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Increasing rates of low-risk prostate cancer incidence in USAF servicemen and selection of treatments

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Abstract

Purpose—Periodic Health Assessments have been mandated for United States Air Force (USAF) servicemen since the mid-1990s. Consequently, we determined whether USAF prostate cancer incidence rates have increased thereafter, how these tumors segregate into low- and intermediate/high-risk categories and treatment choices.

Methods—We queried the Department of Defense Automated Central Tumor Registry for prostate cancers diagnosed in USAF servicemen between 1991–2008 to determine incidence rates, disease risk category and treatments selected.

Results—Age-adjusted rates in white active duty servicemen diagnosed for the most recent period (2005/2008) increased 3 fold relative to the rate in the earliest period (1991–1994) and a similar trend was evident for African American servicemen. Moreover, relative to the Surveillance, Epidemiology and End Results (SEER) population, prostate cancer rates among active duty USAF men between 1995 and 2008 were significantly increased for both racial groups. Importantly, a significantly greater proportion of active duty servicemen (62 %) than retirees (40 %) presented with low-risk disease (PSA < 10 ng/ml, Gleason Sum < 7, T1a-T2a clinical staging). For those individuals with low-risk disease, a significantly greater percentage of active duty servicemen opted for curative surgery compared with retirees (93 and 53 % respectively).

Conclusion—Prostate cancer incidence rates for USAF servicemen have increased over time exceeding rates for the SEER population. Moreover, while the majority of cases are characterized as low-risk, aggressive management is selected.

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Keywords

prostate cancer; low-risk prostate cancer; therapeutic intervention

INTRODUCTION

Prostate cancer is one of the most common malignancies with 192,000 new cases expected in 2010¹. Nevertheless, although the risk of being diagnosed with the disease is high, the risk of dying from the cancer is much lower. In fact nearly eight times more men will be diagnosed with prostate cancer each year than will die of the disease compared with 1.3 and 2.1 for lung and colorectal cancers respectively^{2,3}. Indeed, it is well recognized that 30–50 % of men over 50 years have histological evidence of prostate cancer at autopsy⁴.

The past 2 decades have witnessed stage migration of prostate cancer with 40–50 % of men currently presenting with low-risk cancers (PSA levels <10 ng/ml, clinical staging of up to T2a, Gleason sum of <7, <3/12 positive biopsy cores^{2,5–7} reflecting partly the widespread adoption of PSA screening. Using additional parameters a subset of low-risk disease can be further classified as clinically insignificant⁸. The shift to low-risk disease has stimulated considerable debate as to the management of these cancers for several reasons. First, no matter how well delivered, any treatment is associated with decrements in the quality of life: erectile dysfunction and incontinence^{9,10}. Although bilateral nerve preservation has improved erectile and urinary function outcomes¹¹, often these data are from high volume centers with experienced surgeons and radiation oncologists¹¹. The adverse side effects resulting from therapy are of concern for a more youthful sexually/physically active population. In addition, there are substantial financial costs associated with treatment¹². An alternative option is active surveillance^{5,13,14} whereby an individual with low-risk disease is monitored for disease progression and only those individuals felt to be at risk for progression are treated. Potential advantages of active surveillance include (a) treatment delivery to those most likely to benefit (b) patients less likely to benefit are not subject to the adverse side effects associated with intervention.

Beginning circa 1995, the United States Air Force (USAF) implemented the Preventive Health Assessment (PHA) program for all personnel. PHA requirements are based, partly, on the United States Preventive Services Task Force Guide to Clinical Prevention Services (USAF document AFI 44–170)¹⁵. Because of the hyper-vigilance associated with the PHA program, we undertook a study of active duty and retired USAF servicemen to determine (a) prostate cancer incidence rates and the proportion categorized as low-risk disease and (b) for those servicemen with low-risk disease, treatment preferences. This latter question is of importance for the active duty servicemen considering their youthfulness (93 % retire by age 50) and the potential long-term burden of adverse side effects with therapeutic intervention.

