Early Adoption of Screening and the Changing Pattern of Cervical Cancer in UK Military Women: Evidence from the Scottish Veterans Health Study

Short running title: Cervical cancer in veterans

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ABSTRACT

Objective

To examine the risk of cervical cancer in a large national cohort of military veteran women, followed up for up to 30 years.

Methods

Retrospective cohort study of 5,235 veteran women born 1945-1985, and 20,703 women with no record of service matched for age and area of residence, using Cox proportional hazard models to compare the risk of cervical cancer, overall and by year of birth.

Results

During the follow-up period 1981-2012, there were 18 (0.34%) cases of cervical cancer in the veteran women compared with 81 (0.39%) in the non-veterans. The difference was not statistically significant overall (adjusted hazard ratio (HR) 0.95, 95% CI 0.57-1.59). When analysed by year of birth, veteran women born in 1958 and earlier had a non-significantly higher risk than non-veterans (adjusted HR 1.24, 95% CI 0.68-2.26), whilst veteran women born after 1958 had a non-significant reduction in risk (adjusted HR 0.51, 95% CI 0.18-1.44).

Conclusion

Women born after 1958 who have served in the Armed Forces are at reduced risk of cervical cancer compared with women who have never served, and compared with older veteran women. Small numbers of cases precluded statistical significance. The change in risk pattern in veteran women coincided with the introduction of cervical screening in the Armed Forces, which predated the UK national programme, and provides evidence for the long-term

effectiveness of the Armed Forces' sexual health strategy. The impact of recent changes in the screening age, and of HPV immunisation, should be monitored in the future.

KEY/EDUCATIONAL MESSAGES

- Overall, UK military veteran women are at no greater risk of cervical cancer than non-veteran women.
- Veteran women born 1945-1958 had a higher risk than non-veterans, but the reverse is true of veterans born since 1959 although the difference did not reach statistical significance.
- The early introduction of cervical cytology in the Armed Forces (which predated the NHS programme), proactive sexual health promotion, and high uptake of screening, may be responsible for the changing pattern.

INTRODUCTION

Cervical cancer is the third commonest cancer in women worldwide, although the implementation of screening programmes in developed countries has had a major impact and in the UK, it ranks only 11th, accounting for 2% of all new cancers in women. The peak incidence is in the 4th decade of life although there is a smaller peak in the 9th decade. There is a crude incidence in Scotland of 11 per 100,000, with a lifetime risk of 1 in 112.[1, 2] By 2002/04, there had been a 49% reduction in incidence compared with 1985/87, prior to the introduction of the UK national screening programme. More recently, an increase in incidence, greatest in women aged 20-34, has been reported and has been mirrored in other countries.[3, 4]

Cervical cytology as a screening tool was developed in the 1920s by Papanicolaou but it was not until 1947 that the details of the procedure for sampling the cervix were published.[5] Screening was introduced on an *ad hoc* basis in the UK in 1967,[3] and in 1988 a national programme of call and recall was established.[6] The British Army, which operated a health care service independently from the National Health Service (NHS), established its own Cervical Cytology Screening Service in 1962, collocated with the Army Histopathology Registry at the Royal Army Medical College, Millbank, London. The Royal Navy and Royal Air Force offered similar services. Initially, screening was only offered to women over 35 years of age but in 1967 the service was extended to all women for whom the Army provided primary care.[7] Although there was no formal call/recall system, opportunistic screening was widely offered, often in association with contraceptive or sexual health consultations, and individual primary care nurses devised and operated local call/recall systems. Abnormal results were followed up by the Army Histopathology Registry and, failing receipt

of repeat cytology or a biopsy specimen taken in a military hospital, details of follow-up elsewhere were required to be submitted. This system worked surprisingly well and in an audit of 748 Army women (serving and dependant) in 1985, Zaklama and Birkett found that 677 (90%) had undergone screening in the last 5 years. Four percent had been referred for further investigation following an abnormal result.[8]

