



Bergman, B. P., Mackay, D. F. and Pell, J. P. (2017) Lymphohaematopoietic malignancies in Scottish military veterans: Retrospective cohort study of 57,000 veterans and 173,000 non-veterans. *Cancer Epidemiology*, 47, pp. 100-105.(doi:[10.1016/j.canep.2017.02.001](https://doi.org/10.1016/j.canep.2017.02.001))

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Lymphohaematopoietic malignancies in Scottish military veterans: Retrospective cohort study of 57,000 veterans and 173,000 non-veterans

Short running title: Haematological malignancies in veterans

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Word count (main text) 3035

Conflict of Interest: None

Funding and support: No external funding or support

ABSTRACT

Background

Lymphohaematopoietic malignancies are common in the general population. There have been concerns that military service may be associated with increased risk as a result of occupational exposures. To date, few studies have demonstrated an increased risk, although a disability pension is payable to veterans who were present at nuclear tests and who develop leukaemia (other than chronic lymphocytic leukaemia). The aim of the study was to utilise data from the Scottish Veterans Health Study to examine the risk of lymphohaematopoietic malignancy following military service in a large national cohort of veterans.

Methods

Retrospective cohort study of 57,000 veterans and 173,000 non-veterans born between 1945 and 1985 matched for age, sex and area of residence, adjusted for areal deprivation and followed up for up to 30 years, using Cox proportional hazard models to compare the risk of lymphohaematopoietic malignancy overall, by diagnosis and by sex and birth cohort.

Results

We found no statistically significant difference in risk between veterans and non-veterans either for all leukaemias (Cox proportional hazard ratio 1.03, 95% confidence intervals 0.84-1.27, $p=0.773$), Hodgkin lymphoma (hazard ratio 1.19, 95% confidence intervals 0.87-1.61, $p=0.272$) or for non-Hodgkin lymphoma (hazard ratio 0.86, 95% confidence intervals 0.71-1.04, $p=0.110$).

Conclusion

Our findings provide reassurance that service in the UK Armed Forces is not associated with increased risk of lymphohaematopoietic malignancy.

KEYWORDS

Veterans

Military

Leukaemia

Hodgkin lymphoma

Non-Hodgkin lymphoma

Retrospective cohort study

BACKGROUND

Lymphohaematopoietic malignancies are common in the general population, leukaemia accounting for 3% of all new cancers, with an age-standardised incidence rate of 10·2 per 100,000 per year in the UK. In addition there are 15·1 cases of non-Hodgkin lymphoma per 100,000 population (4% of all new cancers), whilst Hodgkin lymphoma accounts for a further 2·9 cases per 100,000 per year. The lymphomas are the second most common cancers in male adolescents and young adults, whilst leukaemia is the fourth commonest. (Cancer Research UK 2012) Concerns have been expressed that occupational exposures, especially to ionising radiation, (Gardner 1988) fuels, (Austin et al. 1988) and electromagnetic fields (Garland et al. 1990) may result in increased risk in military personnel. In 1980, a US report linked nine cases of leukaemia to participation in military exercises during the 1957 nuclear test explosion. (Caldwell et al. 1980) In 2001, it was reported that military service in the Balkans may have been associated with an increased risk of leukaemia as a consequence of the use of depleted uranium munitions some five years earlier, following the deaths of six Italian soldiers who had served there. (Dyer 2001) By contrast, studies of Porton Down veterans who took part in tests of chemical warfare agents between 1941 and 1989 showed no statistically significant difference in risk of leukaemia or other lymphatic or haematopoietic cancer in comparison with unexposed veterans. (Carpenter et al. 2009) Overall, formal epidemiological evidence has provided a conflicting picture, with most studies reporting no increased risk associated with either radiation, (Muirhead et al. 2003) or exposure to electromagnetic fields (Garland et al. 1990) in military personnel.

Assessing occupational exposures in military personnel presents challenges as there are few official records. Exposure records are especially likely to be suboptimal during conflict, when risks may be greatest. (Cherry et al. 2001) Both training and deployed operational service may involve exposure to a wide range of potentially hazardous substances; although these are controlled wherever practicable, some exposures inevitably remain.(Macfarlane et al. 2005) Therefore, examination of the impact of military service overall on the risk of lymphohaematopoietic cancer is particularly important, but there have been few long-term studies on UK personnel. The Scottish Veterans Health Study provided an opportunity to examine the risk of leukaemia, Hodgkin lymphoma and non-Hodgkin lymphoma in a large national cohort of military veterans irrespective of military experience and exposures, in comparison with age, sex and geographically matched people with no record of military service, in order to examine whether military service overall was associated with increased risk.