MATERIALS AND METHODS

Data were from the Automated Central Tumor Registry (ACTUR), a database established in 1986 by the Department of Defense (DoD) and managed by the Armed Forces Institute of Pathology (AFIP). We requested all prostate cancer cases for active duty/retired Armed Forces personnel for the period 1991–2008 and the data were imported into a FileMaker Pro (v11) database designed for this project. Record de-duplication was performed using ACTUR unique identifiers. This work was accomplished with IRB approvals from all institutions herein. To identify low-risk prostate cancer cases^{16,17}, the database was queried for cases which fulfilled the following criteria: PSA <10 ng/ml, Gleason Sum <7 and

maximum clinical staging T2a. We were unable to utilize tumor volume for defining low-risk prostate cancers ^{6,14,18} because ACTUR does not track this parameter.

Prostate cancer rates were determined for the active duty cohort only as follows. The annual active duty male USAF population at risk for prostate cancer was provided by the USAF Personnel Center (San Antonio, TX) and categorized by age-group (35–39, 40–44, 45–49, 50–54, 55–59, 60–64 years), race and calendar-year-group (1991–94, 1995–99, 2000–04, 2005–08). To provide denominators, USAF active duty male population totals were summed across the individual years of age and calendar time, and the appropriate age- and calendar-year strata were produced for each race category. Mantel-Haenszel tests (adapted for person-time data) and Poisson regression were performed using STATA version 11 (Stata Statistical Software, College Station, TX) for the active duty cohort only. When goodness of fit tests identified overdispersion in the Poisson models, negative binomial regression was performed. In the absence of statistically significant interaction (i.e. heterogeneity across strata) for the active duty cohort, summary incidence rate ratios adjusted simultaneously for age and race were computed to assess the magnitude of association between calendar time period and prostate cancer incidence. Finally, age- and race-specific prostate cancer incidence rates reported from SEER for the time period 2003–2007 (<http://seer.cancer.gov/faststats/selections.php>; accessed 8-23-2010) were used for comparison with the 2005–2008 rates in active duty USAF males. To assess secular trends, USAF and SEER rates for comparison were age-adjusted to the total active duty USAF population aged 35–64 years of age from 1991–2008. Because we could not calculate prostate cancer rates for retired USAF servicemen due to the potential for under-ascertainment (relying solely on ACTUR) and the lack of complete and accurate survival data (i.e., person-years at risk), we restricted our analysis to numerator data. We used the chi square test to assess differences in proportions comparing active duty with retired USAF cases status on prostate cancer prognosis and treatment choices.

RESULTS

Increasing incidence of prostate cancer in active duty USAF servicemen

The total population (active duty and retired) of prostate cancer cases are characterized in the Supplementary Data (see footnote). An increase in age-adjusted prostate cancer incidence was evident over successive time periods for white USAF active duty male populations referencing the 1991–1994 cohort (Figure 1A). Rates were standardized to the total USAF active duty male population age 35–64 years between the years 1991 and 2008. The increased rate for white active duty servicemen was highest (3.04, 95 % confidence intervals 2.01–4.58) for the most recent period (2005–2008) but statistically significant for all periods as determined by Mantel-Haenszel analysis (Table 1). Importantly, for all time periods prostate cancer rates were elevated in white active duty USAF servicemen referencing the age-matched SEER population (Figure 1A). A clear upward trend in age-adjusted rates (Figure 1B) was also evident for African American servicemen increasing from 3.7 (1991–1994) to 39.1 for the most recent period (2005–2008) and consistent with a report ¹⁹ showing increased risk relative to their Caucasian counterparts. The increased rate over time for African Americans was also statistically significant (Table 1) although the paucity of cases for the 1991–1994 period yielded wide 95 % confidence intervals. As reported elsewhere ²⁰ USAF African American males also showed a higher age-adjusted rate compared with the SEER population (Figure 1B). Overall, the prostate cancer incidence rate increased 1.46 fold for each unit increase in time period (95 % CI-1.22–1.75) using negative binomial regression to adjust simultaneously for age group and race. Neither race nor age modified the significant secular trend.

Although we could not calculate prostate cancer rates for retired USAF servicemen due to the potential for under-ascertainment (relying solely on ACTUR) and the lack of complete and accurate denominator data, an analysis of the numerator data available indicated 2,389 and 2,713 cases for the 1995–1999 and 1991–1994 periods respectively. The number of prostate cancer cases decreased thereafter. These latter results are similar to an age-matched cohort in the civilian population with rates peaking in the early 1990s²¹.