The Army Histopathology Registry was disbanded on the closure of the Royal Army Medical College in 1997 and the opportunity was taken to establish a Service-wide call and recall system in collaboration with the National Health Service (NHS). After a competitive tendering process, Warwickshire Health Authority was selected as the NHS partner, although this changed to Coventry and Warwickshire Registration and Screening Service following local reorganisation.[9] The service 'went live' in 2001. Initially, screening was offered to all Servicewomen aged 20 years and over although in 2004 the lower age-limit was changed to 25 years in line with the recommendations which gave rise to a change in national policy in England and Wales.[10] Servicewomen recruited from Scotland, which retained a lower age limit of 20 years, continued to be included in the screening programme prior to age 25 years if they had already had their first test prior to joining the Services.
The service provided to the Armed Forces by the NHS was audited in line with national audit policy although the results were reported separately. Rates of abnormality for the Service community were at the upper end of the national range. Rates of 7% borderline/mild abnormality and 2-2.5% moderate/severe abnormality were reported in most editions of the Annual Report on the Health of the Army (an internal Ministry of Defence publication by the Army Health Unit) between 2001 and 2006, compared with an average of 5.6-6.2%/1.3-1.5% nationally (2002-2011)[11] and may be related to exposure to HPV infection

owing to the high prevalence of genital warts in the Armed Forces.[12] Genital warts affect as many as 20% of male and 10-15% of female attendees at military sexual health clinics and tend to recur at times of stress,[13] especially in relation to overseas deployment. Overall prevalence of genital warts is unknown as military personnel in the UK are able to attend NHS sexual health clinics if they prefer. Catch-up vaccination against HPV is now offered to female recruits under the age of 18 years who are not fully immunised on entry.[14]

The reported prevalence of cytological abnormalities appears to have given rise to a perception of high rates of cervical cancer in Servicewomen compared with civilians; in 2013 a National Screening Audit 'Q&A' response reported that "Women in HM forces or in prison are at higher risk of developing cervical cancer than the general population, however they are not registered with an NHS GP and they do not receive standard NHS screening."[15] This is clearly misleading as the screening programme offered to Armed Forces women has been identical to the NHS programme since 2001. The Scottish Veterans Health Study provided an opportunity to examine whether cervical cancer occurs more frequently in veteran women than in those who have never served, and whether the pattern of risk has changed over time.

METHODS

Design and participants

The Scottish Veterans Health study is a retrospective cohort study that comprises all 56,570 military veterans born between 1945 and 1985 who were registered with NHS Scotland both prior to military service and following discharge, and a 3:1 comparison group of 172,753 individuals with no record of military service matched by age, sex and postcode sector of residence (mean population 5,000). The cohort includes 5,302 female veterans, reflecting the sex balance of the Armed Forces, and 20,707 female non-veterans. The study cohort and methods have been described in detail previously.[16] Participants were identified from their electronic NHS registration records, which provided demographic information as well as the dates of entering and leaving military service, and socio-economic status was categorised by postcode of residence in quintiles derived from the Scottish Index of Multiple Deprivation (SIMD).[17] The records were linked, at the individual level, to routine hospital admissions data and cancer registrations (Scottish Morbidity Record SMR01 and SMR06), and death certificates, to provide information on incidence of cervical cancer and death from cervical cancer. Information was available for follow-up events that occurred between 1 January 1981 and 31 December 2012 inclusive. The electronic NHS 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.

Statistical analysis

Cox proportional hazard models were used to examine the association between veteran status and cumulative risk of cervical cancer, using age as the time dependent variable, age at first record of cervical cancer as the failure time and age at death (if no cervical cancer) as the censor time. Cox proportionality assumptions were tested using methodology based on Schoenfeld residuals.[18] The *a priori* rejection level was set at 0.05. The models were run univariately and then repeated adjusting for the potential confounding effect of SES quintile. The analyses were repeated stratifying by year of birth to examine potential birth cohort effects. All analyses were performed using Stata v12.1 (©1985-2011 StataCorp).

RESULTS

After data cleansing, 5,235 (98.7%) female veterans and 20,703 (99.9%) female non-veterans were included in the analysis. Among the veteran women, 60% had left the Armed Forces by the age of 25 years, while over 80% had left by 30 years of age; the median length of service was 3.9 years (IQR 1.3-7.5 years).