METHODS

The Scottish Veterans Health Study is a retrospective cohort study of all 56,570 military veterans (male and female) who were resident in Scotland and registered for NHS care before and after military service, and who were born between 1 January 1945 and 31 December 1985, and a comparison group of 172,753 individuals with no record of service matched 3:1 for age, sex and postcode sector of residence (mean population 5,000). The cohort was identified from the NHS Scotland database, which covers the entire Scottish population and includes dates of military service where relevant. Individuals were included as 'veterans' if they had both 'Exit to Armed Forces' and 'From Armed Forces' ciphers on the NHS record; they were categorised as 'non-veterans' if both ciphers were absent. Those having only one of the two ciphers were excluded from both groups as their veteran status could not be established with certainty. The study cohort and methods have been fully described elsewhere.(Bergman et al. 2014b) Demographic data obtained from electronic NHS registration records were electronically linked at an individual level to routine hospital admissions data (Scottish Morbidity Record SMR01), cancer registrations (SMR06), and death certificates to provide information on first episode of leukaemia, Hodgkin lymphoma and non-Hodgkin lymphoma (hospitalisation or death) and all-cause death. The NHS demographic record provided dates of entering and leaving the Service for veterans. The maximum period of follow-up was from 1 January 1981 (or date of leaving the Service, for veterans, if later) to 31 December 2012. The data extract was pseudo-anonymised and approval for the study was granted by the Privacy Advisory Committee of the Information Services Division of NHS Scotland.

Deprivation

Details of the Scottish Index of Multiple Deprivation (SIMD) are published by the Scottish Government.(Scottish Government 2012) In Scotland, there are 6,505 datazones, based on postcode of residence, with a mean population of 800. The Scottish Index of Multiple Deprivation (SIMD) for each datazone is derived from information on income, employment, health, education (including skills and training), housing, crime, and access to services. The SIMD has been used to derive quintiles of areal deprivation for the Scottish population; ranging from 1 (most deprived) to 5 (least deprived). We used postcode of residence to categorize the cohort participants according to these quintiles.

Statistical analyses

'Leukaemia' was defined as ICD-10 C90-C95 and ICD-9 203-208, 'Hodgkin lymphoma' as ICD-10 C81 and ICD-9 201 and 'non-Hodgkin lymphoma' as ICD-10 C82-C85 and ICD-9 200 and 202, at any position in the record. Cox proportional hazard models were used to examine the association between veteran status and cumulative risk of any of these lymphohaematopoietic cancers, combined and separately, using age as the time dependent variable, age at first recorded occurrence as the failure time and death (if no lymphohaematopoietic cancer) as the censor time. The *a priori* rejection level was set at 0.05. Cox proportionality assumptions were tested using methodology based on Schoenfeld residuals.(Grambsch and Therneau 1994) The log-likelihood test was used to test for interactions with sex and birth cohort. A landmark analysis was performed using age 20 years as the starting point in order to exclude people with a history of childhood leukaemia or lymphoma, which would have precluded military service. The models were run univariately and then repeated adjusting for the potential confounding effect of deprivation. The analyses were repeated stratifying by grouped year of birth to examine potential birth

cohort effects. Cox proportional hazard models were used to compare case-fatality one and five years following diagnosis between veterans and non-veterans. All analyses were performed using Stata v12.1 (©1985-2011 StataCorp).

Role of the funding source

Nil. No external funding or support was received for this study.

RESULTS

After data cleansing, 56,205 (99.3%) veterans and 172,741 (99.9%) non-veterans were included in the analysis. There were 50,970 (90.7%) male veterans and 5,235 (9.3%) female, reflecting the gender balance of the UK Armed Forces. The earliest date of entering service was January 1960; the latest date of leaving service was December 2012. The mean period of follow-up was 29.3 years, and there was a total of 6.7 million person-years of follow-up among veterans and non-veterans combined. During the period of follow-up, 294 (0.52%) of the veterans had a diagnosis of leukaemia, Hodgkin lymphoma or non-Hodgkin lymphoma, compared with 974 (0.56%) of the non-veterans. The difference was not statistically significant, unadjusted hazard ratio (HR) 0.96, 95% confidence intervals (CI) 0.84-1.10, $p=0.541$. The hazard ratio was unchanged after adjusting for areal deprivation (Table 1). Mean age at diagnosis of leukaemia was 51 years for veterans and 50 years for non-veterans. For Hodgkin lymphoma the mean age at diagnosis was 41 years for veterans and 37 years for non-veterans, whilst for non-Hodgkin lymphoma it was 48 years for veterans and 47 years for non-veterans.

