doha or Unikom after April 1, 1991. While the number of subjects involved in these deployments was relatively small, it was not possible to include them in the cohort using a follow-up start date of April 1, 1991, since their follow-up would have begun before their actual deployment. Hence, for these subjects, it was decided to establish the secondary reference date of October 1, 1991. CF members deployed after that date were ineligible for inclusion in the study. Due to the small size of the group deployed after April 1, 1991, separate analyses were not possible.

The *final reference date* refers to the primary or secondary reference date, as appropriate for the cohort member.

The cancer reference date is an arbitrary date and occurs two years after the final reference date. The two-year lag time was chosen as the starting date for cancer incidence follow-up since it allowed for a minimally acceptable length of time between exposure during deployment and the development of cancer.

The *termination date* is the last day of follow-up for a subject. For the mortality outcome, it is the date of death or December 31, 1999, the last day contained in the linkage file whichever occurred first. For cancer incidence, it is either the date of a first diagnosis of cancer, the date of death for subjects who died without a diagnosis of cancer or December 31 1999, the last day contained in the linkage file.

The *early follow-up period* is the time between the final reference date and December 31, 1995. This period was chosen to divide the follow-up into approximately two equal intervals. The early follow-up period is particularly relevant for adverse outcomes requiring a short time to develop such as stress-induced conditions.

The *late follow-up period* is the time between January 1, 1996 and the termination date. The late follow-up period is particularly relevant for adverse events requiring a longer time to develop such as cancer.

General population comparison group

Mortality rates

The mortality experience of the cohorts was compared to that of the general Canadian population. The number of deaths within age-sex specific groups was taken from the annual Statistics Canada publication series, Cause of Death - Shelf Table. These books include the number of deaths in the given year, by 3 and 4 digit ICD-9 chapters and sub-chapters within age and sex groupings. This publication also includes the estimated population distribution for Canada in that year. These are produced using an inter-censal extrapolation process.

Indirect standardization methods (Rothman & Greenland, 1998) were used to produce a Standardized Mortality Rate (SMR), adjusted for age, sex and year of death. Rates were produced for both the final deployed cohort and final comparison cohort. SMRs are intended to compare a single population (cohort) to the general Canadian population. They cannot be used to compare directly the mortality rates of the two cohorts when the cohorts are different with respect to demographic characteristics. However when the cohorts are matched, the ratio of the two SMRs can serve as an approximation of the relative risk (Gaffey, 1976; Cook, 1979). Because frequency matching was relied on in this study, it is more prudent to use standardized rates to compare the two cohorts.

Cancer incidence rates

The cancer incidence experience of the cohorts was compared to that of the general Canadian population. Only initial primary malignant tumours were included in the analysis. Due to the small number of cancers that were observed, the general population comparison was restricted to a single comparison of all cancers combined.

The period covered was 1992 to 1999. Indirect standardization methods ((Rothman & Greenland, 1998) were used to calculate a Standardized Incidence Rate (SIR), adjusted for age, sex and year of death. SIRs are similar to SMRs in that they are used to compare a cohort to the general population and, despite matching, should not be relied upon to compare directly the cancer incidence of two cohorts.

Outcomes

Four categories of outcomes were examined: total mortality, cause-specific mortality, overall cancer incidence excluding non-melanoma skin cancer and specific topography groupings for cancer incidence. Given the small number of events, there were limited opportunities to explore specific outcomes within these categories. Events had to be collapsed into larger groupings.

Death registration is mandatory in Canada. The registration systems are comprehensive. Since registration is required to complete processing of wills and for other legal reasons, completeness of coverage is excellent.

Cancer registration is performed by all provinces and territories in Canada using a passive system designed to identify all cancer cases. Coverage is estimated at over 98%. While most cases are registered within a few months of diagnosis, some are delayed and the provinces forward the registration files to Statistics Canada only when registration is completed. The delay can stretch to 3 years. To allow for registration of deaths and cancer to be completed, the termination date chosen was December 31, 1999.

In the presentation of the results, empty cells and cells less than 3 along with adjacent cells for which information could be deduced were suppressed or combined with other categories. This approach simplifies the information presented, enhances the reliability of the information, and ensures the confidentiality of the cohort members.

Determination of outcome status

Mortality

To determine vital status and cause of death, probabilistic record linkage techniques (Appendix B) were used to link the Gulf War final Deployed and Non-deployed cohorts to the 1991-1999 Canadian Mortality Data Base (CMDB). Mortality information was linked up to and including December 31, 1999 after the records were matched to the Alive Tax File. This file contains information about the years individuals have filed a tax return, whether there was notification of the death of the filer or whether the filer moved out of the country. Information is available for individuals since 1984.

The pre-match to tax information provides an indication of what to expect during the probabilistic linkage to the Canadian Mortality Data Base (CMDB) and acts as corroborating evidence from an alternate source. Any indication of a death from that information source was flagged on the Gulf War file. The detailed methods for the record linkage are described briefly in Appendix B and are available from Statistics Canada.

During the preparation of the cohort lists and the initial examination of the data file, it became apparent that not all deaths were being identified through the CMDB. The 10 missed deaths were eventually traced to deaths occurring in active personnel, often while based outside Canada. Following this discovery, an examination of DND and other records to ensure complete identification of all deaths was carried out. While it is not possible to be 100% certain that all deaths were identified, the multiple source triangulation process appears to have been successful.

The linkage process created a data file containing one record for each member of the deployed and comparison cohorts. Each record included an identifier to indicate to which cohort the person belonged, the vital status of the veteran at the end of the mortality follow-up period, the time of death (if applicable) and the cause of death. The file also included age, sex, and rank and information about the place of death registration. The file did not contain any names or other identifying information.

Cancer incidence

Incident cases of cancer were identified through a probabilistic record linkage of the cohort lists with the Canadian Cancer Database (CCDB). The detailed methods for the record linkage are available from Statistics Canada. Cancer incidence information was available up to and including December 31, 1999 (Appendix B).

The linkage process yielded a data file containing one record for each member of the cohorts who had been diagnosed with cancer, either before or after deployment. This record included an identifier that indicated to which cohort the person belonged and various numerical codes describing the type of cancer. These codes were a combination of ICD-8, ICD-9, ICD-0-T (Version 1), ICD-0-M(version 1), ICD-0-T (version 2) and ICD-0-M (version 2) codes. In most cases, subjects had more than one type of classification code assigned to their cancer (e.g. ICD-9 and ICD-0-T/-M version 1). The file also contained information on the time and location of the cancer diagnosis, the diagnostic process, and personal information such as age, sex, and rank of the subjects. The file did not contain any names or other identifying information.

Eligibility of outcomes

All deaths occurring between the final reference date and the termination date were eligible for inclusion in the mortality analysis. Persons who died before the final reference date were excluded from the study.

Two different definitions of eligibility were used for cancer incidence. The first definition included all cases of cancer diagnosed between the final reference date and the termination date. The second definition included only cases of cancer diagnosed after the cancer reference date. As noted earlier, the use of a later time for the cancer reference date is justified because cancer occurring within a short interval after deployment can not credibly be linked to exposures during the deployment since the biological process leading to cancer requires at least one to two years following exposure (Rothman & Greenland, 1998).

Subjects were excluded from the cancer incidence study if they are known to have been diagnosed with a malignant cancer prior to the final reference date or the cancer reference date. A person with a pre-existing cancer has a high likelihood of having a different risk profile than someone who was cancer-free at entry in the cohort. In accord with most epidemiological studies of similar design, the focus of the analysis is on the development of an initial cancer.

Outcome coding

Mortality

Due to the small number of deaths, it was not possible to examine cause-specific mortality in depth. Instead, causes of death were combined into disease system and similar groupings. The groupings used in the UK study of mortality in Gulf War veterans were adopted in the present study (Macfarlane, Thomas & Cherry, 2000). These groupings are based on the major Chapters of the ICD-9 with modifications to group E-codes. The groupings are shown in Table 02. Some of the categories used in the UK study have been combined due to the smaller number of deaths in the Canadian cohorts. Despite this, most categories still had only 1 death. Hence, interpretation of the results for most categories was not possible.

Cancer incidence

Due to the small number of expected incident cancer cases, it was not possible to examine cancer-specific incidence rates in depth. Rather, cancer sites were grouped into analytic categories. The primary grouping categories were based on the ICD-9 (Table 03). The analysis also examined incidence rates within a single grouping which combined all malignant cancers except non-melanoma skin cancers, i.e. all of the ICD-9 codes in Table 03.

In order to facilitate analysis, the various cancer codes were converted to a standard coding system. ICD-9 was adopted as the primary coding system. It was chosen since there was a general absence of morphological information for most tumours, even for those that had been coded using ICD-0 and thus should have had such information. The conversion process was done by a computer programme prepared by the International Association for Cancer Registries which assists cancer registries convert between various ICD versions. The programme was applied to all of the classification codes and the final assigned code was manually verified to ensure that there were no unexpected problems. Only tumours that were malignant and non-metastatic were included in the analysis: tumours with ICD-0 ‘behaviour codes’ of 0 (benign), 1 (uncertain behaviour), 2 (in-situ) and 6 (secondary) were excluded from the analysis.

Two subjects reported having been diagnosed with two cancers during the cohort follow-up period. There was one subject with multiple cancers in each cohort. The second and all other cancers were excluded from the analysis due to the small number of such events. The cancer file also included 27 veterans with cancers diagnosed prior to the date of cohort eligibility. They were excluded from the analysis.

Table 02. Mortality outcome: Reporting categories

Cause of Death	ICD-9 Codes
Disease-related causes	001-799
Infectious and parasitic disease	001-139
All cancers	140-208
Benign neoplasms	210-239
Endocrine and immune disorders	240-279
Blood Disorders	280-289
Mental disorders	290-319
Nervous system and sense organs	320-389
Diseases of circulatory system	390-459
Diseases of respiratory system	460-519
Diseases of digestive system	520-579
Other disease-related causes	580-799
All external causes	E800-E999
Motor vehicle accidents	E810-E825
Air and space accidents	E840-E845
Railway, water or other vehicle accidents	E800-807, E826-E838, E846-E848
Accidental poisoning	E850-E869
Accidental falls	E880-E888
Accident due to fire or environmental factors	E890-E909
Accidents due to submersion / suffocation / foreign bodies	E910-915
Other accidents	E916-E929
Suicide	E950-E959
Homicide	E960-E969
Injury undetermined whether accidental	E980-E989
Injury resulting from operations of war	E990-E999

Table 03. Cancer incidence: Reporting categories

Cancer reporting category	ICD-9 Codes
Digestive System	150-159.9
Respiratory system	160-165.9
Melanoma	172-172.9
Female reproductive	174-174.9 179-184.9
Prostate	185
Testicular	186-186.9
Genitourinary system	188-189.9
Brain/CNS	191-192.9
Lymph nodes	196-196.9 200-203.8
Leukemia	204-208.9
Miscellaneous	140-149.9, 170-171.9, 187-187.9,190-190.9, 193-195.8, 199-199.1,

Analyses

The primary analyses involved comparing the two cohorts to each other and to the Canadian population. As originally proposed (Birkett & Brodksy, 2001), one component of the analysis examined differential mortality patterns in the first and the second half of the follow-up. While the proposed approach to the period-specific analyses was to replicate the cohort comparison within the specific time intervals, a time varying covariate approach to Cox modeling was used instead for a more specific comparison of the period differences.

All analyses were performed using SAS 8.0 in a Windows-2000 environment. All computer analyses were performed within a Statistics Canada building using secure computers and secure network links. Prior to analysis, a large number of data management tasks had to be completed. These involved validating the data file, correcting errors and inconsistencies, defining core analytic constructs and assembling the data files in a final analytical file (Appendix C).

No adjustment was made for multiple comparisons. On theoretical grounds, multiple comparisons adjustment is not needed for this type of study. Multiple comparisons methods are used to preserve study-wide type 1 error rates. In the current analysis, a number of a-priori hypotheses were examined. Concerns did not focus on study-wide error rates but rather on the precision of effect estimation. In any event, multiple comparison adjustment would have made no difference to the results. Only one comparison (air crash mortality) was statistically significant and it was based on events that were not independent.

Between Cohort Comparisons

The main objectives of the study were addressed through an internal comparison of the final Deployed cohort and the final Non-deployed cohort for each of the outcome groupings described above when they had a sufficient number of events. Two statistical approaches were used: direct standardization and survival analysis, Kaplan Meier and Cox regression modeling.

Initially, a descriptive inspection of the data was done to identify any apparent temporal or diagnostic groupings. This analysis also provided counts of the number of events and a comparison of the two cohorts on the demographic and other information that was available.

Direct Adjustment

The primary between group comparisons involved computing age-sex adjusted Mortality Rate Ratios (MRRs). Crude mortality rates for both cohorts as well as crude and age-sex standardized MRRs are reported. Age was categorized into five-year age groups. A computerized Lexus diagram approach was utilized to accumulate the years of follow-up for each member of the cohort. Using the final reference date as the starting point, each subject was followed forward in time. Each year, each subject was assigned to the appropriate five-year age stratum. For each person who spent the entire year in a single age stratum, one year was accumulated to that stratum. For each person who changed stratum because of a birthday, the portion of the year prior to their birthday was assigned to the first stratum and the portion of the year after their birthday was accumulated in the next stratum. Person-year accumulation stopped at the date of an outcome if the outcome event occurred or if the subject died for the cancer incidence analysis. Outcome events were assigned to the age-sex stratum to which the subject belonged at the time of the event. The reference population for the direct standardization was the total person-years from both cohorts.