During the period of follow-up, from 1 January 1981 to 31 December 2012, there were 18 (0.34%) cases of cervical cancer in veteran women, compared with 81 (0.39%) in non-veteran women. The mean length of follow-up in veterans with cervical cancer was 12.6 years (SD 8.7), giving a total of 227 woman-years of follow-up, compared with 12.1 years (SD 8.9) equating to 979 woman-years of follow-up in non-veterans.

The overall difference in risk was not statistically significant in the Cox model when veterans were compared with non-veterans, unadjusted hazard ratio (HR) 0.97, 95% CI 0.58-1.61, p=0.906. The difference was similar after adjusting for socio-economic status, HR 0.95, 95% CI 0.57-1.59, p=0.853. Visual inspection of the data by year of birth (Figure 1) indicated a substantial reduction in incidence in veteran women born after 1958 compared with those born in earlier years. For women born 1945-1958, there were 14/2,015 (0.69%) cases of cervical cancer in the veterans compared with 45/8,036 (0.56%) in non-veterans, unadjusted HR 1.31, 95% CI 0.72-2.40, p=0.372, adjusted HR 1.24, 95% CI 0.68-2.26, p=0.480. For women born between 1959 and 1985, the corresponding numbers of cases were 4/3,220 (0.12%) in the veterans and 36/12,667 (0.28%) in the non-veterans, unadjusted HR 0.51, 95% CI 0.18-1.43, p=0.202, adjusted HR 0.51, 95% CI 0.18-1.44, p=0.206, representing a reduction of 83% in the veteran women and 50% in the non-veterans in the 1959-1985 birth

cohort in the adjusted hazard ratios, compared with the earlier birth cohort. Despite the apparent large reduction in incidence of cervical cancer in women veterans born since 1958 compared with non-veterans, the difference did not achieve statistical significance as the small overall number of cases gave insufficient statistical power, OR 0.44, 95% CI 0.16-1.23, p=0.106. In the Cox proportional hazard model, comparing the 1959-1985 birth cohort with the 1945-1958 birth cohort, the unadjusted hazard ratios were HR 0.33, 95% CI 0.10-1.07, p=0.064 for veterans and HR 0.81, 95% CI 0.50-1.30, p=0.376 for non-veterans. The difference reduced slightly after adjusting for deprivation, HR 0.39, 95% CI 0.12-1.27, p=0.120 for veterans and HR 0.85, 95%CI 0.53-1.38, p=0.512 for non-veterans, but the reduction in risk in veterans in the later birth cohort remained apparent although it did not achieve statistical significance.

There was one death from cervical cancer in the veterans (4.4 per 1,000 woman-years), equating to a crude case-fatality rate of 5.6%, compared with 8 deaths in the non-veterans (8.2 per 1,000 woman-years), equating to a crude case fatality rate of 9.9%.

DISCUSSION

Main findings

Data from the Scottish Veterans Study has demonstrated that overall, military veteran women were at no greater risk of cervical cancer than women who had never served, but the risk has changed over time. Veteran women in the earlier birth cohort (1945-1958) demonstrated a non-significantly higher risk of cervical cancer than non-veterans, but there was a greater reduction in risk in veterans born after 1958 than in matched non-veteran women. However, absolute numbers of cases were small and the difference did not achieve statistical significance.

Interpretation

The majority of women born after 1958 joined the Services from 1976 onwards, at a time when the military cervical cytology service was well established and available to all women registered with an HM Forces primary care practice. Although screening was always subject to informed consent, anecdotal recollections suggest that refusal was almost unknown. The results of this study indicate that the widespread acceptance of screening reported by Zaklama and Birkett[8] was highly effective in preventing later cervical cancer in veterans, whether by timely treatment and follow-up of pre-invasive disease or by inculcating a culture of regular screening from an early age in a group who, as fit young Servicewomen, were highly motivated to maintain their health.

