

Sexually Transmitted Infections and Prostate Cancer among Men in the U.S. Military

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Abstract

Studies of self-reported sexually transmitted infections (STI) suggesting an association with prostate cancer may reflect underreporting of such infections among nondiseased subjects. To reduce such bias, we studied archived sera in a cohort of U.S. military personnel known to have high rates of both STIs and prostate cancer. Using a nested case-control design, serum samples from 534 men who served on active duty between September 1, 1993 and September 1, 2003 were examined. Controls were individually matched to cases based on date of serum collection, date of birth, branch of service, military rank, marital status, and race. Each of the 267 case-control pairs had two serum samples: a recent serum sample, taken ~1 year before the case's prostate cancer diagnosis, and an earlier serum sample, taken ~8 years before diagnosis. Each serum specimen was studied for antibodies against

human papillomavirus, herpes simplex virus-2 (HSV-2), and *Chlamydia trachomatis*. Logistic regression accounted for matching and potential confounding factors. Study data indicated no association between prostate cancer and serologic evidence of infections just before the reference date. However, a statistically significant association between prostate cancer and serologic evidence of HSV-2 infection was detected in the earlier sample (odds ratio, 1.60; 95% confidence interval, 1.05-2.44). The strength of this association increased when analyses were restricted to sera collected at least 60 months before diagnosis (odds ratio, 2.04; 95% confidence interval, 1.26-3.29; 204 pairs). If this association is causal, then our findings would suggest a long latency period for prostate cancer development after HSV-2 infection. (Cancer Epidemiol Biomarkers Prev 2009;18(10):2665-71)

Introduction

One in six men is likely to be diagnosed with prostate cancer in his lifetime. In 2009, an estimated 192,280 cases of prostate cancer will be diagnosed in the United States and 27,360 men will have died of prostate cancer (1). Although prostate cancer is a leading cause of cancer morbidity and mortality in men, few risk factors for prostate cancer have been established.

Infectious agents have been associated with a diverse group of cancers including liver, cervix, stomach, nasopharynx, bladder, bile duct, and Kaposi sarcoma (2). Inflammation may both induce and promote cancer through exposure to highly reactive compounds and growth factors and increased cell turnover (3). A review of studies of prostatitis and prostate cancer showed evidence of an increased risk of prostate cancer among men with prior prostatitis (4). It is unclear if inflammation affects the risk of prostate cancer or if it influences a surveillance bias. A meta-analysis evaluating aspects of sexual activity and prostate cancer suggested an association between prostate cancer and sexually transmitted infections [STI; relative risk, 1.4; 95% confidence interval

(95% CI), 1.2-1.7; ref. 5]. However, this was based on self-report rather than on biomarkers. A 2005 meta-analysis on prostate cancer and STIs, which included studies measuring human papillomavirus (HPV) by either serology or PCR, suggested an increased risk of prostate cancer with HPV infection [odds ratio (OR), 1.5; 95% CI, 1.1-2.1; ref. 6].

According to the National Health and Nutrition Examination Survey III of individuals ages ≥ 12 years, herpes simplex virus-2 (HSV-2) was prevalent in 21.9% of individuals in the United States in 1988 to 1994 (7). The prevalence of STIs among U.S. military personnel has been estimated to be higher than that among civilians (8). A 1989 to 1991 study of deployed U.S. military personnel found that they frequently engaged in high-risk sexual behavior and had high rates of STIs (9). Military personnel had a high prevalence of STIs caused by *Chlamydia trachomatis*, HSV-2 infection, and HPV (8). Based on a study in North Carolina in 1996, rates of *C. trachomatis* among individuals in the military were 4-fold higher than rates among similar nonmilitary individuals in North Carolina and the United States (10).

The U.S. military health-care system affords an opportunity to study prostate cancer risk in a relatively homogeneous and young population compared with the general U.S. population. Prostate-specific antigen (PSA) screening is a covered health benefit in the military; thus, men in the military are more likely to have had PSA screening ordered in accordance with published guidelines than are men in the general population. As a result,

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undiagnosed prostate cancer is less likely to occur in men who are members of the U.S. military compared with similar civilian groups. Prior studies among military populations have reported both high rates of prostate cancer (11) and high rates of STIs (8-10, 12); thus, if an association exists between STIs and prostate cancer, it is likely to be observed in this population.