There were 125 (0.22%) cases of adult leukaemia in veterans compared with 365 (0.21%) in non-veterans. For Hodgkin lymphoma the figures were 59 (0.10%) and 182 (0.11%) respectively, whilst for non-Hodgkin lymphoma there were 144 (0.26%) cases in veterans and 538 (0.31%) in non-veterans. The Cox proportional hazard ratios showed no statistically significant differences, either in the unadjusted model or after adjusting for deprivation, adjusted HR 1.04, 95% CI 0.84-1.28, $p=0.720$ for all lymphohaematopoietic malignancies analysed together. There was a small non-significant increase in risk of Hodgkin lymphoma in veterans, adjusted HR 1.18, 95% CI 0.87-1.61, $p=0.279$, which was balanced by a non-

significant decrease in the risk of non-Hodgkin lymphoma, adjusted HR 0·86, 95% CI 0·71-1·04, p=0·110. There were no differences in risk between veterans and non-veterans when stratified by sex. Analysis by birth cohort showed no significant differences for any birth year (Tables 1 & 2). The increased HR for veterans in the 1970-1974 birth cohort was based on only 15 veteran cases and therefore may have arisen by chance; longer follow-up will be needed to clarify this finding.

One year survival did not differ significantly between veterans and non-veterans after a diagnosis of lymphohaematopoietic cancer, adjusted HR 1·13, 95% CI 0·81-1·57, p=0·485.

Five-year survival similarly did not differ, adjusted HR 1·11, 95% CI 0·8-1·41, p=0·367 (Table 1).

DISCUSSION

The Scottish Veterans Health Study has demonstrated no statistically significant differences between veterans and non-veterans in the risk of leukaemia, Hodgkin lymphoma or non-Hodgkin lymphoma (NHL), in a large population-based cohort spanning 30 years of follow-up and, for the veterans, military service over a 50-year period covering a wide range of occupational exposures.

Although the different types of leukaemia and lymphopietic cancers have different aetiologies and risk factors, and many cases are idiopathic, there is some commonality.(Descatha et al. 2005) Documented risk factors encompass exposure to ionising radiation (including radon), (Ron 1998) smoking,(Brownson et al. 1993) benzene, (Austin et al. 1988) previous chemotherapy, genetics, and obesity,(Lichtman 2010) although later studies have cast doubt on the role of radon. (Laurier et al. 2001) Only benzene and ionising radiation have been conclusively demonstrated to be carcinogenic to the haematopoietic system.(Descatha et al. 2005) No clear occupational link has been demonstrated;(Bowen 2008) occupational (predominantly agricultural) exposure to animals has been found to be associated with increased risk but confounding by pesticide exposure could not be excluded.(Svec et al. 2005) Other studies suggest an increased risk in healthcare workers (Blair et al. 2001) cleaners, teachers, child care workers, and hairdressers (Miligi et al. 1999) and catering staff.(Costantini et al. 2001) Military service encompasses a wide range of occupations and activities, and therefore potential exposures. Individual-level exposures may be recorded inconsistently, or not at all, (Cherry et al. 2001) except where statutorily required.(Capleton et al. 2001) Two earlier exposures of military personnel to potential haematopoietic/lymphopietic harm raised widespread concerns;

the exposure of many thousands of UK, US and other Service personnel to ionising radiation in the course of the nuclear tests which took place between 1952 and 1967,(Roff 2002, Muirhead et al. 2003) and the exposure of a large number of US personnel and a smaller number of New Zealand and others to the dioxin-containing defoliant Agent Orange during the Vietnam War.(Frumkin 2003) As UK personnel were not involved in the latter exposure, Agent Orange will not be further considered in this paper.

Of the 20,000 British Service personnel who were involved in the nuclear test programme, the UK Ministry of Defence estimates that only about 10% were exposed to measurable levels of radiation.(Ministry of Defence 2008b) Safety precautions were in accordance with extant standards at the time. Extensive follow-up of exposed personnel and their families has been conducted over the intervening 60 years, and still continues. The results provide an insight into long-term risks of leukaemia in military personnel, and subsequently veterans, through the inclusion of military controls. The first study, a case-control study of over 22,000 participants and a similar number of military controls, was conducted by Doll and colleagues at Oxford and the results were published in 1988.(Darby et al. 1988) Increased rates were found for leukaemia (SMR 113) and multiple myeloma (SMR 111) when compared with national rates, but the incidence of these conditions in the control subjects (SMR 32 and 0 respectively) was much lower than the national rates. At follow-up ten years later, any excess risk of leukaemia or myeloma relative to either controls or national rates had disappeared. Neither all-cause mortality nor cancer mortality differed between participants and controls, and all were lower than national rates. A modest increase in risk of leukaemia was found however after excluding chronic lymphocytic leukaemia (CLL) (which is not considered to be linked to radiation exposure) (RR 1.83, 95%