The results include both point estimates and 95% confidence intervals. For the point estimates, the method relied on a normal approximation to the Poisson distribution. For the MRRs, the method used a normal approximation to the natural logarithm of the MRR. The confidence intervals were calculated with a formula provided by Rothman and Greenland (1998).

For the mortality study, three analyses were carried out. The primary analysis involved the entire time period from the final reference date to the termination date. Since other countries have observed differential mortality events between the first few years following deployment and later years, the mortality analysis was also done for two sub-intervals, from the final reference date to December 31, 1995, referred to as early follow-up and from January 1, 1996 to the termination date referred to as late follow-up.

The cancer incidence study comprised two analyses. The first analysis examined events between the cancer reference date and the termination date. The second analysis examined cancer incidence between the final reference date and the termination date. Because of the substantial lag time required between exposure and the development of cancer, cancer incidence in the early follow-up period was not examined.

Survival analysis

The survival analysis was based on the time between the final reference date and the time to event. Survival analyses were only performed for events where there were sufficient subjects. They were total mortality, disease related mortality, death due to external causes and total cancer incidence. Cox modelling provided estimates of the Hazard Ratio (HR) between the two cohorts. In general, these estimates should be approximately the same as the MRRs.

For the mortality study, time to event was defined as the earlier of two events, date of death or termination date (censored observation). For the cancer study, time to event was defined as the earliest of three events, date of the first cancer after the final reference date, date of death (censored observation) or termination date (censored observation).

For purposes of the analysis, all subjects who did not experience the primary event were deemed to have been censored at the termination date or at their death for the cancer incidence study. No subjects were lost to follow-up, so there was no need to include a censoring date for such losses.

Three methods were used for the survival analysis. First, Kaplan-Meier methods were used to produce survival curves. Because of the restricted range of these curves (0.95 to 1.01), they were not included in the present report. Second, the log-rank test was used to make a crude comparison of the two cohorts. However, since the log-rank test is limited in its ability to adjust for potential confounders, stratified log-rank tests were not reported. Third, Cox survival methods were used to perform a multivariate adjusted comparison of the two groups. Where the sample size was large enough, the comparison adjusted for: sex, age (five-year groups at entry), rank at entry and marital status at entry.

Early versus late mortality

Certain causes of death are most likely in the first few years following deployment (Kang and Bullman, 1996). Other causes, such as cancer, will develop over time and, due to the lag time from exposure to disease, any effect of deployment would be expected to be seen many years after deployment. Therefore, a hypothesis was made that mortality rates in the early and late follow-up periods would be different and the analyses were repeated looking at early mortality (within the first four and a half years) and late mortality (within the last four years). A follow-up beyond the nine years of this study will strengthen the results about outcomes with long lag times (e.g. cancer) but it will not change the results of the analysis from the early mortality data (e.g. due to accidental death). Therefore, the latter provides some evidence of the health effects of deployment to the Gulf.

The standardized rates provided an indication of the period differences. However, they did not provide a statistical test of the between period differences in MRR. Cox models were used to test the period effect using a time-dependent covariate approach to model a differential hazard ratio (HR) in the two periods. Essentially, a new variable was added to the Cox model where the new variable was ‘0’ for the early period and the value of the cohort membership for the late period. This enabled the HR to be different in the two periods. This approach yielded slightly different results from the standardized analysis since the reference population used in the standardized analyses (the total population) was different from the one used in the Cox analysis. Given the small number of events, caution must be exercised in interpreting the statistical significance of the results (See Limitations).

Comparison to the general population

Indirect standardization methods were used to produce Standardized Mortality Ratios (SMRs) and Standardized Incidence Ratios (SIRs). They were used to compare mortality and cancer incidence of the two cohorts to the general Canadian population. Military members are generally

healthier than their civilian counterparts because they are pre-screened for disease prior to service entry, can be released upon diagnosis of certain diseases and have an occupational requirement to be physically fit. This phenomenon is akin to what has been referred to as the healthy worker effect. Therefore, it was expected that mortality rates in both cohorts would be lower than the rates in the general population despite variation in the healthy worker effect among different causes of death and different elapsed-time periods of observation. In the US Gulf War veterans mortality study, the SMR for all causes was 0.44 while the SMRs for cause-specific deaths ranged from 0.03 to 0.82 depending on the cause (Kang & Bullman, 1996).

As noted earlier, records of the cause-specific mortality in Canada for age and sex groups for the period 1991 to 1999 were available. The number of deaths was abstracted from these records and entered into a computer file. The intra-censal estimates of the age-sex population counts in Canada for each of these years were added to the file. Using a process similar to the one employed for the direct standardization, the number of events which would have been expected to occur in each cohort if the age-sex-period specific rates in the cohort had been the same as the rates found in the Canadian population were calculated. The ratio of the observed number of events to the expected number gave the SMR (or SIR). A value of 1.0 indicates that the observed mortality in the cohort was the same as that observed in the Canadian population. Values less than 1.0 suggest a lowered mortality in the cohort while values greater than 1.0 suggest a higher than expected mortality in the cohort. In addition to the point estimate, 95% confidence intervals were calculated. Due to the small number of events observed, confidence intervals were based on an exact Poisson method rather than on the more common normal approximation (Rothman & Greenland, 1998).

As mentioned previously, the biggest problem with the comparison to the general population is that all of the SMR or SIRs will be expected to be less than 1.0 due to the healthy worker effect which may differ across mortality causes and across time periods. This was observed in the two year follow-up of the US Gulf War mortality study (Kang & Bullman, 1996).

Ethics review

The ethics review process for this study was complex. The Record Linkage aspects of the study were reviewed by Ethica Clinical Research, an external research board. They granted a final certificate of ethical approval on November 13, 2003. The statistical analysis plan of the study was also reviewed by the Ottawa Hospital Research Ethics Board because the contract person for the study was associated with the University of Ottawa. The Ethics Board provided its final ethics certificate on October 9, 2003.

Exclusions

There were 13 subjects who did not report a sex and 20 subjects with no reported date of birth. Since sex and age are key stratification variables for both the age-standardization and SMR analyses, these subjects could not be included and were removed from all analyses. There were eight subjects who were under age 15 on entry into the cohort. These subjects were enrolled in the cohort based on the Gulf War Medal List. This error was corrected prior to analysis. The data file included mortality information for ten subjects who died in 2000 or 2001. These deaths are outside the follow-up window that ended on Dec. 31, 1999. The vital status of these 10 subjects was recoded to alive. Subjects who died before their assigned entry date into the cohort were excluded from the cohort.

Results

Characteristics of the veterans in the Deployed and Non-deployed cohort

The final study cohorts totalled 11,210 veterans, 5,117 in the Deployed cohort and 6,093 in the Non-deployed cohort (Table 04). The large majority of the veterans overall (94.5%) and in both cohorts were men, 94.8% in the former and 94.2% in the latter. The mean age at entry into each cohort was similar, 30.7 years and 31.1 years respectively. However, despite the efforts at frequency matching, there was a significantly different age distribution in the two cohorts. The Deployed cohort had a higher proportion in the age group 25-29 (33.0% vs. 28.5) and a lower one in the 30-34 year age group (23.7% vs. 28.5%). These differences support the importance of reporting age-adjusted mortality and incidence rates rather than relying on crude rates. The rank distribution of the two cohorts was comparable with 52.0% of the cohorts belonging to the lower non-commissioned member (NCM) ranks. The repartition among marital status category was also similar in the two cohorts, with 72.8% of the cohorts being currently married or living common-law. Most of the remaining subjects (17.2%) had never been married. As well, the average length of follow-up was equivalent in the two groups, 103.0 months and 103.6 months, respectively. This is not surprising since there were no losses to follow-up in either cohort.

Table 04. Demographic characteristics of the veterans by cohort

Characteristics	Total		Deployed Cohort		Non-deployed Cohort	
	N	%	N	%	N	%
Total	11,210	100	5,117	100	6,093	100
Sex						
Male	10,591	94.5	4,850	94.8	5,741	94.2
Female	619	5.5	267	5.2	352	5.8
Age in years at entry						
mean (sd)	30.9(7.3)		30.7 (7.0)		31.1 (7.5)	
range	17-63		18-63		17-62	
Age groups						
15-19	88	0.8	40	0.8	48	0.8
20-24	2,063	18.4	893	17.5	1,170	19.2
25-29	3,425	30.6	1,688	33.0	1,737	28.5
30-34	2,586	23.1	1,213	23.7	1,373	28.5
35-39	1,453	13.0	639	12.5	814	13.4
40-44	1,044	9.3	403	7.9	641	10.5
45-49	386	3.4	181	3.5	205	3.4
50+	165	1.5	60	1.2	105	1.7
[p<0.0001]						
Rank						
NCM, low	5,830	52.0	2,666	52.1	3,164	51.9
NCM, high	3,158	28.2	1,489	29.1	1,669	27.4
Officer, low	1,359	12.1	549	10.7	810	13.3
Officer, high	859	7.7	409	8.0	450	7.4
Missing	4		4		0	
[p=0.0002]						
Marital Status						
Never married	1,892	17.2	894	17.9	998	16.7
Married or common-law	7,993	72.8	3,642	72.8	4,351	72.8
Previously married	1,096	10.0	465	9.3	631	10.5
Missing	229		116		113	
[p=0.12]						
Number of deaths	96		42		54	
Months of follow-up						
mean(sd)			103.0(5.9)		103.6(5.4)	
range			0-104		1-104	

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.
Note. Detail may not add to totals because of rounding.

Mortality

Characteristics of the veterans who died

Selected characteristics of the 96 veterans who died are presented in Table 05. There were 42 deaths in the Deployed cohort and 54 deaths in the Non-deployed cohort. All were men in the former and 94.4% were men in the latter. On average, deceased veterans in the Deployed cohort were significantly younger ($p < .05$) at entry in the cohort than those who were in the Non-deployed cohort, 31.7 and 35.6 respectively, a difference close to 4 years. As expected, the difference was similar when age at the time of death was examined, 35.9 vs. 40.2 years ($p < 0.05$). On average, the timing of the deaths in the Deployed group and the Non-deployed group was comparable at 48.3 and 56.3 months, respectively. As well, there were no differences between the two cohorts when the deceased veterans were compared on military rank and marital status. However, the Deployed cohort had a higher proportion of members involved in flying related occupations compared to the control group, 9.1% and 3.7%, respectively (Table 06)

Table 05. Demographic characteristics of the veterans who died

Characteristics	Total		Deployed Cohort		Non-deployed Cohort	
	N	%	N	%	N	%
Total	96	100	42	100	54	100
Sex						
Male	93	96.9	42	100	51	94.4
Female	3	3.1	0	0	3	5.6
Age in years at entry						
mean (sd)	33.9 (9.1)		31.7 (8.7)		35.6 (9.2)	
range	19-62		19-52		20-62	
[p=0.037 for means]						
Age groups						
15-24	18	17.7	10	23.8	8	14.8
25-29	15	15.6	9	21.4	6	11.1
30-34	18	18.8	7	16.7	11	20.4
35-39	18	18.8	7	16.7	11	20.4
40-44	16	16.7	5	11.9	11	20.4
45+	11	11.5	4	9.5	7	13.0
Rank						
NCM, low	39	40.6	20	47.6	19	35.2
NCM, high	38	39.6	14	33.3	24	44.4
Officer, low & high	19	19.8	8	19.0	11	20.4
[p=0.59]chi-square=1.93 3df						
Marital Status						
Never married	9	17.3	3	15.0	6	18.8
Married or common-law	33	63.5	11	55.0	22	68.8
Previously married	10	19.2	6	30.0	4	12.4
Missing	44		22		22	
Age in years at death						
20-24	8	8.3	4	9.5	4	7.4
25-29	12	12.5	8	19.1	4	7.4
30-34	14	14.6	9	21.4	5	9.3
35-39	23	24.0	7	16.7	16	29.6
40-44	14	14.6	5	11.9	9	16.7
45-49	14	14.6	5	11.9	9	16.7
50+	11	11.4	4	9.6	7	13.0
p=0.030 for means						
Months of follow-up						
mean(sd)	52.8(31.6)		48.3(31.0)		56.3 (31.8)	
range	0-103		0-99		1-103	

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.
Note. Detail may not add to totals because of rounding.

Table 06. Military Occupational Classification (MOC) codes at the final reference date by cohort

	Deployed Cohort		Non-deployed Cohort	
	N	%	N	%
Total	5,139	100	6,077	100
All flying related MOC	472	9.1	227	3.7
Pilots	282	5.5	127	2.1
Flight engineers	89	1.7	21	0.3
Navigators	101	2.0	79	1.3

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Between cohort comparisons

Entire follow-up mortality

Table 07 contains information for each cohort on the number of deaths, the crude and adjusted mortality rate ratios (MRR) by cause of death grouped into broad ICD-9 categories and aggregated into total mortality, mortality due to disease related causes and all external causes.