Previous meta-analyses evaluating prostate cancer suggest an association between prostate cancer and STIs (5, 6); however, most of the pooled data were based on self-report, and as STIs often reflect undesirable behavior, they are subject to considerable reporting biases. The goal of this study was to eliminate recall bias by examining STIs and prostate cancer associations through analysis of sera collected in a cohort of military personnel before prostate cancer diagnosis. An increased relative risk for prostate cancer after STIs would suggest a possible infectious component in the development of prostate cancer, which could have several important public health implications.

Materials and Methods

We conducted a matched case-control study nested within the U.S. military population. Regular active-duty personnel are periodically evaluated by serologic test for HIV infection and an aliquot of their sera is preserved in the Department of Defense Serum Repository. The Serum Repository also stores pre- and post-deployment sera for all active-duty, Guard, and Reserve U.S. service members. Subjects testing positive for HIV were not eligible for study. The eligible subjects for this study were active-duty men, ages ≥ 18 years, serving in the U.S. Army, Air Force, Navy, or Marine Corps during the study period from September 1, 1993 to September 1, 2003, with at least 2 years of active-duty service before their reference date. The reference date for the matched pair was the diagnosis date of prostate cancer. For each case, the Department of Defense Serum Repository collected an aliquot from each of two serum samples, with the recent serum sample most closely preceding the prostate cancer diagnosis and the earlier serum sample most distant from the cancer diagnosis. Both of the control's serum samples were matched to the case's serum draw dates within 90 days. To allow for two serum samples, we required both cases and controls to have served at least 2 years of active-duty service before their reference date.

Cases. Prostate cancer cases were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic code 185 in electronically maintained Department of Defense hospitalization records. To identify prostate cancer cases, hospitalization data were obtained from the Standard Inpatient Data Record and the Health Care Service Record. Standard Inpatient Data Record and Health Care Service Record are computerized databases of standardized discharge diagnoses for hospitalizations within the Military Health System and for hospitalizations billed to the Department of Defense by private facilities. Cases were validated using either procedure codes, pathology reports, or the Department of Defense Automated Central Tumor Registry. Information from the patient's first encounter with prostate cancer in either Standard Inpatient Data Record or Health Care Service Record was merged with demographic and mili-

tary data at the time of entry into the study and at the time of diagnosis. Men who were diagnosed with prostate cancer before September 1, 1993 or had a prostate cancer diagnosis that could not be validated were excluded.

Controls. Controls were selected by random number procedure in an equal number as cases (1:1 matched to cases) from the remaining military personnel who had not been diagnosed with prostate cancer. Controls were matched to cases based on specific factors (as follows) at the time of diagnosis of the case. Matched controls were active-duty at the time the case was diagnosed and had a serum specimen collected within 90 days of the case (for each of two specimens). Our matching criteria included date of birth (± 1 year), branch of service (Army, Air Force, Marines, and Navy), and military rank (enlisted and officer). Based on standard matching criteria, the Department of Defense Serum Repository staff also matched controls for marital status (married, never married, or other) and race (White, Black, or other), which we were informed of after receiving the sera.

Of the 398 eligible cases identified, 89 did not have adequate sera or sera volume necessary to conduct the STI analyses. Of the remaining 309 cases, 41 could not be matched to an appropriate control, leaving 268 cases matched to 268 controls. One subject only had a recent serum; thus, this matched pair was excluded, leaving 267 matched pairs. Institutional review board approval was sought and granted.

Exposure Assessment. Sera aliquots from the Department of Defense Serum Repository were shipped on dry ice to researchers at the University of Iowa and were stored at -80°C . Serum specimens were then split and sent to separate laboratories for STI serologic testing. The laboratories that performed the serologic assays were blinded with respect to case-control status.