The majority of active duty USAF servicemen present with low-risk prostate cancer

We then determined the percentage of USAF servicemen presenting with low-risk disease (Figure 2)^{16,17}. Since PSA values were only tracked by ACTUR after 2003, we were restricted to 2004–2008 for this query. For active duty servicemen, of 132 prostate cancer cases, 62 % (82 cases) were classified^{16,17,22} as low-risk disease with the remaining 38 % (50 cases) categorized as intermediate (PSA 10–20 ng/ml, Gleason Sum=7 or Clinical Stage =T2b) or high risk disease (PSA >20 ng/ml, Gleason Sum 8–10 or clinical stage T2c). In regard to retired USAF servicemen, 40 % (552 cases) were classified with low-risk disease similar to the rate evident for the civilian population (40–50 %) ⁵. This difference in % of low-risk prostate cancer cases between active duty and retired USAF servicemen was statistically significant (chi square=24.21, 1 df p<0.0001).

Selection of treatment choices for active duty USAF servicemen and retirees with low-risk disease

Recent reports and editorials have debated^{14,23} the aggressive management of low-risk prostate cancer since many of these tumors will not progress over the patient's lifetime, although typically such studies are with an older population⁵. Moreover, most treatments yield a substantial decrement in the quality of life^{10,24}, issues of concern to youthful males (as are active duty servicemen) who are sexually/physically active and who may value fertility preservation²⁵.

In view of these considerations, we then determined the proportion of cases with low-risk disease that elected treatment. Although we had identified 82 active duty servicemen with low-risk disease, not all could be categorized as treated/untreated in part due to their management at non-MTF facilities. Additionally, for some cases, there were ambiguities as to whether treatment had been delivered and these were also excluded. This constrained the dataset to a total of 62 servicemen with low-risk disease, 94 % (59 cases) who elected for therapeutic intervention (Figure 3). Treatment rates were slightly lower (89 %, 489 cases) for retired servicemen (Figure 3) although this difference was not statistically significant (p=0.1066).

We then determined treatment options selected by active duty servicemen with low-risk disease extending the dataset to include 14 cases treated at non-MTFs where treatments were specified. Active duty servicemen overwhelmingly opted (Figure 4) for radical prostatectomies (70 of 76 cases-92 %) with retirees selecting prostatectomies at a lower rate (262/498 cases-53 %) this difference being statistically significant (chi square= 42.18, 1 df p=0.00001).

DISCUSSION

We report herein a temporal increase in prostate cancer incidence rates for active duty USAF servicemen but that the majority of these tumors are low-risk. A similar trend in prostate cancer incidence rate was also observed across all branches of the US Armed Forces^{19,20} and in all 3 studies, there is little evidence that rates are leveling off for the white servicemen. Our findings also indicate a higher incidence rate ratio for this

malignancy using the general population as reference again consistent with other studies ^{20,26}. The reasons underlying this disconcerting increase in incidence rates are not clear but several possibilities can be entertained. First, these findings might reflect increased surveillance via mandatory annual PHAs. Second, USAF personnel belong to an open access medical system in contrast to the SEER population. A third, less plausible, explanation is that USAF servicemen are exposed to environmental/workplace factors ^{20,27–29} that yield an increased cancer incidence.

This is the first study to characterize low-risk prostate cancer and treatment in servicemen. Although most low-risk cancers will not progress ⁵, nevertheless, the majority are treated aggressively with decrements in the quality of life ¹⁰. The majority (62 %) of active duty servicemen present with low-risk disease at a rate even higher than that for the general population (40–50 %) ⁵. Conceivably, the larger proportion of low-risk disease in active duty men is due to increased diagnostic activity although we cannot be certain since ACTUR provides no information as to whether disease is screen-detected. For retirees, the proportion diagnosed with low-risk cancer (40 %) was less than the active duty cohort but more in line with that reported for the civilian population ^{5,7}. Others have identified an age-associated increased risk for higher-risk disease ²².

Considering that the majority of active duty servicemen are diagnosed with low-risk disease, we were surprised to find that nearly all opted for therapeutic intervention. The reasons for this choice are unclear although the decision for treatment may reflect, partly, job requirements unique to these servicemen. Nevertheless, the high treatment rate was still somewhat unexpected since natural history studies have indicated that the majority of these cancers will remain indolent over the patients' lifetime. However, such studies are typically with an older population ^{4,14} and for a 10 year, or less, follow up period. Thus, studies with a youthful USAF population (average age at diagnosis=48 years) may demand longer follow up periods.