Overall mortality between the two cohorts was similar (adjusted MRR = 0.97, 95% C.I. = 0.65, 1.45). The age-sex adjustment had little impact on the crude MRR estimate. As well, the rates of disease related and external causes related mortality were not significantly different between the two cohorts (adjusted MRR =0.71, 95% C.I. = 0.41, 1.25 and adjusted MRR = 1.47, 95% C.I. = 0.79, 2.74, respectively).

In terms of specific cause of death groupings, most categories had no or one death and thus could not be analyzed. The only cause groupings that were analysed were all cancers, circulatory system, motor vehicle accidents, air/space crashes and suicide.

There was no difference between the cohorts on cancer mortality or on circulatory system deaths. However, the latter had a mortality rate in the Deployed cohort which was 50% lower (adjusted MRR= 0,49) than in the Non-deployed cohort. This difference did not achieve statistical significance (95% CI: 0.17 to 1.4).

Only one category showed any marked difference in mortality between the cohorts. Mortality due to air/space crashes was 4.77 times higher in the Deployed cohort than in the Non-deployed cohort. Despite the small number of air/space deaths (10 in total), this difference achieved statistical significance (95% CI: 1.01 to 22.5). The wide confidence intervals reflect the small number of events in this category.

Suicide had an observed MRR which was slightly above 1 in the Deployed cohort (1.17) but there was no statistical evidence of an elevated risk. There was no difference in mortality rates due to motor vehicle accidents between the Deployed and Non-deployed cohorts.

Table 07. Number of deaths, crude and adjusted mortality ratios by main cause of death and cohort, 1991-1999

Cause	Deployed Cohort		Non-deployed Cohort		Crude MRR (95% CI)	Adjusted MRR (95% CI)
	N	%	N	%		
All Causes	42	9.5	54	10.2	0.93 (0.62-1.40)	0.97 (0.65-1.45)
Disease related (001-799)	20	4.5	36	6.8	0.67 (0.39-1.15)	0.71 (0.41-1.25)
All cancers (140-208)	10	2.3	15	2.8	0.80 (0.36-1.78)	0.91 (0.41-2.00)
Circulatory system (390- 459)	5	1.1	12	2.3	0.50 (0.18-1.42)	0.49 (0.17-1.40)
All external causes (E800-E999)	22	5.0	18	3.4	1.46 (0.79-2.73)	1.47 (0.79-2.74)
Motor vehicle crash (E810-E825)	3	0.7	5	0.9	0.72 (0.17-3.00)	0.78 (0.19-3.26)
Air/space crash (E840- E845)	8	1.8	…	…	4.79* (1.02-22.5)	4.77* (1.01-22.5)
Suicide (E950-E959)	9	2.0	9	1.7	1.20 (0.48-3.02)	1.17 (0.46-2.95)

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Note: Based on the entire follow-up period.

Detail may not add to totals because of suppressed cells with less than 3 events.

*p <=.05
… Number less than 3

Early follow-up mortality, 1991-1995

The data on early follow-up mortality are presented in the same way as was done for total mortality (Table 08). The total number of deaths for the first five years of follow-up was 49. Due to the small number and to the pattern of deaths in the early mortality follow-up, the age-sex adjustment had a comparatively large effect.

The overall mortality was similar between the two cohorts (MRR=0.95 with 95% C.I. = 0.46 to 1.95). In contrast, the adjusted mortality risk ratio due to external causes (injuries/accidents) was higher in the Deployed cohort than in the Non-deployed cohort (MRR = 3.72, 95% C.I. = 1.31 to 10.6). The latter finding is different from what was observed for the entire follow-up period and was the only statistically significant one.

Cause-specific mortality could only be examined for five groupings: all cancers, circulatory system, motor vehicle accidents, air/space crashes and suicide. All were in the same direction as their respective overall mortality and none of the differences reached statistical significance but one. The rate of deaths attributable to circulatory diseases was significantly lower in the Deployed cohort than in the Non-deployed one (adjusted MRR=0.13; 95% C.I. = 0.02 to 0.77).

Table 08. Number of deaths, crude and adjusted mortality ratios by main cause of death and cohort, early follow-up period, 1991-1995

Cause	Deployed Cohort		Non-deployed Cohort		Crude MRR (95% CI)	Adjusted MRR (95% CI)
	N	%	N	%		
All Causes	25	10.4	24	8.3	1.25 (0.72-2.19)	0.95 (0.46-1.95)
Disease related (001-799)	8	3.3	19	6.6	0.51 (0.22-1.16)	0.44 (0.16-1.23)
All cancers (140-208)	4	1.7	8	2.8	0.60 (0.18-2.00)	0.93 (0.26-3.33)
Circulatory system (390- 459)	…	…	6	2.1	0.40 (0.08-1.99)	0.13* (0.02-0.77)
All external causes (E800-E999)	17	7.1	5	1.7	4.09* (1.51-11.1)	3.72* (1.31-10.6)
All external causes (E800-E999), excluding air/space crash	9	3.7	5	1.7	2.16 (0.73-6.46)	1.57 (0.50-4.89)
Motor vehicle crash (E810-E825)	…	…	3	1.0	0.80 (0.13-4.80)	0.58 (0.09-3.76)
Air/space crash (E840- E845)	8	3.3	0	0	Undefined[1]	Undefined[1]
Suicide (E950-E959)	7	2.9	…	…	4.21 (0.87-20.3)	2.82 (0.58-13.7)

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Note: The follow-up period extends from the final reference date to December 31, 1995

Detail may not add to totals because of suppressed cells with less than 3 events.

p <=.05
… Number less than 3

[1]Calculation was not possible because there was no event in one group.

Late follow-up mortality, 1996-1999

The data on late follow-up mortality are presented in the same way as was done for total mortality and early follow-up mortality (Table 09). The total number of deaths from January 1, 1996 to the termination date was 47. Due to the small number and to the pattern of deaths in the late mortality follow-up, the age-sex adjustment had a comparatively large effect.

The overall mortality in the late follow-up remained similar between the two groups (MRR=0.72, 95% C.I. = 0.39, 1.34). Disease-related mortality was similar in the two cohorts (MRR = 0.96, 95% C.I. = 0.46, 2.03). However, in contrast to the results obtained in the early follow-up period, mortality due to external causes in the late follow-up period was not different between the two cohorts (MRR=0.49, 95% C.I. = 0.17, 1.45).

Cause-specific mortality could only be examined for three groupings: all cancer, circulatory system, and suicide. In contrast to the findings based on the early follow-up, none of these achieved statistical significance.

Table 09. Number of deaths, crude and adjusted mortality ratios by main cause of death and cohort, late follow-up period, 1996-1999

Cause	Deployed Cohort		Non-deployed Cohort		Crude MRR (95% CI)	Adjusted MRR (95% CI)
	N	%	N	%		
All Causes	17	8.4	30	12.4	0.68 (0.37-1.22)	0.72 (0.39-1.34)
Disease related (001-799)	12	5.9	17	7.0	0.84 (0.40-1.76)	0.96 (0.46-2.03)
All cancers (140-208)	6	2.9	7	2.9	1.02 (0.34-3.04)	1.32 (0.44-4.00)
Circulatory system (390- 459)	3	1.5	6	2.5	0.60 (0.15-2.38)	0.59 (0.15-2.38)
All external causes (E800-E999)	5	2.5	13	5.4	0.46 (0.16-1.29)	0.49 (0.17-1.45)
Suicide (E950-E959)	…	…	7	2.9	0.34 (0.07-1.64)	0.32 (0.06-1.55)

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Note: The follow-up period extends from January 1, 1996 to the termination date.

Detail may not add to totals because of suppressed cells with less than 3 events.

… Number less than 3

Survival Analysis

Cox regression models were used to examine the effect of deployment status on survival. Age and rank were used as control variables when there were a sufficient number of events to do so. The adjusted hazard ratios results are presented in Table 10. Note that the hazard ratio (HR) has essentially the same meaning as the MRR reported in the previous section. Overall, the results of the survival analyses were compatible with the results based on the direct standardization.

Table 10. Adjusted hazard ratios (HR) for deployment status by selected causes of death

Cause	Adjustment factors	Adjusted HR (95% CI)
All causes	Four 10 yr age groups Rank	0.98 (0.65 -1.46)
Disease related (001-799)	Four 10 yr age groups Rank	0.70 (0.40 – 1.21)
All cancers (140-208)	Four 10 yr age groups Rank	0.85 (0.38 -1.90)
Circulatory system(390-459)	Three 10 yr age groups (upper 2 combined) Rank	0.50 (0.18 – 1.44)
All external causes (E800--999)	Four 10 yr age groups Rank	1.53 (0.82 – 2.86)
Motor vehicle crash (E810-825)	Two age groups (<35 and >= 35) Rank (NCM, low vs rest)	0.74 (0.18 – 3.11)
Air/space crash (E840-E845)	Three 10 yr age groups (lower 2 combined) Rank	5.50* (1.16 – 26.0)
Suicide (E950-E959)	Four 10 yr age groups Rank (officer groups combined)	1.17 (0.46 – 2.95)

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.
*p<=.05

For several of the groupings, an analysis was done to examine the potential difference in event rates in the early and late follow-up periods (Table 11). This testing involved defining a time-varying covariate that was '0' in the early period and an indicator variable for cohort membership in the late period. This enabled the cohort effect to be different in the two periods. A test of the

standardized coefficient (beta) for the added variable serves as a statistical test for a comparison between an early and late period effect. The ratio shown in the second column of Table 11 pertains to the hypothesis that the rate ratio in the first and second half of the follow-up are different. Thus, for suicide, the result of the test indicates that the HR in the first half was significantly different form the HR in the second half of the follow-up. Due to the small sample size, only age was used as a control variable.

Table 11. Hazard ratios (HR) for deployment status and early and late mortality effects by selected causes of death

Cause	Early follow-up HR (p-value)	Early/Late follow-up HR (p-value)
All causes	1.30 (p=0.36)	1.81 (p=0.15)
Disease related (001-799)	0.53 (p=0.13)	0.59 (p=0.36)
All cancers (140-208)	0.65 (p=0.48)	0.58 (p=0.51)
Circulatory system(390-459)	*	*
All external causes (E800--999)	**4.17 (p=0.005)**	**8.78 (p=0.003)**
Motor vehicle crash (E810-825)	*	*
Air/space crash (E840-E845)	+	+
Suicide (E950-E959)	4.08 (p=0.08)	**12.1 (p=0.028)**

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Note: Adjusted for age only.

***** Test not performed due to small cell sizes.
+ Test not performed due to highly unbalanced mortality distribution

All Deaths

The results of the univariate log-rank test showed no difference in overall mortality between the two cohorts (p=0.72). As well, after multivariate adjustment, age (using four 10-year age groups) was the only statistically significant variable. There was no difference between the cohorts (p=0.90) and no evidence of any difference in early and late mortality from other causes (p=0.15).

All Disease-related

Univariate log-rank tests revealed no difference in mortality between the two cohorts (p=0.14). However, there were strong mortality differences across rank categories (p=0.0009) with 'NCM, low' having the lowest mortality. There was also a strong age gradient (p<0.0001) that might explain the rank effect. These effects were replicated in the univariate Cox model with HR=7.8 for the oldest age group.

No differences were seen between the cohorts after multivariate adjustment (p=0.19). The strong age effect was again found but there was no effect of rank. After adjusting for age (using four 10-year age groups), there was no evidence of any difference in early and late mortality from other causes (p=0.36).

All Cancers

Univariate log-rank tests showed no difference in cancer mortality between the two cohorts (p=0.52) or between men and women (p=0.59). However, there were strong mortality differences across rank categories (p=0.0070) with 'NCM, low' having the lowest mortality. There was also a strong age gradient (p<0.0001) that might explain the rank effect. Results from the Cox modeling yielded similar results with the rank variable having a statistically significant effect (p=0.010). Age showed a strong effect with the hazard ratio for the highest age group being 23.4 compared to the lowest.

No differences were seen between the cohorts after multivariate adjustment (p=0.69). A very strong age effect was still present. Rank was no longer a significant covariate. There was no evidence that the proportional hazards assumption had been violated. After adjusting for age

(using four 10-year age groups), there was no evidence for any difference in early and late mortality from cancer (p=0.51).

Circulatory System

Univariate log-rank tests showed no difference in mortality related to the circulatory system between the two cohorts (p=0.18) or between men and women (p=0.32). A marginal effect was seen for rank categories (p=0.047) with 'NCM, low' having the lowest mortality. There was an age gradient that could not be tested using the log-rank since the lowest age group had no events. In the univariate Cox analysis, age was combined into three groups. Neither age nor rank had an effect (p=0.07). No differences were seen between the cohorts after multivariate adjustment (p=0.20). The number of cases was too small to support examination for early/late period effects.

Miscellaneous disease-related causes

Other mortality causes had no cases or too few cases to be analyzed. Creating an overall miscellaneous category would not have provided meaningful information.