HSV-2 antibody tests were done using the HerpeSelect 2 ELISA IgG Test kit (Focus Technologies). The manufacturer's instructions stated that an index value < 0.90 was considered negative, > 0.90 to < 1.10 was considered equivocal, and > 1.10 was considered positive. Analyses were interpreted by including equivocal with negatives so that < 1.10 was considered negative and > 1.10 as positive. HPV analyses were done using an ELISA assay for IgG antibodies to virus-like particles derived from HPV6, HPV11, HPV16, and HPV18 (13). Each microtiter plate included a positive control and a negative control. Analyses of sera were run in duplicate and averaged. Positive results were defined as an absorbance index > 1.0 . All samples that showed large differences in absorbance between parallel wells, those with absorbance in the range of 20% above the cutoff value, and 15% to 20% of randomly selected samples in the set were retested to confirm results. Tests for antibodies to *C. trachomatis* were done using the microimmunofluorescence method described by Wang et al. (14) for serotypes B to K. This method detects antibodies to pooled serogroups BED (B-group), CJHI (C-group), and GFK (intermediate group) of *C. trachomatis*. Any result $> 1:16$ was considered positive for antibodies to *C. trachomatis*.

Analyses. Descriptive statistics were used to compare cases and controls for time between sera collection and matching variables. Logistic regression conditioned on the one-to-one matching of controls to cases was used to

Table 1. Demographic characteristics of active-duty U.S. military men at time of entry into study, 1993 to 2003, compared with matched case-control pairs

	Matched case-control pairs (n = 267), n (%)	Total military* (n = 2,761,151), n (%)
Age (y) [†]		
<36	4 (1.5)	2,464,703 (89.3)
36-40	14 (5.2)	183,820 (6.7)
41-45	82 (30.7)	81,311 (2.9)
46-50	80 (30.0)	25,784 (0.9)
>50	87 (32.6)	5,533 (0.2)
Military rank		
Enlisted	116 (43.4)	2,469,243 (89.4)
Officer	151 (56.6)	291,908 (10.6)
Service branch		
Army	117 (43.8)	961,756 (35.5)
Air Force	35 (13.1)	576,547 (21.3)
Marines	20 (7.5)	412,873 (15.3)
Navy	95 (35.6)	754,986 (27.9)
Marital status		
Married	237 (88.8)	1,055,375 (38.2)
Not married	30 (11.2)	1,705,776 (61.8)
Race		
White non-Hispanic	192 (71.9)	1,931,664 (70.0)
Black non-Hispanic	67 (25.1)	474,932 (17.2)
Other	8 (3.0)	354,555 (12.8)

*Active duty for at least 6 months during September 1, 1993 to September 1, 2003.

[†]Age at reference date (the case diagnosis date).

examine associations between STIs and prostate cancer. Analyses examined potential confounding due to length of service beyond confounding controlled for by one-to-one matching on date of birth (and other matching factors). Although matching factors could not be examined in the analyses, we stratified the data by date of birth to examine STI analyses separately for older and younger subjects (<50 and ≥50 years). Similarly, we ran stratified

analyses by marital status (married versus all others) and race (Blacks versus all others). Analyses were also conducted on specific subtypes of HPV and *C. trachomatis* as described under the exposure assessment section above.

To further examine the potential latency period, for the earlier serum (collected an average of 7.8 years before diagnosis), we ran a second model excluding any pairs that had their sera collected <60 months before diagnosis. A dose-response variable for the number of STIs a subject had (0, 1, or 2-3) was computed across HSV-2, HPV16 or HPV18, and *C. trachomatis*. Due to the small number of subjects with 3 STIs (8 on early serum and 12 on recent serum), subjects with either 2 or 3 STIs were pooled together. Analyses treated the number of STIs as a categorical variable, and then we reran the analyses with the three categories of STIs (0, 1, or 2-3) as a continuous variable to compute the P_{trend} and a trend OR. We report the difference in this trend comparing the lowest category (no STIs) to the highest category (2-3 STIs). The trend OR fits a line to the β coefficients for each category, assuming an equal increase in the log (OR) for each category level (15). P_{trend} values are reported for ordered categorical variables.