The majority of Servicewomen in our cohort left the Armed Forces after a short period of service. Thus, for veterans resident in Scotland, ascertainment of cases of cervical cancer, with a peak incidence in the 4th decade, is likely to be reasonably complete, with few cases

missed as a result of having occurred whilst still serving. Data obtained from Defence Statistics (Health) in a Freedom of Information enquiry show that between 1 April 1991 and 31 December 2012, only 4 cases of cervical cancer occurred in the 2,463 women throughout the UK followed up from the Gulf and Era cohorts who were serving at the time of the 1991 Gulf War, most of whom will have become veterans in the intervening 21 years to the end of follow-up. An estimated 10% of all UK veterans are resident in Scotland; under-ascertainment in the Scottish veterans cohort is therefore unlikely.

A consequence of raising the age at entry to the screening programme to 25 years has been that many women now leave the Services prior to having their first smear, and thus do not have the opportunity to establish a pattern of regular screening during the period when the ready availability and good uptake of contraceptive services and sexual health advice in the Armed Forces provide a valuable opportunity for health promotion. Whilst there is no evidence that a lack of screening in younger women results in harm,[19] uptake of screening after leaving the Services may be now reduced in comparison with previous years when a pattern of screening was usually established whilst serving. No conclusions can yet be drawn as to whether this will have any impact on cervical cancer rates in veterans, although the recent promotion of HPV vaccination will have a confounding effect on the results of future research.

Previous Studies

A review of the literature reveals a paucity of studies on cervical cancer in veterans. A US Department of Veterans Affairs study examined 4,140 female Vietnam veterans and a similar number of female veterans who had not served in Vietnam and found no difference

in their rate of cervical cancer, OR 1.11, 95% CI 0.74-1.66.[20] For active duty personnel in the US, Yamane found an increased standardised incidence ratio of 3.19, 95% CI 2.74-3.70, for cervical cancer compared with the US population for the period 1989-2002,[21] but in contradiction, Zhu found no significant difference for those of white ethnicity with an incidence rate ratio (IRR) of 0.92, 95% CI 0.75-1.11, and a reduction in risk for those of black ethnicity, IRR 0.43, 95% CI 0.28-0.62, using Defence-wide and national data covering the period 1990-2004. There was a non-significant decline in incidence in white military women, compared with a significant decline in national incidence.[22] Data from our study indicate that military service reduces the risk of cervical cancer in women born after 1958, the incidence of cervical cancer in this group having fallen further than in the non-veteran women.

Strengths and limitations

The strengths of the present study are that it was based on a large cohort covering the whole of Scotland over more than 30 years of follow-up. The majority of the women reached the peak age for cervical cancer incidence during the study follow-up period, even if they had been serving in the Armed Forces. Since the diagnosis of cervical cancer was taken from hospital admission, cancer registration and death records, it is 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. We were able to adjust the results for socioeconomic status. For women who are military veterans, we have been able to access follow-up data from the Gulf Veterans study which has provided a further estimate of cervical cancer rates in Servicewomen and veterans.