All External causes

According to the univariate log-rank tests, there was no difference in mortality attributed to external causes between the two cohorts (p=0.23), across rank categories (p=0.85) or across age groups (p=0.13). The lack of effect was also found in the univariate Cox models. No differences were seen between the cohorts after multivariate adjustment (p=0.18). The results were not adjusted according to military element (air force, navy or army personnel).

Motor vehicle accidents

The results of the univariate log-rank tests indicate that there was no difference in mortality attributed to MVA between the two cohorts (p=0.52) or between men and women (p=0.39). The effect of rank and age could not be tested since some strata had no events. All deaths due to MVA occurred among the non-commissioned members. However, following re-coding of rank and age into two groups, high and low, there was no significant effect of either age or rank. No differences were detected between the cohorts after multivariate adjustment (p=0.68). The number of cases was too small to support examination of early/late period effects.

Air/space crashes

The univariate log-rank tests revealed a statistically significant difference in mortality between the two cohorts (p=0.029). There was also a statistically significant difference across rank categories (p=0.015) with commissioned members (officers) having about a 5-fold higher risk. An age effect could not be tested since some strata had no events. After recoding age, univariate Cox modeling revealed a higher risk in the Deployed cohort (hazard ratio = 4.76, p = 0.0048). Higher ranked soldiers were at higher risk (HR = 5, p=0.048) but no age effect was seen. The significant difference in the cohort effect was present after multivariate adjustment (hazard ratio = 4.60, P = 0.032) as well as the risk associated with a higher rank. There was no confounding of the cohort effect. Because there were no deaths in the Non-deployed cohort in the early period, it was not possible to compare early and late period mortality. Any attempt to model an early/late effect led to numerical instability.

Suicide

All of the suicide deaths were in males. There was no apparent pattern observed in the case scenarios. There appears to be some temporal clustering of suicides. Five cases in the Deployed cohort occurred in the one year period between Jan 25, 1994 and Jan 9, 1995. Six cases in the Non-deployed cohort occurred in the 18-month period between Mar 28, 1997 and Nov 1, 1998. For half (9 out of 18 or 50%) the suicide involved the use of some weapon.

No difference in mortality between the two cohorts (p=0.70), or across age groups (p=0.74) were detected with the univariate log-rank tests. The effect of rank could not be tested using the log-rank test since some strata had no events. All suicides deaths occurred in men, so sex could not

be tested in Cox modeling. After re-coding, no effect of rank (p=0.45) or age (p=0.75) in a univariate Cox model was detected

No differences were seen between the cohorts after multivariate adjustment (p=0.74). However, the Cox model analysis for early/late period differences yielded a statistically significant period effect (p=0.028). The ratio of the mortality from suicide in the Deployed cohort to that in the Non-deployed cohort in the early follow-up period was 12 times higher than the same ratio in the late follow-up period.

Summary

There was no significant difference in the overall risk of death between the Deployed and Non-deployed cohorts; the total number of deaths amounted to 96, 42 in the Deployed cohort and 54 in the Non-deployed cohort.

Over the full follow-up period, there was no significant difference in the rate of suicide between the two groups (nine events in each group). While the suicide rate in the first half (1991-1995) of the follow period was higher among the Deployed group, this was compensated by a lower rate in the latter half (1996-1999) of the follow-up period. Due to the small number of events, this finding was not statistically significant and could be due to chance.

There was a statistically significant increased risk of death from airspace crashes in the Deployed group. This result may be explained by the fact that there were three times as many members in flying occupations, such as pilots, navigators, flight engineers, in the Deployed cohort as there were in the Non-deployed cohort.

In contrast to the US and UK studies, during the early and full follow-up periods, there was no increased risk of death due to motor vehicle crashes in the Deployed cohort compared to the Non-deployed cohort.

Comparisons to the Canadian population

The mortality experience of the two cohorts was compared to that of the general Canadian population (tables 12 and 13) using indirect standardization methods to produce Standardized Mortality Ratios (SMRs) that are similar in interpretation to the MRRs. SMRs were calculated for six groups: all cause mortality, disease-related, all external causes, circulatory system, air/space crashes and suicide because of the small number of events in most of the other mortality groupings.

Deployed cohort

For the Deployed cohort, all causes mortality and the disease related SMRs were under 1.0 suggesting that the Deployed cohort had a reduced mortality from these causes compared to the general population (Table 12). This is not surprising and likely reflects the healthy worker effect.

In contrast, the SMR for air/space crash was estimated a 27.2 (95% C.I. = 11.8, 53.6). This means that the Deployed cohort had a mortality rate from air/space crashes that was 27 times higher than the mortality from that cause in the general population.

Table 12. Standardized mortality ratios (SMR) of the deployed cohort

	Observed	Expected	SMR (95% CI)
All causes	42	75.2	0.56* (0.40-0.75)
Disease related (001-799)	20	45.6	0.44* (0.27-0.68)
CHD deaths	3	7.39	0.41 (0.08-1.19)
All external causes (E800-E999)	22	29.6	0.74 (0.47-1.12)
Air/space crash (E840-E845)	8	0.29	27.2* (11.8-53.6)
Suicide (E950-E959)	9	11.9	0.76 (0.35-1.43)

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.
p<=.05

37%Non-deployed cohort

For three of the groupings (all causes, disease related and all external causes), the SMR was significantly below 1.0, suggesting that the Non-deployed cohort had a reduced mortality from these causes compared to the general population (Table 13). However, the circulatory system, air/space and suicide related mortality in the Non-deployed cohort was comparable to that of the general population.

Table 13. Standardized mortality ratios (SMR) of the Non-deployed cohort

	Observed	Expected	SMR (95% CI)
All causes	54	94.4	0.57* (0.43-0.75)
Disease related (001-799)	36	59.2	0.61* (0.42-0.84)
CHD deaths	10	10.1	0.98 (0.47-1.81)
All external causes (E800-E999)	18	35.2	0.51* (0.30-0.81)
Air/space crash (E840-E845)	…	0.35	5.68 (0.69-20.5)
Suicide (E950-E959)	9	14.2	0.64 (0.29-1.21)

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

… Number less than 3

*p<=.05

Comparison of study findings on mortality to other published results

The Canadian cohort of Gulf War veterans is smaller than the US and UK cohorts but larger than the Australian cohort. The four studies are summarized in Table 14. The US cohort is the largest with 621,902 deployed military personnel and 746,248 non-deployed military personnel and 4,506 deaths in the deployed group and 5,918 in the non-deployed group over a seven-year follow-up. The UK study is about 10% the size of the US study. It was based on 53,416 deployed and 53,450 non-deployed military personnel with 395 deaths in the deployed group and 378 in the non-deployed group. Mortality up to December 31, 1999 was examined. The Australian study is the smallest with 1,833 deployed military personnel and 2,847 non-deployed military personnel. The study examined mortality up to December 31, 2000. There were 43 deaths. All of the studies used an analytic approach similar to the one used in the present analysis.

Direct comparison of the rate estimates from the various reports is difficult because the studies used different reference populations to generate the adjusted rates and rate ratios. As well, the US and UK personnel were demographically different than the Canadian personnel. The Canadian forces personnel were more likely to belong to the navy or the air force while the UK and US had a much larger army component. Moreover, there were age differences among the four studies with the Canadian cohort having a higher mean age than the other three cohorts. In addition, both the Canadian and Australian cohorts had about 20% of the participants who were commissioned officers while, in the US and UK cohorts, the proportion of officers was around 11 to 12%. It is difficult to determine if Canadian military personnel were more likely to be married than the US military personnel since the marital status of the latter was measured at the time of the Gulf and Kuwait War but the marital status of the former was measured at the time of the final reference date. These differences could have an effect on external cause mortality. As well, the lack of a uniform reference population to adjust for these differences could introduce some bias in the comparison of adjusted rates between studies. However, the use of MRR lessens the effects of these differences since adjusted MRRs are relatively insensitive to the choice of a reference population.

Overall Mortality

All the published studies have reported no excess in overall mortality in deployed veterans. The MRRs are not directly comparable because different reference populations were used for the age-standardization. However, in all four studies, the all-cause MRR has been essentially 1.0. It was estimated at 0.95 for the US cohort (Kang & Bullman 1996; Writer, DeFraites & Brundage 1996; Kang, Bullman, Macfarlane, & Gray 2002) 1.05 for the UK (Macfarlane, Thomas & Cherry,

2000), and 1.4 for the Australian cohort (Sim, Abramson, Forbes, et al., 2003). These MRRs are similar to the MRR of 0.97 observed in the Canadian study.

Table 14. Comparisons of the four Gulf War cohort studies

	US study[&]	UK study[&&]	Australian study[&&&]	Canadian study
Sample size				
Total	1,368,150	106,866	4,680	11,210
Deployed	621,902	53,416	1,833	5,117
Non-deployed	746,248	53,450	2,847	6,093
Number of deaths				
Total	10,424	773	43	96
Deployed	4,506	395	20	42
Non-deployed	5,918	378	23	54
Age: mean(sd) *				
Total	29.3 (approx)	27.2 (approx)	28.7	30.9 (7.3)
Deployed	28.4	27.2 (approx)	28.1(6.4)	30.7 (7.0)
Non-deployed	30.2	27.3 (approx)	29.3 (6.4)	31.1 (7.5)
Percent men				
Total	89.6	97.9	100 (by design)	94.8
Deployed	93.0	97.9	100	94.2
Non-deployed	84.8	97.9	100	94.5
Percent officers				
Total	11.9	11.1	24.1	19.8
Deployed	9.5	11.2	22.1	18.7
Non-deployed	13.9	11.1	25.3	20.7
Percent married				
Total				
Deployed	54.2	NR	NR	72.8
Non-deployed	53.9	NR	NR	72.8
	54.7	NR	NR	72.8

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.
*Mean age was estimated for the UK and Australian studies. Neither report mean age directly. The UK value is based on an age group frequency table for the total study sample only. The mean age for the Australian study is based on age at date of survey participation. Ten years were subtracted to obtain an estimate of the age at the time of the Gulf War.

NR = not reported
&Kang & Bullman 1996; Writer, DeFraites & Brundage 1996; Kang, Bullman, Macfarlane, & Gray 2002
&&Macfarlane, Thomas & Cherry, 2000
&&&Sim, Abramson, Forbes, et al., 2003.

Cancer incidence

There were a total of 109 incident cancer cases. Twenty-seven were out of scope because they were diagnosed before the reference date or involved more than one cancer. Of these 27 cases, 7 were Deployed cohort and 20 were in the Non-deployed cohort.

Characteristics of the veterans diagnosed with cancer

There were 38 cases of incident cancer in the Deployed cohort and 44 cases in the Non-deployed cohort. Descriptive information about the characteristics of the 82 veterans who were diagnosed with incident cancer occurring after the cancer reference date is found in Table 15. The majority were men, 92.1% in the former and 93.2% in the latter. The average age at entry into the cohort for veterans who developed cancer was very similar in the two cohorts: 38.5 years and 38.0 years, respectively. The time after entry to the diagnosis of cancer was similar as well, 53.0

months for the Deployed cohort and 64.0 months for the Non-deployed cohort. Twenty-two military personnel (26.8%) diagnosed with cancer after the final reference date died during follow-up. On their death certificates, the underlying cause of death for all but one of these military personnel was cancer.

Table 15. Demographic characteristics of veterans who were diagnosed with cancer

Characteristics	Total		Deployed Cohort		Non-deployed Cohort	
	N	%	N	%	N	%
Total						
Sex	82	100.0	38	100.0	44	100.0
Male	76	92.7	35	92.1	41	93.2
Female	6	7.3	3	7.9	3	6.8
Age in years at entry	38.3 (9.1)		38.6 (7.9)		38.0 (10.1)	
mean (sd)	21-58		21-52		21-58	
range						
Age groups						
15-29	15	18.3	5	13.2	10	22.7
30-34	14	17.1	8	21.1	6	13.6
35-39	12	14.6	5	13.2	7	15.9
40-44	20	24.4	9	23.7	11	25.0
45+	21	25.6	11	28.9	10	22.7
Rank						
NCM, low	21	25.6	7	18.4	14	31.8
NCM, high	41	50.0	22	57.9	19	43.2
Officer, low	10	12.2	6	15.8	4	9.1
Officer, high	10	12.2	3	7.9	7	15.9
Married or common-law						
Yes	56	78.9	27	81.8	29	76.3
No	15	21.1	6	12.1	9	23.7
Missing	11		5		6	
Months prior to cancer diagnosis						
Mean(sd)	58.9(28.8)		53.0(32.1)		64.0(24.8)	
Range	3.1-105.8		3.1-105.8		9.2-104.1	

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Note. Detail may not add to totals because of rounding.

Between cohorts comparisons

Direct standardized rates

Overall incidence and site-specific cancer incidence were examined. There were 71 new cases of cancer diagnosed after the cancer reference date and before the termination date, 29 in the Deployed cohort and 42 in the Non-deployed cohort. The results are presented in Table 16.