Results

The distribution of demographic factors in our case-control study compared with the total military population over the study period is described in Table 1. Because controls were matched to cases on several of these variables, we list the number of matched pairs for characteristics in Table 1. The minimum length of service among our 267 matched pairs was 3.5 years, with an average length of service of 22.4 years among cases and 21.1 years among controls. Subjects differed from all active-duty military with respect to age, military rank, marital status,

Table 2. Crude ORs for 267 matched pairs of prostate cancer cases and controls for elevated antibodies against HSV-2, HPV, and *C. trachomatis*

	Cases	Controls, n (%)		OR (95% CI)	OR (95% CI)
		-	+	All subjects	Restricted subjects*
Recent serum: mean 10 mo before diagnosis					
HSV-2	-	139 (52.1)	47 (17.6)	Reference	
	+	55 (20.6)	26 (9.7)	1.17 (0.79-1.73)	
HPV16 or HPV18	-	182 (68.2)	40 (15.0)	Reference	
	+	37 (13.9)	8 (3.0)	0.92 (0.59-1.45)	
Any HPV (6, 11, 16, or 18)	-	128 (47.9)	59 (22.1)	Reference	
	+	63 (23.6)	17 (6.4)	1.07 (0.75-1.52)	
<i>C. trachomatis</i>	-	207 (77.5)	27 (10.1)	Reference	
	+	29 (10.9)	4 (1.5)	1.07 (0.64-1.81)	
Earlier serum: mean 94 mo before diagnosis					
HSV-2	-	156 (58.4)	35 (13.1)	Reference	Reference
	+	56 (21.0)	20 (7.5)	1.60 (1.05-2.44)	2.04 (1.26-3.29)
HPV16 or HPV18	-	179 (67.0)	38 (14.2)	Reference	Reference
	+	43 (16.1)	7 (2.6)	1.13 (0.73-1.75)	1.20 (0.74-1.95)
Any HPV (6, 11, 16, or 18)	-	122 (45.7)	62 (23.2)	Reference	Reference
	+	61 (22.8)	22 (8.2)	0.98 (0.69-1.40)	1.00 (0.67-1.50)
<i>C. trachomatis</i>	-	205 (76.8)	23 (8.6)	Reference	Reference
	+	31 (11.6)	8 (3.0)	1.35 (0.79-2.31)	1.80 (0.96-3.38)

NOTE: HSV-2 index value is positive for >1.1, HPV optical density value is positive for >1; and *C. trachomatis* titer value is positive for >1:16. Matched on the following characteristics at the reference date: date of birth, branch of service, military rank, date of serum specimen, marital status, and race. *Subjects whose earlier serum was collected >60 mo (60-166 mo) before diagnosis (n = 204 pairs).

Table 3. Dose-response ORs among 267 matched pairs of prostate cancer cases and controls for an increasing of number of STIs (HPV16 or HPV18, HSV-2, or *C. trachomatis*)

No. STIs*	No. controls			OR (95% CI)	
	0	1	2-3	All subjects	Restricted subjects [†]
Recent serum					
No. cases					
0	97	31	19	1.0 (reference)	
1	45	26	16	1.50 (0.99-2.28)	
2-3	19	9	5	0.94 (0.56-1.58)	
	Linear trend for increase of 2 STIs			$P_{\text{trend}} = 0.660$	
				1.12 (0.68-1.83)	
Earlier serum					
No. cases					
0	102	29	16	1.0 (reference)	1.0 (reference)
1	47	27	7	1.47 (0.96-2.24)	1.83 (1.10-3.04)
2-3	20	11	8	1.54 (0.88-2.69)	1.86 (1.00-3.44)
	Linear trend for increase of 2 STIs			$P_{\text{trend}} = 0.054$	$P_{\text{trend}} = 0.012$
				1.67 (0.99-2.81)	2.10 (1.18-3.77)

NOTE: Matched on the following characteristics at the reference date: date of birth, branch of service, military rank, date of serum specimen, marital status, and race.

*Number of positive STI antibody analyses: 1 = at least one positive result, 2 = at least two positive results, and 3 = all three positive. STIs that were counted for a positive: HSV-2, HPV (16 or 18), or any antibodies for *C. trachomatis*.

[†]Subjects whose earlier serum was collected >60 mo before diagnosis ($n = 204$ pairs).

and race (Table 1). Given that pairs were matched based on these factors, Table 1 data suggest that older men, officers, married men, and Blacks were more likely to be diagnosed with prostate cancer than their military peers. However, the higher proportion of officers in our nested case-control study could be related to older age or higher socioeconomic status or may be due to more years of service (23.2 years for officers and 19.9 years for enlisted; $P < 0.0001$ for t test of the difference).