CI 1.15-2.17).(Muirhead et al. 2003) The UK Government awards a War Disablement Pension for leukaemia (other than CLL) in those who were present at the nuclear test sites, based on the reports by the National Radiological Protection Board (NRPB)(Muirhead et al. 2003, Darby et al. 1988) although without acknowledging a causal link.(Ministry of Defence 2008a) The award of compensation to veterans of other major national Armed Forces for lymphohaematopoietic malignancies is dominated by the sequelae of Vietnam service and is not a valid comparator.(McBride et al. 2013)

The number of Scottish veterans who took part in the nuclear test programme could not be determined but as approximately 10% of the Armed Forces is recruited from Scotland,(Ministry of Defence 2012) a figure of around 2,000 is likely. Participation in the nuclear test programme concluded in 1967, therefore only around 10% of our cohort would have been eligible to participate but as the overall percentage of the Armed Forces who took part was small, it is likely that very few did so. As there were only 40 cases of leukaemia excluding CLL in the entire nuclear test participant cohort followed up to 1998,(Muirhead et al. 2003) the contribution from these veterans within our cohort is likely to have been minimal.

Chronic high-level exposure to benzene is a known risk factor for acute myeloid leukaemia (AML).(Natelson 2007) Military personnel are most likely to have been occupationally exposed to benzene as a component of either vehicle fuel or aviation fuel,(Capleton and Levy 2005) but neither of these specific exposures has been shown to be associated with increased risk of AML.(Lynge et al. 1997, D'Mello 2007)

Smoking is linked to an increased risk of AML,(Pogoda et al. 2002) which in part results from the presence of benzene in cigarette smoke.(Korte et al. 2000) A study of leukaemia and smoking in US veterans found a relative risk of 1.53 in smokers relative to non-smokers for all types of leukaemia, whilst an odds ratio of 1.2 was reported in a general population study (Kinlen and Rogot 1988, Kane et al. 1999). We have previously reported an increased risk of smoking-related cancer in older members of the Scottish veteran cohort (Bergman et al. 2016), which is consistent with reported high rates of military smoking in the 1960s when many of the Scottish veteran cohort were young soldiers.(Richards and Crowdy 1961) It might therefore be anticipated that a higher risk of leukaemia would be found in the older veterans. As we found no statistically significant difference, we conclude that the 9% population attributable fraction for smoking as a risk factor for leukaemia (Danaei et al. 2005) may be too small to give rise to any discernible difference in our cohort.

Risk factors for both Hodgkin lymphoma and non-Hodgkin lymphoma (NHL) are similar to those for the leukaemias and include age, gender and family history. A number of studies suggest that smoking is a risk factor for Hodgkin lymphoma,(Briggs et al. 2002) whilst the evidence in respect of smoking is inconclusive for NHL.(Morton et al. 2005) Radiation, chemotherapy and immunosuppression are also risk factors for NHL; (Krishnan and Morgan 2007) the latter two are unlikely to be a source of risk in military personnel during service but may become relevant in later life.

We were able to adjust for areal deprivation, but found little difference on adjusting for this variable. The role of socio-economic status in relation to lymphohaematological malignancy in adults is unclear although there is some evidence of increased risk in people resident in proximity to industrial sites (Benedetti 1999) which are generally associated with higher

levels of deprivation.(Dolk et al. 1995) In other studies, we have shown an association between areal deprivation and veterans' risk of smoking-related disease,(Bergman et al. 2014a, Bergman et al. 2016) adding further weight to our conclusion that smoking does not appear to be an important risk factor for lymphohaematopoietic malignancy in our cohort.

The strengths and limitations of the present study are similar to those described elsewhere.(Bergman et al. 2014b) A major strength that it was based on a large cohort covering the whole of Scotland with 30 years follow-up. The diagnosis of leukaemia, Hodgkin lymphoma and NHL was taken from hospital admission, cancer registration and death records, and is therefore likely to be both reliable and reasonably complete in respect of those events occurring within Scotland. The use of record linkage to analyse individual level data directly derived from health records allowed a robust cohort study design to be employed. The results were able to be matched or adjusted for potential confounders including sex and deprivation. It was possible to do subgroup analysis by sex and birth cohort.