The total cancer incidence was similar in the two cohorts (IDR= 0.88, 95% C.I. = 0.55, 1.42). The most common cancer in the cohorts was digestive cancer. In total, there were 15 cases of digestive cancer diagnosed during follow-up, 13 of those being diagnosed after the cancer reference date. Most of the cancers occurred in the colon or rectum (7 out of 10 in the Deployed cohort and 4 out of 5 in the Non-deployed cohort).

It had been hypothesized a-priori that the Deployed cohort might show an excess of three types of cancer, leukemia, lymphoma and melanoma. The data did not support this hypothesis.

The only cases of prostate cancer (n=5) and brain cancer (n=4) occurred in the Non-deployed cohort.

Table 16. Unadjusted and age- and sex-adjusted cancer incidence density ratios (IDR) based on cases from the post-cancer reference date, 1993-1999

	Deployed Cohort		Non-deployed Cohort		Crude IDR (95% CI)	Adjusted IDR (95% CI)
	N	%	N	%	N	%
All cancers	29	8.5	42	10.3	0.83 (0.52-1.33)	0.88 (0.55-1.42)
Digestive (150-159.9)	8	2.3	5	1.2	1.92 (0.63-5.86)	2.01 (0.66-6.18)
Respiratory (160-165.9)	3	0.9	…	…	1.80 (0.30-10.8)	2.48 (0.41-15.0)
Prostate (185.0)	0	0	5	1.2	Undefined[1]	Undefined[1]
Testicular (186-186.9)	3	0.9	5	1.2	0.72 (0.17-3.01)	0.64 (0.15-2.71)
Genitourinary (188-189.9)	3	0.9	…	…	1.80 (0.30-10.8)	1.93 (0.32-11.6)
Brain/CNS (191-192.9)	0	0	4	0.8	Undefined[1]	Undefined[1]
Lymph nodes (196-196.9, 200-203.8)	3	0.9	6	1.5	0.60 (0.15-2.40)	0.68 (0.17-2.75)
Miscellaneous (140-149.9, 170-171.9, 187-187.9, 190-190.9, 193-195.8, 199-199.1)	6	1.8	7	1.7	1.03 (0.35-3.06)	1.09 (0.36-3.28)

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Notes: The post cancer reference date was used in these analyses. The post cancer reference date is an arbitrary date and occurs two years after the final reference date.
Detail may not add to totals because of suppressed cells with less than 3 events.

… Number less than 3
[1]Calculation was not possible because there was no event in one group.

The basic patterns just reported are also observed if one examines cancer incidence including the cases diagnosed post deployment but before the Cancer Reference Date (n=82). The observed excess of digestive cancer is stronger but still is not statistically significant (Table 17). Given the lag time between exposure and cancer development, this analysis is less relevant than the one done using the Cancer Reference Date. Moreover, this study had sufficient power to examine "overall" risk of cancer but was not powerful enough to detect differences between the cohorts in terms of site-specific cancers (e.g. digestive, respiratory, prostate). Therefore, the results pertaining to site-specific cancers do not reach statistical significance, are exploratory in nature and should be interpreted with caution.

Table 17. Unadjusted and age- and sex-adjusted cancer incidence density ratios (IDR) based on cases from the post reference date, 1991-1999

	Deployed Cohort		Non-deployed Cohort		Crude IDR (95% CI)	Adjusted IDR (95% CI)
	N	%	N	%	N	%
All cancers	38	8.6	44	8.3	1.03 (0.67-1.59)	1.13 (0.73-1.74)
Digestive (150-159.9)	10	2.3	5	0.9	2.39 (0.82-7.00)	2.67 (0.91-7.84)
Respiratory (160-165.9)	3	0.7	…	…	1.80 (0.30-10.7)	2.36 (0.39-14.2)
Prostate (185.0)	0	0	5	0.9	Undefined[1]	Undefined[1]
Testicular (186-186.9)	3	0.7	5	0.9	0.72 (0.17-3.00)	0.70 (0.17-2.93)
Genitourinary (188-189.9)	4	0.9	…	…	2.39 (0.44-13.1)	2.63 (0.48-14.4)
Brain/CNS (191-192.9)	…	…	4	0.8	0.60 (0.11-3.26)	0.64 (0.12-3.48)
Lymph nodes (196-196.9, 200-203.8)	4	0.9	7	1.3	0.68 (0.20-2.33)	0.76 (0.22-2.59)
Leukemia (204-208.9)	3	0.7	0	0	Undefined[1]	Undefined[1]
Miscellaneous (140-149.9, 170-171.9, 187-187.9, 190-190.9, 193-195.8, 199-199.1)	7	1.6	8	1.5	1.05 (0.38-2.88)	1.12 (0.41-3.11)

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Notes: The post reference date was used in these analyses. It includes cancer cases diagnosed immediately post deployment and does not allow for a 2-year lag-time as does the post-cancer reference date.
Detail may not add to totals because of suppressed cells with less than 3 events.
… Number less than 3
[1]Calculation was not possible because there was no event in one group.

Survival analysis
Cox regression models were used to examine the effect of deployment status on cancer incidence when age and rank were controlled if the cell size permitted to do so. The hazard ratios (HR) are presented in Table 18 and confounding attributed to the Deployed group is noted. The cancer reference date was used. The results based on the reference date were generally similar to the ones presented here.

Table 18. Adjusted hazard ratios (HR) of cancer incidence for cohort effect, overall and by selected sites

	Adjustment Factors	Adjusted HR (95% CI)
All cancers combined[1]	Four 10 year age groups Rank	0.86 (0.54 -1.39)
Digestive cancers	Three 10 year age groups (lowest 2 combined) Rank (officers combined)	2.00 (0.62 - 6.12)
Testicular cancer	Three10 year age groups (upper 2 collapsed) Rank	0.76 (0.18 – 3.24)
Cancer of lymph nodes	Four 10 year age groups Rank	0.65 (0.16 – 2.62)
Miscellaneous cancers	Three 10 year age groups (lowest 2 combined) Rank (only NCM)	1.12 (0.37 – 3.33)
[1]Non-melanoma skin cancer was excluded from the analysis		

Data Sources: Department of National Defence and the Mortality and Cancer Incidence Databases.

Total cancers (n=71)
Univariate log-rank tests showed no difference in incidence between the two cohorts (p=0.49). There was strong evidence for a rank gradient (p=0.0005) and an age gradient (p<0.0001). Univariate Cox models showed no cohort effect (p=0.42) but replicated the rank effect (p=0.006) and age gradient (p<0.0001, HR = 9.7 for highest age group). After multivariate adjustment, the cohort effect remained non-significant (p=0.54).

Digestive cancer (n=13)
There was no difference in digestive cancer incidence between the two cohorts (p=0.25) at the univariate level. However, there was a strong incidence gradient across age groups (p<0.0001). Due to some groups having no events, the lowest two age groups and the two officer categories were combined. Univariate Cox models found evidence of a rank effect (p=0.047, HR=3.71 for the NCM, high group) and a strong age effect. No differences were seen between the cohorts after multivariate adjustment (p=0.23). There was no evidence for confounding of the between cohort effect.

Testicular Cancer (n=8)
Results of the univariate log-rank test indicated no difference in testicular cancer incidence between the two cohorts (p=0.64). No cases were seen in men over age 45 and no trend was observed by rank. After combining the two highest age categories, univariate Cox analysis revealed no evidence of an effect on risk by cohort, age or rank. No differences were seen between the cohorts after multivariate adjustment (p=0.71). No confounding was noted of the between cohort comparison.

Lymph Nodes (n=9)
No difference in lymph nodes cancer incidence between the two cohorts (p=0.46) was found. There was no evidence of an incidence gradient by either rank (p=0.42) or age (p=0.29). These results were replicated with the univariate Cox models. No differences were detected between the cohorts after multivariate adjustment (p=0.55). No confounding was noted of the between cohort comparison.

Miscellaneous cancers (n=13)
Based on the univariate log-rank tests, there was no difference in incidence between the two cohorts (p=0.96). There were no miscellaneous cancers in any officers. Hence, a dichotomous variable for rank was created: NCM low, yes/no. There was some evidence of an incidence gradient by age (p=0.040). Results of the univariate Cox models found no cohort or rank effect but a significant trend by age (p=0.040, HR = 3.8) for the highest age group. No differences were seen between the cohorts after multivariate adjustment (p=0.84). There was no confounding effect of the between cohort difference.

Some types of cancer occurred in only one cohort. The small number of cases precluded a statistical analysis. Five cases of prostate cancer were observed and all were diagnosed in members of the Non-deployed cohort. They followed the expected age-distribution, occurring in people older than age 45 at the time of their recruitment date. As well, four cases of brain/CNS cancer were diagnosed post-cancer reference date, all in the Non-deployed cohort. In contrast, three cases of leukemia were observed after the cancer reference date and all were in the Deployed cohort.

Summary

There is no evidence that the Deployed cohort had an elevated risk of developing cancer overall, compared to the Non-deployed cohort. Likewise, when the analysis is restricted to events occurring after the cancer reference date, a significantly increased incidence in the Deployed cohort could not be detected.

Comparison to the Canadian population

The total incidence of cancer diagnosed after the cancer reference date was compared to the cancer incidence in the general Canadian population using indirect standardization to produce a Standardized Incidence Rate (SIR). Given the small numbers, topography-specific SIRs were not examined.

For the Deployed cohort, the SIR was 0.78 (95% C.I. = 0.52, 1.12). For the Non-deployed cohort, the SIR was 0.87 (95% C.I. = 0.63, 1.18). The rate of cancer incidence of either cohort was not significantly different from that of the general population.

Comparison of study findings on cancer incidence to other published studies

An examination of cancer incidence in the UK Gulf War cohort study has recently been published (Macfarlane, Biggs, Maconochie, et al., 2003). The follow-up period ended on December 31, 1999. Data are also available from the Australian study but the results are based on 19 incident cancer cases. The follow-up period in this study extended to December 31. 2000. There has not been an analysis of the US Gulf War cohorts for cancer incidence beyond a small study on testicular cancer incidence (Knoke, Gray & Garland, 1998). Information about these studies is presented in the mortality section of this report and is summarized in Table 14.

The UK study followed the cohorts for just over 10 years using a record linkage protocol (Macfarlane, Biggs, Maconochie, et al., 2003). It reported no difference in the 10 year incidence rate for all cancers combined between the deployed and non-deployed veterans (IDR=0.99; 95% C.I. = 0.83, 1.17). As well, there were no significant differences in incidence for any of the site-specific analyses.

The UK study was able to examine the impact of personal risk behaviours and specific exposure during deployment. No evidence that any of the measured personal risk behaviours acted as a confounder for cancer risk was found. Results from the UK cohort also indicated no evidence that exposures in any of the specific theatres were associated with an increased risk of cancer.

Limitations

One of the major limitations of the present study is the small sample size and the young age of the participants. These two factors led to a low number of events that may have reduced the power of the study to detect group differences in cause-specific mortality and in specific types of cancer incidence. The sample size was also a factor in the analysis with the early and late period. However, the power of the study was sufficient to detect differences between the cohorts on overall mortality and cancer incidence and, in general, the results are consistent with those of other, much larger cohort studies from the US and the UK.

The entire follow-up period may have been too short to detect certain cancers and certain cause specific mortality such as deaths attributed to cardiovascular disease. The late follow-up period was probably too close to the final reference date for some long-term risk effects to be manifest.

It is possible that the deployed cohort was healthier than the comparison cohort because of the pre-deployment screening process. In contrast, the inclusion of subjects who were medically unfit for deployment may have introduced some noise in the comparison. While, the amount of error would be small, it might have pulled the estimates towards the null value, leading to an under-estimation of the effect of deployment on health.

There was a paucity of exposure information available for analysis. Less than half of the Deployed cohort was present in the Gulf War during the period of actual fighting but it was not possible to identify the military personnel who were there during that time. The analyses did not control for command or element (e.g., air force, navy or army) or MOC that differed between the study groups. Therefore, the comparability in terms of risk of the Deployed and Non-deployed cohort may have been compromised.

Likewise deployment history and number of deployments were not considered in the analyses. Therefore, information on physical exposures (e.g., chemicals, immunization) or stress could not be inferred. All members of the Deployed cohort would have had moderate exposure to psychological stresses as evidenced by the higher rates of PTSD in military personnel having had multiple deployments (Statistics Canada, 2003). It is likely that the Non-deployed cohort would have had similar exposure due to other deployments. This may have compromised the comparability of the two cohorts, reduced the effect of deployment to the Persian Gulf, or masked between cohort differences in mortality and cancer incidence.

The mortality and cancer incidence results could not be adjusted for individual behaviours such as smoking, heavy drinking or drug use. Hence, it is possible that the overall negative results might be masking a deployment risk differential if the two cohorts differed on health-related behaviours. However, according to the GG survey, which used the same study group, self-reported smoking and alcohol intake did not differ between the Deployed and Non-deployed cohorts.

In addition to the lack of information on individual behaviours, one major limitation in interpreting the cancer incidence data is the lack of information on occupational exposure to specific potential carcinogens. Moreover, it is possible that the members of the two cohorts differed on their degree of cancer risk.