The recent serum was drawn an average of 10 months before the reference date (median, 5 months; range, 0-76 months). The average, median, and range of follow-up time after the earlier serum draw were 94, 93, and 15 to 166 months, respectively.

Among all subjects, 126 men had elevated antibodies for HSV-2 in both serum samples; for 28 subjects, tests of the earlier sample were negative, whereas tests of the more recent sample were positive. Among the 5 subjects that showed evidence of elevated antibodies for HSV-2 in the early sample but not in the more recent sample, 2 had borderline negative values in the more recent sample. HPV antibodies were elevated in both serum samples for 124 men; for 32 subjects, tests of the earlier sample were negative, whereas tests of the more recent sample were positive. In addition, 42 samples tested positive then negative. In tests for *Chlamydia*, 34 men had elevated antibodies in both serum samples, 30 tested negative on the earlier sample and positive on the recent sample, and 36 were positive then negative on the earlier and recent serum samples, respectively.

No associations were observed between prostate cancer and elevated STI antibodies measured in recent serum samples (Table 2). However, an association was seen with elevated antibodies against HSV-2 in the earlier serum. Because most risk factors for cancer have a latency period of several years or decades, we further restricted the analyses of the earlier serum to the subset collected at least 60 months (5 years) before the reference date. When the earlier

serum antibody analyses were restricted to these 204 case-control pairs, the OR (95% CI) for HSV-2 increased slightly to 2.04 (1.26-3.29) and an increased association that was marginally significant was seen between *C. trachomatis* infection and the occurrence of prostate cancer (OR, 1.80; 95% CI, 0.96-3.38). When positive results for HSV-2 were categorized as weak (index value >1.1-3.5) and strong (index value >3.5) for the earlier serum assays, a significant increasing trend ($P = 0.003$) was seen for risk of prostate cancer (data not shown). No associations were found between prostate cancer and elevated antibodies to any HPV (Table 2). Type-specific analyses of HPV6, HPV11, HPV16, or HPV18 also showed no associations with prostate cancer (data not shown). A positive but nonsignificant association was observed between prostate cancer and increased antibodies to *C. trachomatis* serogroup GFK in the earlier serum samples (OR, 1.83; 95% CI, 0.68-4.96; data not shown). Finally, an analysis was conducted to look at the association between number of STIs (HSV-2, HPV16 or HPV18, or *C. trachomatis*) and prostate cancer (Table 3) using a linear dose-response model. No association was seen with the recent serum (collected just before diagnosis). For the earlier serum, a linear increase in risk of 110% was seen for two additional STIs among matched pairs whose specimens were collected at least 60 months before diagnosis (45% for an increase of one STI). None of these analyses were confounded by length of service.

Additional analyses of the 267 matched pairs were stratified by age (<50 and ≥ 50 years), marital status, and race. Analyses showed slightly stronger risks for subjects ages <50 years (OR, 1.92; 95% CI, 1.17-3.14; $n = 324$), single men (OR, 1.77; 95% CI, 0.40-7.39; $n = 34$), and Black men (OR, 1.74; 95% CI, 0.87-3.47; $n = 134$) with evidence of HSV-2 infection in the earlier serum. Although the mean age of Black men was younger than that of White men (45 versus 48 years), age did not confound the association between prostate cancer and HSV-2 among Blacks. Differences were not seen in the recent serum.

Discussion

STIs have been implicated in several studies as a risk factor for prostate cancer. Although previous meta-analyses evaluating prostate cancer and STIs showed an increased risk (5, 6), most of the evidence was based on self-report, which can be strongly biased. With a goal of reducing such biases, our study examined associations between STIs and prostate cancer using sera collected in a cohort of military men before prostate cancer diagnosis. Intriguingly, our data based on the earlier serum specimens, collected on average 7.8 years before prostate cancer diagnosis, showed an increased risk of prostate cancer among men who had elevated antibody titers against HSV-2. The association with HSV-2 was strengthened when analyses of the earlier sera were restricted to those specimens collected at least 5 years before diagnosis. If HSV-2 infection is causally related to prostate cancer, then our findings would suggest a long latency period after HSV infection. This is important in that most risk factors for cancer show a latency period of many years.