Any active treatment of prostate cancer is often associated with a decrement in the quality of life in multiple domains. For those active duty USAF servicemen with low-risk disease who elected therapy, nearly all (92 %) underwent prostatectomy. In the civilian population, although men similar in age are more likely (80–88 %) to opt for prostatectomy, this choice can vary drastically (11–82 %) depending on practice site ^{21,23}. A much smaller number (6/76, 8 %) of active duty servicemen opted for radiation a rate close to the 5 % reported for civilian males of similar age ²³ but less than the 20 % reported for a general population cohort of comparable age ²¹. It was unclear whether alternatives (e.g. active surveillance, subtotal glandular ablation) to preserve sexual function were considered ³⁰ but, if so, presumably were then declined. This high rate of aggressive therapy for active duty servicemen probably reflects two concerns. First, with a long lifespan ahead and thus the potential for disease progression, these individuals, in consultation with their physician, might conclude that therapeutic intervention is the best option regardless of side-effects. Second, according to Air Force medical standards, a diagnosis or ongoing surveillance for cancer may be potentially disqualifying for world-wide deployability or continued service. Although definitive treatment is not required by Air Force policy, it is possible that these medical standards may have an influence on an individual's decision to pursue treatment.

In contrast to their active duty counterparts, a smaller fraction of retirees opted for prostatectomy (53 %), 35 % elected radiation and the remainder selected androgen ablation or systemic treatments. These numbers are similar to a study on a cohort of mostly retired servicemen ¹⁰ (average age=63 years) in which 48–51 % selected radical prostatectomy, and 24–34 % and 2–3 % opted for radiation and hormonal therapy respectively. Still, treatment selection for low-risk prostate cancers can vary widely between practice sites ²³. Indeed,

some investigators²³ have argued that treatment selection for low-risk disease represents a model for “preference-sensitive” health care in which the patient or clinician’s preferences, beliefs or values drive decision making in the absence of strong scientific evidence.

Although the population size is small, we have found that prostate cancer incidence rates in active duty USAF servicemen are significantly elevated relative to the SEER population and continue to climb. The majority of these prostate cancers are low-risk but nevertheless are managed aggressively. ACTUR is a passive system and it is possible that our calculated rates are low due to undercounting. Our findings warrant investigations to determine the extent to which this increased rate of prostate cancer reflects screening and the fraction of low-risk cases classified as insignificant disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1B

Figure 1. Age Adjusted prostate cancer incidence rates for USAF servicemen and the SEER population

Panels A-White, Panel B-African Americans. Because of SEER reporting conventions, the closest corresponding time periods are: 1993–1997, 1998–2002, 2003–2007.

Figure 2. Characterization of prostate cancers as low- or intermediate/high-risk in USAF servicemen

Low-risk disease was defined using the following criteria: PSA < 10 ng/ml, Gleason Sum < 7 with a clinical staging of T1c or T2a. Intermediate/High-Risk was all other cases. The values above each bar indicates the number of cases. A Chi Square Test was used to test for statistical significance.

Figure 3. Determination of treatment rates for prostate cancer in USAF servicemen

Only those servicemen managed at a MTF for their prostate cancer was included in this analysis due to the ambiguities of treatment delivery at non DoD facilities. Values above each bar represent the number of cases. Differences in the % treated cases between the two groups (Active Duty, Retired) were tested for statistical significance using a Chi Square Test.

Figure 4. Selection of prostate cancer treatments

Radiation includes both external beam and brachytherapy. Differences (%) between the active duty and retired groups for the selected treatment (prostatectomy) was tested for statistical significance using a Chi Square Test.

Table 1

Age adjusted Mantel-Haenszel prostate cancer incidence rate ratios by race and time period using total USAF active duty male population age 35–64 from 1991–2008 as the standard population.

Race	Time Period	# Cases	Incidence Rate Ratio	95 % Confidence Interval
White	1991–1994	27	1.0	Referent
	1995–1999	64	2.03	1.30–3.18
	2000–2004	94	2.63	1.74–3.98
	2005–2008	76	3.04	2.01–4.58
African American	1991–1994	2	1.0	Referent
	1995–1999	19	7.07	2.04–24.5
	2000–2004	33	12.06	3.91–37.16
	2005–2008	22	11.18	3.35–37.34