At the same time, comparisons between military and civilian population within a country are subject to the healthy worker effect. Similarly, it is possible that either of the cohorts might exhibit risk behaviours that differ from those of the general Canadian population (e.g. differential smoking prevalence). This would compromise the interpretation of the SIR as well.

Although the power of the study was estimated to be sufficient to detect some outcomes, it may have been overestimated in the cancer incidence component as the follow-up period is comparatively short. There can be a substantial lag between exposure and the development of cancer. In many cases (e.g., cigarette smoking and lung cancer), this lag is partly due to the need to accumulate sufficient exposure to produce the DNA damage required for malignant transformation. Once a malignant clone has become established, time is required for the tumour to develop blood supply and grow to a detectable size. Leukemia and lymphoma frequently have the shortest lag time between exposure and onset. However, even following major radiation exposures, a five-year lag is common.

On the one hand, the number of tests that were done does not permit one to rule out that the significant findings of this study are the result of chance. On the other hand, the present study has the potential for failing to find significant differences because the number of events was small, especially when cause specific outcomes were analyzed. The 95% confidence intervals provide an empirical estimate of the size of difference that might have been missed by the study. In many cases, these confidence intervals were large, suggesting that it is possible that the study might have missed a large impact on mortality or cancer incidence. However, the differences in overall mortality and cancer incidence between the deployed and non-deployed cohorts were estimated with a sufficient number of events to rule out a large impact of deployment on these two indicators.

Discussion

This report has examined the mortality and cancer incidence of 5,117 Canadian military personnel who were deployed to the Persian Gulf in 1990/91. They were compared to that of 6,093 military personnel who were eligible for deployment to the Gulf but who were not deployed. The Non-deployed cohort was frequency matched on age and sex to the Deployed cohort. All military personnel were followed until December 31, 1999 yielding an average of 103 months of follow-up. Record-linkage methodology was used to identify a total of 96 deaths between the final reference date and the termination date and a total of 71 incident cancer cases between the cancer reference date and the termination date. Direct standardization methods were used to compute Mortality Rate Ratios and Incidence Density Ratios to compare the two cohorts and to make comparisons between the early and late follow-up periods. Survival methods (Log-rank and Cox regression) were also used when the number of cases allowed it. While the primary comparison was between the two cohorts, a secondary analysis was done to compare both cohorts to the general population. Indirect standardization methods were used to do so.

Mortality

All cause mortality

There was no evidence of any difference in all cause mortality between the two cohorts. The actual number of deaths and PYs of follow-up were similar to numbers predicted in the feasibility

study and the power of the study was sufficient to detect differences in "overall" mortality. As well, total mortality in both cohorts was significantly lower than that of the general Canadian population. The SMRs were in the range that would have been expected since the Canadian Forces is a group of healthy workers. The results of the Canadian study were compared to similar studies published in the US, UK and Australia. The most consistent feature across all these studies including the present one was the absence of any evidence for an increase in overall mortality for military personnel deployed to the Gulf.

Disease-related mortality

There was no increase in mortality due to diseases in the Deployed cohort compared to that of the Non-deployed cohort and the Canadian population. As well, there were no unexpected clusters of deaths that might suggest particular risks for deployed personnel to the Persian Gulf. Two causes accounted for most of the disease related mortality: cancer (45%) and circulatory diseases (30%). No other category accounted for more than 5% of deaths due to a disease-related condition. This is not unexpected given the pattern of deaths in Canada. Disease-related mortality was not different between the cohorts in the early and the late follow-up periods. Inability to control for smoking and other health behaviours among military personnel may have contributed to the lack of significant difference between the Deployed and Non-deployed groups. However results from the GG study, which were based on a similar cohort, did not indicate a difference in smoking rates between these two groups. The lack of significant differences between the two cohorts is likely because the study had limited power to detect differences in disease-specific categories where the number of events was very small.

It is interesting to observe that the circulatory system mortality was similar in the Non-deployed Cohort and the general population. The same was observed for the Deployed cohort. This suggests that both cohorts may have some risk factors that are increasing their risk of circulatory system mortality since one would have expected a lower SMR due to the healthy worker effect. Information on individual risk and health behaviours is needed to interpret this finding.

The Canadian disease-related mortality estimates were similar to those found in the UK study and the US study. These findings are perhaps a reflection of the healthy warrior effect (Haley 1998; Kang & Bullman 1998). In all the studies, a similar mortality rate from diseases between the Deployed and Non-deployed military personnel was a consistent finding. In fact, there was evidence to suggest a lowered mortality from diseases, perhaps as a result of a selection bias in identifying military personnel eligible for deployment.

External causes related mortality

Over the course of the nine years of follow-up, there was no statistically significant increase in mortality from external causes between the cohorts. Similarly, the overall mortality rate from external causes was not different in either the Deployed or Non-deployed cohort compared to the Canadian population.

Not surprisingly, the Deployed cohort was at increased risk of death due to air/space crashes as they were more likely to belong to flying occupations (pilots and navigators). Canada's contribution to the Kuwait and Gulf War of 1990/91 involved a large air force component. Other studies have documented that pilots (either civilian or military) have a higher risk of dying from air crashes than the general population (Band, Spinelli, Ng, Moody & Gallagher, 1990; Salisbury, Band, Threllfall & Gallagher, 1991). In this study, the deployed group had a higher proportion of members involved flying occupations (9.1%) compared to the control group (3.7%), thus, the higher rate of air crashes in the Deployed group (Table 05). As well, the two study groups were not matched according to element (air force, navy, and army) or MOC and the MRRs for this study were not adjusted for element or MOC.

The interpretation of air crash deaths is complex since a number of persons, including passengers, may be killed in a single event. Analyzing air crashes by the number of events instead of number of persons killed revealed that there were 2 relevant crashes in each study cohort and the proportion of crashes due to human error was in the expected range. According to the Directorate of Flight Safety, for both CF and civilian crashes, about 80% are due to human error.

It was unexpected that the mortality rates from external causes in the Canadian cohorts appeared somewhat lower than the rates observed in the US or UK studies. Random variation in mortality rates due to the small number of deaths in the Canadian study may account for such a finding. As well, CF deployed personnel were older and were less likely to belong to the army or land element and may explain differences in external mortality between the Canadian and the US and UK studies.

Early follow-up mortality, 1991-1995

All cause mortality between the two cohorts was not different in the early follow-up period. However, the rate of deaths attributable to circulatory diseases was significantly lower in the Deployed cohort than in the Non-deployed cohort in the early period. This may reflect the lower average age of the Deployed cohort and some pre-screening criteria. However, information on individual risk and health behaviours would be needed to fully interpret this finding.

Mortality due to external causes was higher in the Deployed cohort in the early period mainly because of deaths in the air/space crashes and suicide categories. Factors which explain the higher number of events in air/space crashes were discussed above. They include the higher proportion of military personnel in air space related occupations, the inclusion of deaths from air/space that involved passengers who would not have been in a position to influence the outcome of the flight and the lack of independence among the observed deaths from a given air/space crash.

While the suicide rate in the first half (1991-1995) of the follow-up period was higher for the Deployed group, this was compensated by a lower rate in the latter half (1996-1999) of the follow-up period. Over the full study period there was no difference in the rate of suicide between the cohorts. Due to low numbers, none of the suicide estimates were statistically significant meaning the most likely explanation for this finding was the expected random fluctuation in suicide rates over time as opposed to a detrimental effect of service in the Persian Gulf. Neither the US or UK cohort studies which had sufficient power to detect an effect of deployment on suicide, reported an elevated risk of suicide among personnel deployed to the Gulf. Recent analyses of CF suicides (Department of National Defense, 2005) indicate that members with a history of deployment had lower suicide rates than members who were not deployed and that CF suicide rates are consistently lower than rates found in the general population. An earlier independent study (Sakinofsky, Lesage, Escobar, et al., 1996), as well, did not find that deployment was a risk factor for suicide in the CF.

Despite the small number of suicides on which this finding is based, it is consistent with other observations that suggest a different pattern of mortality from suicide in the early and late follow-up periods.

The lack of statistical significance in most of the other categories is related to the small number of events which in turn yielded large confidence intervals and created instability in the point estimate for the MRR.

The US study reported no excess in suicide mortality in the first two years after deployment to the Gulf. The UK cohort has not reported on early term suicide rates but found no difference in overall suicide rate.

The US study reported an excess in mortality from motor vehicle accidents in the early follow-up period. The small number of MVA deaths in the Canadian cohort precluded identification of differences in MVA mortality in the early and late follow-up periods. It is possible that the lower MVA mortality could reflect differential risk patterns in the Canadian cohorts. These might be related to occupational or operational factors (e.g. work placements and tasks on overseas deployments). In addition, the Canadian Forces has undertaken an aggressive program of reducing MVA. This could have contributed to the reduced mortality. An examination of the number and severity of motor vehicle incidents and their survival rate could help clarify that finding.

Late follow-up mortality (1996-1999)

No differences were found between the cohorts on overall mortality, disease-related mortality and mortality due to external causes in the late follow-up period. The lack of statistical significance

may be due in part to the small number of events. In addition, in this analysis, it was not possible to adjust for subsequent deployments.

Cancer incidence

The overall cancer incidence rate in the Deployed cohort was similar to that in the Non-deployed cohort. As well, there was no obvious excess of any specific type of cancer in either cohort. Hypotheses about specific cancers were not supported but the power of the study was too low to detect any differences between cohort in the rate of site-specific cancers. Comparison to cancer incidence to the general Canadian population found no evidence for an increased incidence in either cohort. It is possible that the short follow-up time, about 7 years after the cancer reference date, may not have allowed sufficient time for exposure effects to be manifested. Likewise, the lack of control for individual cancer risk factors such as smoking was not available for analysis.

The UK and Canadian studies found no statistical evidence of an increase in cancer incidence. The UK study was able to examine the impact of personal risk behaviours and specific exposure during deployment. They found no evidence that any of the measured personal risk behaviours acted as a confounder for cancer risk. This is reassuring for the Canadian cohort analysis where such risk information was not available. The UK cohort also found no evidence associating any of the specific theatre exposures with an increased risk of cancer. A longer follow-up is required to determine if these findings will be upheld.

Conclusion

These results are consistent with those of other larger studies on the health of Gulf War veterans of other countries. Canadian Gulf War veterans (both retired and currently serving) did report symptoms and common illnesses at significantly higher rates than other veterans of the same era. However, they did not appear to be at increased risk of dying or developing cancer.

This study also documented that military populations have lower rates of all-cause and disease-related mortality than the general population. A “healthy worker” effect caused by the exclusion from military service of persons with serious chronic illnesses likely accounts for this finding.

The study was large enough to detect differences in the overall risk of death and cancer. However, the small number of events in specific disease categories or types of cancer reduced the ability to detect differences between the Deployed and Non-deployed cohorts.

Since the number of Canadian Gulf War Veterans was fixed, it was not possible to increase the sample size of this investigation. Given that the delay between the exposure to a health hazard and the development of cancer or disease may be several decades, the linkage could be repeated to increase years of follow-up.

The methodology employed in this report could be used to re-examine the outcomes of the present study after 14 years of follow-up data become available. This would allow for an examination of longer term trends in overall and cause specific mortality and cancer incidence. However, a longer follow-up period will not address the major limitation of this study, which is the overall size of the Gulf and Kuwait War veteran cohort.

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Appendix A: Background Information about the Creation of the Study Cohorts

The identification of the study cohorts proved problematic. The initial design was based on the two cohorts established by Goss Gilroy (GG) for their survey in 1997 (Gilroy, 1998). One cohort consisted of members of the Canadian Forces who had been deployed to the Persian Gulf during the time of the 1990/91 conflict. The second cohort consisted of members of the Canadian Forces who had not been deployed to the Persian Gulf during this time but who had been eligible to be so deployed. The GG Report (Gilroy, 1998) presented a description of the cohort identification process they used for the survey.

We identified a number of problems with using the cohorts as defined in the GG report for the record linkage study. An initial review indicated that the cohorts used in the GG study had been filtered by excluding military personnel who had died between 1991 and 1997 and by excluding about 600 people for whom no mailing address could be found. Since these exclusions would have created a serious potential for bias, the GG cohort lists were modified prior to use in the record linkage.

DND undertook to obtain further information about the construction of the cohorts. After considerable effort from personnel from DND and GG, it was determined that the original cohort lists prepared by GG, which included the dead military personnel and those with no addresses, were still available (the Master Cohort Lists). The creation of the Master Cohort List of names for the cohort had originally been performed by Goss Gilroy in 1996-1997. It was the result of the combination of records from multiple DND sources. These sources included DND administrative records, pension, other information from Veterans Associations and information from a variety of other approaches including advertisements in veteran, military and national newspapers. The Master Cohort List formed the second attempt at defining the study cohorts.

The Master Cohort List produced by Goss Gilroy contained the name, service number, rank, birth date and SIN for 4,476 Gulf War veterans and 6,223 controls. A copy of the Master Cohort List was provided to Statistics Canada for use in the record linkage study. For their survey, GG were able to obtain address information for 4,226 Gulf War veterans (94%) and for 5,922 of the comparison group (95%). In addition, they found that 23 of the Deployed Cohort had died between 1991 and 1997 and that 25 deaths had occurred in the military personnel selected for the control group. While these subjects were excluded from the GG survey, they are included in the Master Cohort List.