The increased risk for prostate cancer with a longer latency should be further examined in other populations with high levels of HSV-2 infections using serology with an adequate length of time between sera collection and prostate cancer diagnosis. A previous study of HSV-2 serology with an average of 17 years follow-up to prostate cancer diagnosis found no association; however, that study differed from our study of U.S. military personnel in several ways. The Finnish study population had a low prevalence of elevated antibodies against HSV-2 (16), which may have limited the study's power to detect an association among their 163 cases and 288 controls. The lower prevalence may in part be due to older age of their cases (age 75 years on average) compared with our average diagnosis age of 48 years. Both of these average ages are a bit extreme with a median age of diagnosis of 68 years in the United States (1). It is also possible that deterioration of samples over 20 years before analyses may have affected the data in the Finnish study. Their sera were collected between 1968 and 1972, and prostate cancer cases were diagnosed through 1991. Thus, cases (and their matched controls) were apparently linked to sera sometime between 1991 and when the article was submitted for publication (2004). Other previous studies relied on self-report as a measure of exposure (17, 18) or collected data on HSV-2 infection post-diagnosis of prostate cancer (19-21). Self-report of STIs is problematic with a high potential for underreporting especially among nondiseased subjects. Although HSV-2 has been reported to infect prostate tissue (19), diagnosis of STIs after prostate cancer lacks the appropriate temporal sequence to suggest causation. In addition to the lack of a temporal sequence, a mechanism for HSV-2 initiating or promoting prostate cancer has not been identified. As HSV-2 infections are seldom completely cleared from the body, antibodies against HSV-2 may fluctuate over time, especially after clinical flare-ups. Thus, future research may want to consider examining antibody levels over time.

The lack of association between prostate cancer and evidence for HPV or *C. trachomatis* infection for our earlier serum specimens (longer latency) is supported by a few other studies. A study with at least 10 years follow-up to prostate cancer found no association with *C. trachomatis* infection (22). In addition, no association was seen with

HPV16, HPV18, or HPV33 infection in a nested case-control study where the majority of prostate cancer cases were seen ≥ 10 years after infection (23). Another study with ≥ 20 years of follow-up found no association with *C. trachomatis*, HPV11, or HPV33 infection but found an increase in risk with HPV18 infection (OR, 2.6; 95% CI, 1.2-5.8) and a suggested increase with HPV16 infection (OR, 2.4; 95% CI, 0.7-7.6; ref. 24). In a nested case-control study with case diagnoses occurring an average of 26 years after enrollment, a marginal association with HPV16 infection (OR, 2.7; 95% CI, 0.9-7.9) was found (25). Overall, these data suggest no association between prostate cancer and *C. trachomatis* infection but a possible association with HPV16 and HPV18 infections many years after prostate cancer diagnosis that merits further examination.

We found no association between increased STI antibodies and prostate cancer in the recent serum specimens (collected an average of 10 months before prostate cancer diagnosis). This is similar to a recent study by Huang et al. (26), which found no association between prostate cancer and elevated antibodies against HSV-2, HPV16, HPV18, or *C. trachomatis* in sera collected an average of 18 months before diagnosis. However, in a subset analysis, they did find an association between prostate cancer and elevated IgA antibodies against *C. trachomatis* among Blacks. We did not see this same association among Blacks in our study. Another study with a mean time between blood draw and diagnosis of only 3.1 years also found no association with HPV16, HPV18, HPV33, or *C. trachomatis* infection (27). Two additional studies using sera collected after diagnosis found no association with HPV16 or HPV18 infection (28, 29). Thus, the seroepidemiologic literature does not support an association between prostate cancer and recent STI.