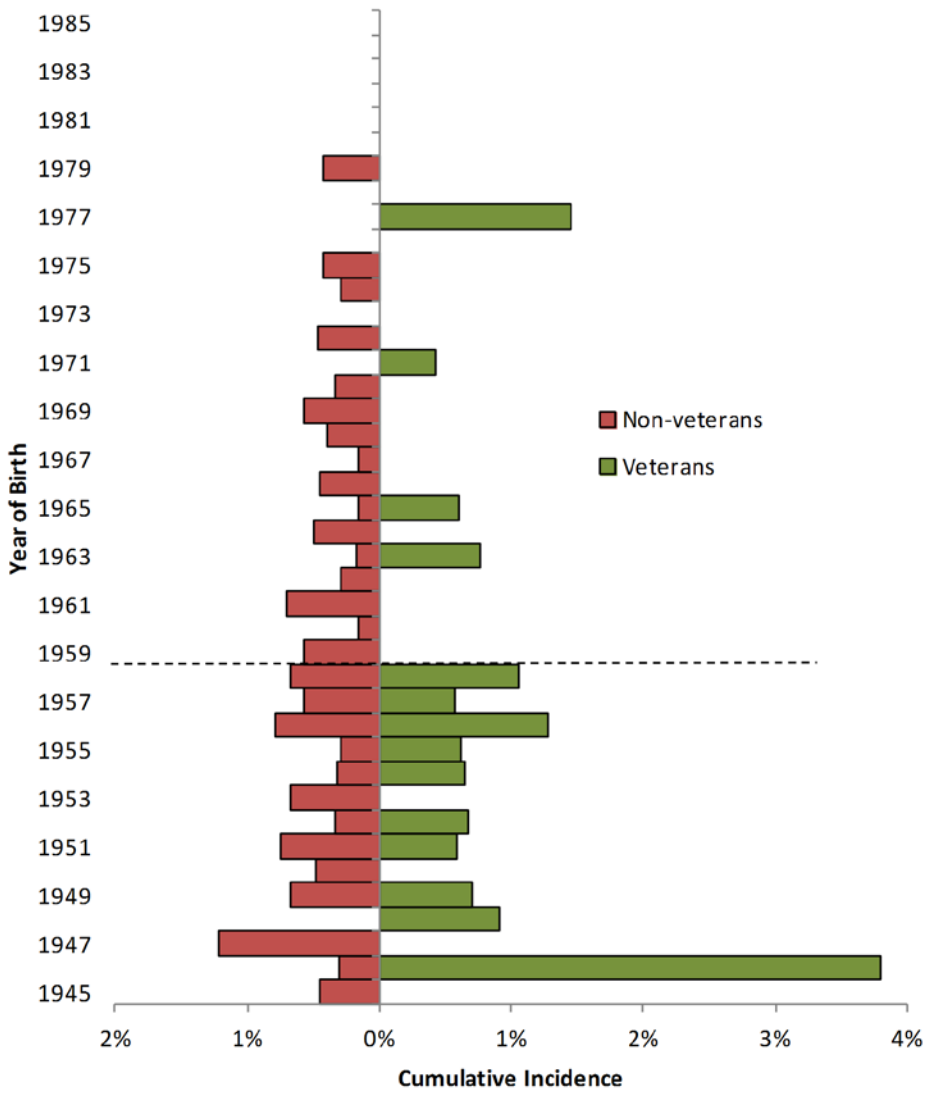
Limitations of the study include loss to follow-up of subjects due to migration away from Scotland, which could not be quantified, and the lack of any follow-up data prior to 1 January 1981 although as the oldest of the cohort were only aged 36 years at that date, the number having been diagnosed with cervical cancer by then is likely to be small. Women with Reserve service only were not separately identifiable in the electronic record and were therefore included with the non-veterans. They receive screening from the NHS and the effect will have been to reduce the apparent magnitude of any differences associated with military service. Because of very small numbers of cases, the results, although indicating a difference between veterans and non-veterans and a changing pattern over time, did not achieve statistical significance.

CONCLUSION

Female veterans born since 1958 have a reduced risk of cervical cancer compared with age matched civilians with no record of military service, notwithstanding the higher rate of cytological abnormalities in serving women reported elsewhere, although the overall number of cases was small and the reduction in risk was not statistically significant. Although the risk has fallen in both veteran and non-veteran women when those born after 1958 are compared with women born 1945-1958, the reduction was greater in the veterans. Active promotion and delivery of screening, high uptake and opportunistic sexual health promotion in Service primary care are all likely to have been contributory factors. The impact of having raised the age of entry to the screening programme in 2004, resulting in many women now leaving the Services prior to becoming eligible for screening, should be examined in the future, as these women approach the peak age of incidence of cervical cancer.

FIGURE LEGEND

Figure 1 – Cumulative incidence of cervical cancer by year of birth – veterans and non-veterans



Dashed line represents upper boundary of 1945-1958 birth cohort

ETHICS APPROVAL

Privacy Advisory Committee, NHS Scotland.

PAC reference 27/12.

Individual consent was not required as this was a secondary data study using a pseudo-anonymised database extract.

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