Subsequent work by DND and Statistics Canada revealed a number of other sources from which cohort members could be identified. These were used to supplement to GG Master Cohort List. In addition to the GG Master Cohort List, cohort members were identified from the following sources: death file search; DND medal list; Camp Doha participation; Unikom participation; Deployment history records; Gulf Deployment; Gulf Medal list; and the UN medal list. In many cases, subjects were identified on more than one list. A total of 511 names were added to the cohort list as a result of this process. In total, this process identified 11,279 cohort members, of whom 10,699 (95%) were on the original Goss Gilroy master list. This list formed the initial data file provided by Statistics Canada for analysis.

However, during the initial descriptive analysis of the two cohorts, it became apparent that this third cohort list also contained errors. It was noted that eight subjects were under age 15 at their putative date of entry into the cohort. Since this is clearly impossible, the data file was examined for data entry errors. It was discovered that there was a problem with the UN Medals list. HMRS People Soft had been requested to provide additional information about veterans on the original UN medal list which had been provided in paper format and contained only the names of 299 people identified from this source. It was discovered that the list returned from People Soft contained erroneous information for 38 persons. This was because there were 38 names on the UN Medal list where the name appeared twice in People Soft (i.e. there were two people in the Canadian Forces with exactly the same name). In preparing the list of Gulf War participants, People Soft staff had chosen the first name that appeared in their list once they completed the cross matching procedure. In some cases, this proved to be an invalid match. It was confirmed by DND that, according to People Soft, none of these persons were deployed to the Persian Gulf. Therefore, these 38 names were removed from the study cohort.

Following all of these revisions, the final study cohort consists of 11,233 military personnel, 5,139 in the Deployed cohort and 6,094 in the Non-deployed cohort. These were the cohort group which were the basis for the analyses.

In March 2004, after the analyses had been complete and the draft report had been submitted to Statistics Canada, Goss Gilroy provided some additional information. It indicated that a number of members of the two cohorts were actually medically unfit for deployment. GG reported that 157 of 4,482 members of the Deployed cohort were unfit for deployment (3.5% of the original deployed cohort which contained about 1,000 people less than the full Deployed cohort In the Non-deployed cohort, 281 of the original sample of 6,181 were labelled unfit (4.5%). There is no information to indicate neither why these people were retained in the sample nor if some of the unfit members in the Deployed cohort were among those later re-classified as non-deployed.

A second issue raised in comments submitted by GG after completion of the analyses concerned matching. It had originally been indicated that the two cohorts were matched on age and sex. However, the supplemental material stated that no matching had been done. The original sample selection description appeared to state that the Non-deployed cohort was selected using stratified sampling within age/sex groups. This is frequency matching as long as the proportion of subjects within each stratum reflects the proportion on the Deployed cohort. However, GG provided no information about the sample proportions within strata. In any event, the analysis was performed adjusting for age and sex differences between the cohorts. Hence, the issue of matching is not essential to the interpretation of the results.

Finally, GG used a sampling strategy of a primary sample and a replacement sample for people who could not be reached. The record linkage should have been based in the original sample members only. It is not 100% clear if that was actually done. However, based on the reports received during the process of assembling the cohort, it is reasonable to assume that the Non-deployed cohort did not include any members who were on the replacement sample list.

Appendix B: Record Linkage Methods Used by Statistics Canada

Data files

Gulf War Cohort File

An internal linkage was carried out on the Gulf War cohort file to identify and eliminate duplicates. This cohort file contained variables such as full names, sex, full birth date, social insurance number, residential address, city, province and postal code, spousal information, and the full date of death, when available.

"Alive" Follow-up

The validity of a cohort study depends fundamentally on complete ascertainment of the events of interest (e.g. cancer incidence, deaths) and the vital status of all cohort members. An evaluation of the extent to which follow-up losses have occurred is important, documentation of low loss rates adding to the credibility of the results. An "alive" follow-up was carried out using the Historic Tax Summary File to determine the vital status of cohort members at the end of the follow-up period, to aid in the identification and confirmation of deaths, and to help evaluate the mortality search.

The Historic Tax Summary File contains approximately 28 million records and covers the years from 1984 onwards. The file contains no financial data; rather, it only includes the minimum amount of data required to ascertain the vital status and location of individuals. The social insurance numbers from the cohort file were matched to the summary file to extract matching records. Names and birth dates from the tax records were then compared to those from the cohort file to verify that the records were, in fact, referring to the same individual. False matches were removed. For those cohort records with an accepted match, the following variables were appended to the nominal roll records: last tax year filed, filing province, date of death (if applicable), postal code, standard geographical code and an historical tax filing flag vector. These variables were added to help with the record linkage process and also with the manual resolution of uncertain matches. As well, after completion of the mortality linkage, these data provided an indication of the number of individuals not linked to the CMDB that could be presumed "alive" as opposed to lost to follow-up.

Canadian Mortality Data Base

The Canadian Mortality Data Base (CMDB) is a computer-readable file of all deaths registered in Canada, as well as voluntarily reported deaths of Canadian residents occurring in the United States. The CMDB currently captures over 200,000 deaths in each year and the data are available back to 1950. There are over approximately 8 million deaths in the CMDB. Data in the CMDB are obtained through the vital statistics system for national reporting of vital statistics data. Mortality data are submitted to Statistics Canada periodically by all provincial and territorial Vital Statistics offices. The data are processed, edit checks performed and, in some cases, coded at Statistics Canada.

Mortality data are further processed by the Occupational and Environmental Health Research Section of the Health Statistics Division, in Statistics Canada, and maintained in a format suitable for record linkage projects in the form of the CMDB. Processing includes standardizing data fields, such as names, and generating fields required for record linkage, such as the phonetic NYSIIS (New York State Individual Intelligence System) surname codes. Duplicate mortality records, which contain data variations, such as alternate surnames, may be created during processing of the file.

Historically, the CMDB has captured a single underlying cause of death, which is coded in the ICD version in effect at the time of death: ICD-6 (1950-1957); ICD-7 (1958-68); ICDA-8 (1969-1978), ICD-9 (1979-1999), and ICD-10 (2000).

Canadian Cancer Data Base

At the national level, cancer incidence data for the years 1969-1991 was collected through the National Cancer Incidence Reporting System (NCIRS), and for the years 1992 to the present it is collected through the Canadian Cancer Registry (CCR). The provincial cancer registries and the health authorities in the two territories send their cancer incidence records to Statistics Canada where they are edited and standardized. Statistics Canada also transforms the data into a format suitable for record linkage, thereby creating the Canadian Cancer Data Base (CCDB). The CCDB is an historical file in machine-readable form, which contains over 3.2 million cancer events from 1969 onwards.

The provincial/territorial registries include persons diagnosed with a malignant cancer from 1969 onwards. The CCDB covers all individuals whose usual place of residence is Canada or who are non-permanent residents. Benign, in-situ and uncertain lesions are not consistently reported by all provinces and have been omitted from the study. The availability of identifying information on the CCDB has varied over time. All incidence cases in the CCDB are given a diagnosis code according to the International Classification of Diseases, 9th Revision (ICD9), which has been in use since January 1979. Cancer incidence classifications used from 1969 to 1979, ICDA-8 codes, were re-coded to ICD9 for each jurisdiction.

Methodology

The following linkages were carried out:

(1) A basic internal linkage to identify duplicates within the cohort file;
(2) An “alive” follow-up to determine the vital status of individuals in the cohort;
(3) A linkage to the Canadian Mortality Data Base (CMDB); and
(4) A linkage to the Canadian Cancer Data Base (CCDB).

Pre-Processing, Internal Linkage and “Alive” Follow-up

Upon receipt of the cohort file, an initial quality assessment was carried out to determine the completeness, and the validity of the data. This procedure serves to identify data errors (such as invalid dates) or omissions that may prevent the correct linkage of a record. The quality assessment also allows the staff at Statistics Canada to become more familiar with the data in the cohort file, which is required prior to developing and refining the linkage strategy. A basic internal linkage was done to identify and remove duplicates.

Once the initial quality assessment was complete, the file was pre-processed. Pre-processing the file involved two steps:

1) Editing and preparing frequency checks to further identify potential errors; and
2) Expansion of the data to increase the chances for a correct linkage.

During this phase all records were run through a sex check routine, which compared given names and sex codes on the cohort file to a Statistics Canada internal file that contained typically male and female names. An alternate version of the record was created for all records with doubtful given name/sex code combinations, with the opposite sex code assigned. This was necessary since the sex code is used as part of the pocket criteria (see Preparing Linkage Pocket). The records on the cohort file were also put through a number of routines to verify and standardize the spelling of names. Where there was some question as to the accuracy of the data but confirmation was not available, an alternate or duplicate record was created which contained a variation of the data item in question. Expanding the data through the creation of alternate records increases the chances for a correct linkage.

An “alive” follow-up was carried out as described previously. As the final step, the “alive” follow-up information was added to the file.

Preparing Linkage Pocket

As is the convention in probabilistic record linkage, it was necessary to identify a pocket within which records would be compared and pairs created. A pocket contains a group of records, which have a common value in the specified field. Using the defined pocket, as an example, records in File A, (cohort), would be compared only to records on File B, containing the same pocket value.

For this study, a concatenation of the sex code and the NYSIIS code generated from the surname was used as the main pocket. The NYSIIS system is an encoding system that simplifies the spelling of surnames so that spelling variations from various source files might be eliminated when doing a comparison between records, thus improving the possibility of establishing a link. The NYSIIS code pocket available for this linkage included all records from the pre-processed cohort as well as the alternate records that were generated during the pre-processing of the file. Note that the sex code was part of the pocket as well, which explains the emphasis in Section 1.1 on ensuring the correct sex code was assigned.

Rule definitions and outcomes

In order to link the cohort file to the CMDB and the CCDB, it was necessary to define comparison rules. Comparison rules specify the criteria to be used in determining whether two records relate to the same individual. In order to define these criteria it was necessary to determine which identifiers from each file would provide the most useful information. This was determined in part by the discriminating power of the identifier, the reliability of the data item and the level of completeness of the identifier, and experience with past linkages.

The compare rules specified the relationships, and outcomes resulting from each comparison. The two most obvious outcomes of a comparison are full agreement and disagreement. Where more than one relationship could be defined or where allowance was to be made for errors in the data, several levels of outcomes, or partial agreements, were defined. Information required to define the rules and outcomes was obtained in part from analysis and pre-processing of the files and in part from previous experience in mortality and cancer linkages of a similar nature. The initial rules and outcomes were tested and refined using a sample of the data prior to running the full mortality linkage. Some rules and relationships are obvious and are common to other linkage projects. For example, one would expect that records, which pertain to the same individual, would probably agree on surname and given names and on date of birth. Other rules are more complex and specific to the data sets being linked.

Development of weights

The theory of probabilistic record linkage works on the premise that certain comparison results are characteristic of truly linked pairs while others are characteristic of truly unlinked pairs. Therefore, each rule outcome is assigned a weight, derived from probabilities of occurrence, which will argue for or against the match, depending on whether the outcome is characteristic of linked or unlinked records.

The unlinked weight components were calculated based on the frequency with which the rule outcomes were observed among record pairs that do not belong together, which is approximately equal to the frequency with which the rule outcomes would be observed among randomly paired records. The initial linked weight components were estimated based on experience with previous follow-up projects and information obtained from pre-processing the cohort file. These weights were used during the creation of record pairs and were later refined through an iterative process of weight refinement.

Following the creation of record pairs, some of the unlinked weight components were replaced with frequency or value-specific weights, which are calculated, based on the level of agreement of a specific value of the identifier. Using frequency weights, agreement on a rare surname will carry a higher weight than agreement on a very common surname, while general weights would not make such a distinction.

Comparison Phase

In this phase, the cohort file was compared to the Statistics Canada files (CMDB, CCDB) using the comparison rules, the weights were assigned based on rule outcomes, and the upper, lower and cut-off thresholds were set. The probabilistic record linkage process produces a total weight for a record pair that offers a quantitative measure of the likelihood two records refer to the same entity. Theoretically, record pairs with a weight above the upper threshold are accepted as "definite" links. Record pairs with a weight below a lower threshold are rejected as non-links. Record pairs with a weight that falls between the thresholds form the "grey zone", which requires manual review and resolution.

The probabilistic record linkage process is often run iteratively, with refinements of weights and comparison rules between iterations. For this reason, the record pairs with a total weight below the lower threshold are still stored for further use. There is, however, a further cut-off threshold below the lower threshold, below which the record pairs are not kept and are thus not available for re-evaluation in further iterations. This is done to save on computer resources.

Records were paired for comparison as a potential linkage only if they had the same sex and NYSIIS coding, or birth date agreement or death date agreement, and these pairs were evaluated using the specified rules with their associated weights. Any pairs with a total weight falling below the cut-off threshold were not considered potential matches and were eliminated from further processing.

For both the mortality and cancer linkages, a large sample of record pairs over a range of total weight values was reviewed manually to decide whether each pair represented a true link or not. This process helped to refine the lower threshold settings, thereby raising its value to reflect where true links were discovered.