Limitations of the study include possible loss to follow-up of subjects due to migration away from Scotland, and the lack of any follow-up data prior to 1 January 1981. We have made the assumption that there was no systematic difference in migration between veterans and non-veterans. For those who are military veterans, we have not been able to link to in-service health or service records and thus leukaemia, Hodgkin lymphoma or NHL occurring during service will not have been captured until the individual left the service and returned to NHS care; nor can any link to specific military trades or exposures be explored. Therefore, we have examined 'military service' overall as a potential risk factor. All hospital admissions for leukaemia were grouped together as a single code, as were admissions for Hodgkin

lymphoma, and for non-Hodgkin lymphoma, precluding analysis by subtype. The long period of follow-up encompasses changes in the understanding of lymphohaematopoietic malignancy, further necessitating the broad approach to disease classification which we have used in this study. Veterans with Reserve service only could not be identified from NHS records and were therefore included among the non-veterans. This could have weakened any association with military service, although Reservists played only a limited role in the early period of service considered in this study and would not have deployed to the nuclear test sites.

CONCLUSION

The Scottish Veterans Health Study provides reassurance that military veterans aged up to 67 years are not at increased risk of leukaemia, Hodgkin lymphoma or non-Hodgkin

lymphoma compared with non-veterans matched for age, sex and area of residence.

Smoking is the only risk factor which might have theoretically influenced the risk in veterans

but any effect may be too small to be perceptible, even in this large cohort.

ACKNOWLEDGEMENTS

We thank the NHS Central Registry (NHSCR) and the Information Services Division, NHS Scotland (ISD) for extracting and linking the dataset.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests. BPB is a British Army veteran and former military medical officer.

AUTHOR CONTRIBUTION STATEMENT

BPB conceived the idea and designed the study, with advice from JPP and DFM. BPB carried out the data analysis, which was overseen by DFM, and interpreted the findings. BPB wrote the first draft of the report, which was critically reviewed and edited by all authors. All authors approved the final article.

DECLARATION

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Table 1. Cox proportional hazard model of the association between veteran status and risk of haematological/lymphopoietic malignancy overall, by sex, and by birth cohort, and one and five year survival

	Veterans	Non-veterans	Univariate			Multivariate^a		
	N=56,205	N=172,741	HR	95% CI	P value	HR	95% CI	P value
Overall	294	995	0.96	0.84-1.10	0.541	0.96	0.84-1.10	0.593
Men	275	898	0.97	0.84-1.11	0.644	0.97	0.85-1.12	0.690
Women	19	97	0.80	0.48-1.35	0.405	0.81	0.48-1.36	0.427
Birth year	1945-1949		0.87	0.70-1.12	0.280	0.88	0.69-1.13	0.322
	1950-1954		1.01	0.78-1.31	0.916	1.01	0.78-1.30	0.967
	1955-1959		0.94	0.70-1.26	0.657	0.94	0.70-1.27	0.700
	1960-1964		1.06	0.72-1.57	0.759	1.06	0.72-1.57	0.757
	1965-1969		0.81	0.51-1.30	0.387	0.83	0.52-1.33	0.431
	1970-1974		1.63	0.86-3.11	0.135	1.64	0.86-3.13	0.132
	1975 onwards		1.02	0.21-4.69	0.984	1.00	0.22-4.64	0.994

One year survival	1.15	0.82-1.60	0.417	1.13	0.81-1.57	0.485
Five year survival	1.13	0.89-1.43	0.305	1.11	0.88-1.41	0.367

HR hazard ratio; CI confidence interval

^a adjusted for deprivation

* Haematological/lymphopietic malignancy – leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma

High HR in 1970-1974 results from a very small number of non-veteran cases in this age-band.

Table 2. Cox proportional hazard model of the association between veteran status and risk of haematological/lymphopoietic malignancy by diagnosis

	Veterans n=56,205	Non- veterans n=172,741	Univariate			Multivariate ^a		
			HR	95% CI	P value	HR	95% CI	P value
Leukaemia	125	373	1.03	0.84-1.27	0.782	1.03	0.84-1.27	0.773
Hodgkin lymphoma	59	189	1.17	0.86-1.59	0.318	1.19	0.87-1.61	0.272
Non-Hodgkin lymphoma	144	545	0.85	0.78-1.03	0.096	0.86	0.71-1.04	0.110

HR hazard ratio; CI confidence interval

^a adjusted for deprivation

* Haematological/lymphopoietic malignancy – leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma

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