To study the relationship between prostate cancer and STIs (without recall bias), it was necessary both to have a large repository of serum samples collected before diagnosis and to have recent samples and samples collected over 5 years before diagnosis. The Department of Defense Serum Repository was the only source, to our knowledge, that provided such a capability. As a result of using a military population for this study, the median age for prostate cancer cases in this study was 48 years. This is considerably less than the median age for prostate cancer cases in the general population, which is 68 years (1). As a result, the etiology of prostate cancer causation in younger men may not represent that observed among older men who comprise the majority of prostate cancer cases. For example, STIs more commonly occur among younger men rather than among men of advanced age who would normally be at risk of prostate cancer. Based on what we know about cervical cancer, 75% of 40 reviewed studies suggested a latency period of < 12 months after HPV infection (30); latency periods between infections and cancer are believed shorter than for other cancer exposures. Because men ages 18 to 29 years are at greatest risk for STIs, we would expect such an "exposure" to cause prostate cancer at an earlier age if the association is real; thus, the use of a military population to study STIs and prostate cancer was deemed appropriate.

The association between STIs and prostate cancer remains controversial. The effects of infections, in general, on prostate cancer are not clearly understood. Studies of prostate cancer have examined associations with inflammation and other conditions, such as epididymitis, cirrhosis, urethritis, and several infectious agents, including

Trichomonas, cytomegalovirus, and EBV but results have been inconsistent (31-36). The effects of STIs on prostate cancer etiology are not clearly understood given the inconsistent findings in studies of other infections. HSV-2 was found early on in prostate tumors (19, 37); however, more recent corroborating data seem to be lacking. It is possible that men with HSV-2 are followed more closely than uninfected men and may be screened for prostate cancer at an earlier age; however, the lack of association between prostatitis and evidence of HSV-2 infection does not support such a surveillance bias. As data regarding military PSA screening rates were not available, we cannot comment further on the potential screening bias among military personnel. Overall, present and prior findings suggest that additional research on how such infections may be related to prostate cancer is needed.

Our study has several strengths including the choice of a population with high rates of both prostate cancer and STIs, including *C. trachomatis*, HSV-2, and HPV infections (8, 10, 11). Such high rates make both STIs and prostate cancer important health issues for military personnel. As PSA screening is a covered health benefit in the military, it seems more likely that prostate cancer will be detected among military personnel than in men in the general population. Although prostate cancer rates in military personnel may be higher than in the overall U.S. population due to better access to care and more frequent PSA screening (introduced in 1987-1988; ref. 38), this study represents a large, fairly homogeneous cohort. Accurate exposure measurement is an important issue when looking at STIs. However, many studies of prostate cancer and STIs rely on self-report and lack the specificity of biomarker laboratory data. The major strength of this study is the availability for examination of sera that were drawn several years before the diagnosis.

Although our study has several strengths, it also has limitations. Unfortunately, PSA screening and cancer stage data were not available in this electronic database. The additional matching criteria on marital status and race assigned by Department of Defense Serum Repository staff, which were not in the study protocol, may have overmatched cases and controls on variables potentially related to STIs as suggested in Table 1. This potential overmatching likely made the control group more like the cases and would tend to bias ORs toward 1.0. This was supported by the larger ORs seen in single men (for HSV-2) and Black non-Hispanic men (for HSV-2 and HPV; data not shown). We should note that a positive or negative result for antibodies for a given serum sample only reflects antibody levels at one point in time. *C. trachomatis* infection can be treated and cleared or may exist in men with few or no symptoms. HPV infections may also exist with few or no symptoms and may be cleared by the body; thus, finding similar numbers of negative/positive and positive/negative tests for HPV and *Chlamydia* was not surprising. However, HSV-2 infection is often a chronic condition that is not cleared. Although all laboratory tests have potential for error, indeterminate or borderline antibody counts, particularly for HSV-2, could reflect no recent infection before the blood draw for that serum sample. Additionally, we do not know how long after an infection or flare-up antibodies remain elevated. We do not know if men in the military with STIs (other than HIV) are followed and screened more than other men; if

so, this could account for the association seen here with HSV-2 and prostate cancer but would not be consistent with the lack of association between prostate cancer and HPV or *C. trachomatis* infection.

Conclusion

We examined antibodies for HSV-2, several HPV types, and *C. trachomatis* at an average of 94 and 10 months before prostate cancer diagnosis. Our findings suggest little or no association with evidence of infections just before the reference date. However, we did find an association between prostate cancer and HSV-2 infection, which tends to be a chronic infection, in sera collected an average of 7 years before diagnosis. If this association is real, it would suggest that men diagnosed with HSV-2 should be encouraged to seek regular prostate cancer screening.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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