Record pairs were then grouped to bring together all pairs that referred to the same individual. In this way, all competing links could be evaluated collectively during manual resolution, and a decision made as to which, if any, was a good link.

Manual resolution

For both the mortality and the cancer linkages, manual resolution of potential links was completed on site at Statistics Canada by members of the study team who were sworn in as "deemed employees".

The complete death registrations were also available on microfilm/CD-ROM, and were used to check or confirm data items as required during manual resolution for the mortality study. The online version of the CMDB was also searched for deaths noted on the original cohort file, or identified on the "alive" follow-up files, but not found through record linkage with the CMDB.

Death Linkage Quality Check

To assess the quality of the current mortality linkage, any record that had an indication of a death prior to the study, either as reported by DND, on the cohort file or through the "alive" follow-up process, which failed to find a correct link this time was reviewed manually. The online version of the CMDB, a secured Oracle application with limited-use access, was searched for these deaths using broad search criteria so that variations in data fields would not be a deterrent to finding the appropriate death record.

Analyses files

The mortality and cancer analysis files were prepared on completion of the manual resolution and finalization of the linkages. The name variables did not appear on the files and were replaced by a unique sequence number. Other variables were: sex; marital status; date of birth; year in; year out; rank; a cohort indicator flag; and, a death indicator flag (from DND). For those found to be deceased, the additional variables included: date and province of death; the underlying cause of

death; the date and province/territory of birth; autopsy code; and, the total mortality linkage weight.

The cancer analysis file contained the same set of DND variables. For those matched to the CCDB the additional variables included: residence province and census division at date of diagnosis; date and province of birth; date of diagnosis; diagnostic information (such as ICD9, ICD-O topography and morphology, morphology code and indicator, source of registration, method of diagnosis, laterality, primary site number); patient vital status from the cancer file; date and province of death (if applicable); and the total cancer linkage weight.

Maintaining Confidentiality

All analytical work was done using these files within the secured domain of Statistics Canada offices. Any external researcher had an enhanced security check, took the oath of secrecy and was declared a "deemed employee" of Statistics Canada. All output results were of a statistical variety and the standard reliability and confidentiality rules were applied before inclusion in a final report.

Appendix C: Data Management for Primary Files

Data Management

This section presents a description of the process used to validate the analytic files, the data errors found, the variable coding and the decisions taken. The data sets were provided in two separate files. The first file contained about 11,000 subjects, giving the unique Sequence Number and basic information about the subject. It included mortality information where appropriate: date and place of death, cause of death (ICD-9 code) plus other information such as whether an autopsy had been performed. This file listed every subject in the cohort, whether they had died during follow-up or not. It also contained a variable that provided information on how each subject had been identified for the study.

The second file had 109 records and was composed of subjects who had been diagnosed with cancer. It contained the Sequence Number that was used to link the files. While this file repeated the personal information contained in the first file on these 109 subjects, most of the information in the file was related to the cancer diagnosis, including the place and date of diagnosis and ICD coding of the cancer.

Initial programmes were produced to read the data files. It was necessary to use character variable to read the ICD codes since these contained non-numeric data (e.g. C) and were right justified without decimal points. Further, the records did not have a fixed record length. This occurred because the cause of death information was at the end of the record and the records were not 'right padded' with blanks. Hence subjects who had not died were missing this information with the result that their record was truncated several characters shorter than the record for subjects who had died.

Statistics Canada provided elements of the data dictionary from related studies that defined the codes for the numerical values of the variables in both files. There was some confusion about the timing of when certain variables were measured (e.g. marital status). After consultation with DND, it was determined that all personal information related to the time period of the Gulf War (1990-1991) rather than to the time of the Goss Gilroy survey (1997). There are some very young officers in the cohorts (e.g. a captain at age 22). This suggests that the rank may have been the rank at the time of the GG survey for at least some subjects. The results have used the rank as provided in the data file. It is also possible the issue with ranks arose from the same problem that led to a 15 year old being included in the file, that is, incorrect linkage of names to CF records done at PeopleSoft for a small group of subjects identified through paper records.

All subjects with a cause of death listed were manually checked. This involved several steps:
The vital status and autopsy variables provided in the data file were cross-tabulated. This revealed a problem. Nineteen people were listed as 'alive' but also were coded as having had an autopsy. All but one of these people had a cause of death listed. This provided strong evidence that the vital status variable in the mortality file was not the summary vital status. Rather, it appeared to have been measured at some intermediate time point, most likely when the Goss Gilroy survey was done. Hence, a new vital status variable was created based on the ICD cause of death information.

A listing was produced of the cause of death. These were manually cross-referenced to the ICD manual. This revealed that ICD codes greater than 800 were E-codes even though the 'E' was missing from the code in the file. This process also identified three unusual causes of death that were cross-referenced with actual death certificates and corrected where applicable.
Twenty-five subjects were listed as having died of cancer. These were cross-referenced manually with the cancer file. Four subjects were identified who had cancer as a cause of death but who were not in the cancer file (cancer types: Kaposi's sarcoma, rectal neoplasm, malignant melanoma and brain neoplasm). It is likely that these subjects were diagnosed outside Canada. After consultation, it was decided to add these subjects to the cancer file. After the review of the death certificate for one of these veterans with cancer, it was discovered that the cancer had been diagnosed in 1989 and this person was ineligible for inclusion in the analysis of cancer endpoints. The other three subjects were added to the cancer file.

The cancer file includes a mixture of codes from ICD-8, ICD-9, ICDO-T(v1), ICDO-M(v1), ICDO-T(v2) and ICDO-M(v2). The codes were manually checked and each subject was assigned three definitive codings: ICD-9, ICDO-T(v2) and ICDO-M(v2). The analysis relied on ICD-9 codes. This is because the ICDO system codes leukemias and lymphomas using mainly the ICDO-M value while coding other cancers using ICDO-T codes. While the information is valid, it makes analysis more complicated. For other cancers, the ICDO-M codes contain information of no interest to the primary analysis and were ignored completely. In any event, it transpired that for most subjects, there was insufficient information to assign ICDO-M codes.

The first step in the cancer coding involved producing a print-out of the ICD values for every subject with a cancer. These codes were transcribed manually to a listing sheet and linked to the corresponding textual description of the cancer. This was done by a manual inspection of the ICD-9 and ICDO coding manuals. In addition, the ICD-9 codes were converted to ICDO (v2) codes. This process produced both ICDO-T and ICDO-M codes although the ICDO-M codes were uninformative for most tumours (other than leukemias, lymphomas and melanomas). The ICD-9 to ICDO conversion was done using a programme developed jointly by the International Agency for Cancer Research (IARC) and the International Agency for Cancer Registration (IACR). This programme (IARC/IACR Cancer Registry Tools v 1.01) was downloaded from their web site http://www.iacr.com.fr/software.htm

Following this process, each cancer had between three and six classification codes. They were manually compared for each subject. In all cases, the codes were either identical or consistent. Three ‘definitive’ cancer codes were assigned for each subject as part of the manual review: ICD-9, ICDO-T (v2) and ICDO-M (v2). The following process was used. In all cases of solid tumours, all of the replicate ICD codes recorded in the file for a subject gave the same classification. Also, in all cases, the ICDO-M code produced by the automated ICD-9 conversion was: 8000/3 (Malignant, NOS). After review, two classification codes were assigned: the original ICD-9 code and the ICDO-T(v2) code produced by automatic conversion. The ICDO-M(v2) code was taken from that provided in the original file (if available) or else was assigned ‘8000/3’.

In ICD9, leukemias, lymphomas, melanomas. are assigned a classification code. However, in ICDO, the type of neoplasm is coded into the ICDO-M variable while the ICDO-T is either ’80.9’ (primary site unclear) or ’77.9’ (multiple lymph nodes). There appeared to be a consistent difference in the use of these two ICDO-T codes between the original Statistics Canada coding and the coding from the automated ICD9 conversion. The original ICD9 code was retained. When available, the ICDO-T and ICDO-M codes provided in the original file were included as long as they did not conflict with the ICD9 codes. If they did, they were ignored. If the file did not contain an ICDO coding, the coding from the conversion programme was used.

The new codes were stored in a third data file. This file was linked into the two primary analysis files. After linkage, the original cancer classification variables were dropped and all analyses were done using the newly assigned codes.

This review identified five problematic records. These were referred to Statistics Canada for consideration and advice. Three cases which were coded as borderline, uncertain or non-malignant tumour were dropped from the analysis. In the two others, the ICD-9 code was used.

Next, a manual comparison of the listed cause of death for all subjects who died of cancer in comparison to their cancer type as given in the cancer file was done. In all cases, the information was the same or consistent.

A review of the cancer file revealed that the province of registration (for subjects who had died) was coded using a different system than that used for the mortality coding. The cancer file provincial coding was changed to match the one used in the mortality file.

An initial ‘sanity’ check was run to compare information in the mortality and cancer files that should be the same. This revealed that the information was identical except for three subjects. In these three subjects, the cancer file was missing information about the province and year of

registration for the person's death. The variables from the mortality file were used only when they were contained in both data sets.

A preliminary analysis file was created by merging the three source data files. The variable list was pruned and converted into the final list. This involves re-naming some variables. The variables that were not needed were 'dropped' from the permanent SAS file. Finally, the name variables were assigned 'labels' and formats.

A number of key analytical variables were derived. They were participation in Camp DOHA/UNIKOM, reference date, age at entry, vital status at end of study, age at death (if applicable), death classification based on 23 cause-specific groups and on the external/disease dichotomy, follow-up to death or end of follow-up, grouped age at entry variables (10-year and 5-year groupings), autopsy flag variable and various other time variables and flags which are required in the various analysis programs.

A final analysis file was created from the preliminary analysis file. The main difference between the two files is that the Final Analysis File contains a series of summary variables for the person-years of follow-up related to the various analyses that were performed.

Two file definitions, one for use at the university and one for use at Statistics Canada were created. The appropriate section was chosen based on a macro variable. This facilitated writing code that would work at both worksites. Note that the university programmes were run using 'dummy' data created at random to support program development. This was done to comply with the confidentiality requirements of Statistics Canada restricting access to the data files on the secure computer system within the Statistics Canada building. All programmes were further tested and de-bugged on the real datasets at Statistics Canada prior to performing the definitive analyses.

Coding Issues

Rank

Rank was coded into four categories, based on the standard classification used by DND. There were 18 subjects who could not be coded and were assigned missing value codes. They are retained in the main analyses but would be excluded from any analysis that used rank as an explanatory variable.

Location At The Time Of The GG Survey

This information was not used in the analysis. The following observations are made in case it is to be included in future analyses.

The provincial name at the time of the GG survey was subject to substantial problems. For example, there are three different spellings for Ontario (ON, ONT, OUT). Since these variables were not used in any of the analyses, no attempt was made to correct them. Further, they were not retained in the primary analysis file. For similar reasons, the 'code' for the province at the time of the GG survey was dropped.

The postal code at the time of the GG survey was reasonably complete but was not of interest in the analysis. It was dropped from the primary analysis file. If a future analysis wanted to use postal code (for example, as a surrogate for SES), the analysis file would have to be re-created. However, since the postal code is based on the time of the GG survey rather than at the time of the Gulf War, this variable may have limited relevance.

Most subjects (97.2%) failed to record a 'city' of residence at the time of the GG survey. In light of the huge amount of missing data and the lack of relevance to the analyses, this variable was dropped from the primary analysis file.

Information On Death Registration

There were 106 recorded deaths in the original file. However, 10 of these deaths occurred after December 31, 1999, the end of death registry follow-up. This yielded 96 total deaths during the follow-up period.

The year of death was coded as a two-digit year. When read as a numeric variable, people dying in 2000 and 2001 were coded as dying in '0' and '1' respectively. Code was written to convert the year of death into a four-digit year, taking into account the Y2K problem.

Subjects who died before their assigned entry date into the cohort were excluded from the cohort since the cohort entry date was selected to be after the tour of duty in the Gulf had ended. Hence, soldiers who died during the deployment would be listed as belonging to the cohort but would not be eligible for follow-up.

Subjects who died after the end of follow-up were re-coded to indicate their vital status as of the end of follow-up.

Cause Of Death

One subject died as a result of a blood transfusion (E879.9). The cause of death for this subject had been obtained from the DCSA Casualty database. They had assigned a cause of death coded as E879.9. Staff at DND reviewed the file on this person. This review revealed that the correct cause of death code should have been 441.0 (Aortic aneurysm or dissection). The cause of death was corrected in the data file.

Miscellaneous

One subject was missing the day of the year when his cancer was diagnosed. The date was in the cancer file as: 03/00/1996. It was converted to 03/15/1996.

Sanity Errors

The first data editing check involved comparing information which was contained in the cancer and mortality files and which should have been identical. This check was only possible for the subjects who were diagnosed with cancer. Three errors were found. In each case, it was a soldier who had been diagnosed with lymphoma and had subsequently died from the cancer. The cancer had been detected and the subject was in the 'cancer' file. However, the fact and time of death was not recorded in the cancer file. This was handled correctly because the information in the mortality file superseded the information on the cancer file for death related variables.