Prostate Cancer Incidence and Prostate-Specific Antigen Testing Among HIV-Positive and HIV-Negative Men

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Background: We investigated whether the reported lower incidence of prostate cancer in HIV-positive men is a result of confounding factors or reduced screening.

Methods: We conducted a cohort study of 17,424 HIV-positive and 182,799 HIV-negative men enrolled in Kaiser Permanente (KP). Subjects were followed from the first KP enrollment after January 01, 1996 for KP Northern California (KPNC) and January 01, 2000 for KP Southern California until the earliest of prostate cancer diagnosis, loss to follow-up, or December 31, 2007. Poisson regression was used to compare cancer rates by HIV status adjusting for age, race, smoking, alcohol/drug abuse, overweight/obesity, and diabetes. For the KPNC subset, we analyzed additional available data by HIV status on testosterone deficiency, and on prostate-specific antigen (PSA) tests as a proxy for cancer screening.

Results: The prostate cancer incidence rate was 102/100,000 person-years in HIV-positive men (n = 74 cases) and 131/100,000 person-years in HIV-negative men (n = 1195 cases), with an adjusted rate ratio of 0.73 (95% confidence interval: 0.57 to 0.92; $P = 0.008$). The reduced risk among HIV-positive men was greater for higher-stage cancers, which are less likely to be biased by screening differences than lower-stage cancers. In the KPNC subset, more HIV-positive (90.8%) than HIV-negative men (86.2%) received a PSA test by age 55 ($P < 0.001$). Decreased risk for HIV-positive men remained when examined only among those with a previous PSA test, and with adjustment for testosterone deficiency (rate ratio = 0.55; 95% confidence interval: 0.39 to 0.80; $P = 0.001$).

Conclusions: Prostate cancer incidence rates are lower in HIV-positive compared with HIV-negative men, which is not explained by screening differences or the risk factors evaluated.

Key Words: prostate cancer, screening, health care, men who have sex with men, HIV

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INTRODUCTION

Combination antiretroviral therapy (ART) use has prolonged the lifespan of HIV-positive individuals, with more than half expected to be over 50 years of age in the United States by 2015.[1] Men in this group are now increasingly diagnosed with prostate cancer, with an over 7-fold increase during 1991–2005.[2] Despite rising incidence, there is no evidence of an elevated risk of prostate cancer, independent of age, among HIV-positive individuals compared with the general population. In fact, several studies have identified a 20%–50% lower age-adjusted risk of prostate cancer among HIV-positive compared with HIV-negative men.[3–8] The reason for this reduced risk is unclear, but may be that there are differences in prostate cancer screening[5,7,8] or prevalence of risk factors by HIV status. It is important to understand whether the lower risk of prostate cancer among HIV-positive men is due to less frequent screening, revealing a potential disparity that would need to be addressed; a biological effect, which would help advance our understanding of this common cancer; or a confounding bias that should be accounted for in future studies.

Comparisons of prostate cancer risk by HIV status need to consider differences in screening because most cases are asymptomatic at the time of diagnosis. In one of the only studies to evaluate use of prostate-specific antigen (PSA) testing among HIV-positive men, Shiels et al[8] reported lower PSA

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testing rates in a cohort of low-income men with AIDS compared with external general population estimates.[9] However, to the best of our knowledge, there are no studies that have evaluated prostate cancer risk by HIV status while accounting for screening practices in the same population.

The prevalence of prostate cancer risk factors may also differ by HIV status. Lower serum testosterone may be protective against prostate cancer,[10] and HIV-positive men are more likely to experience hypogonadism for a variety of reasons, including pituitary impairment.[11,12] HIV-positive individuals have a lower risk of other hormone-associated malignancies, including breast and thyroid cancers,[3,4] lending support to the theory that hormone dysregulation contributes to decreased cancer risk in this population. Diabetes may also be an important mediator, given that it is more common among HIV-positive individuals taking certain protease inhibitors (PIs) or nucleoside reverse-transcriptase inhibitors[13,14] and may have a protective effect against prostate cancer,[15–18] possibly by reducing androgen receptor levels.[19]

In this study, we evaluated prostate cancer incidence rates overall and by cancer stage among HIV-positive and HIV-negative men from the same health care system. We also aimed to determine whether the previously reported lower incidence rates of prostate cancer in HIV-positive men can be explained by reduced screening, mediating effects of testosterone deficiency or diabetes, or confounding effects of race/ethnicity or other risk factors.

METHODS

Study Design, Setting, and Participants

We conducted a cohort study from 1996 through 2007 of HIV-positive and HIV-negative individuals within Kaiser Permanente (KP) Northern and Southern California (KPNC and KPSC, respectively), large integrated health care delivery systems providing comprehensive medical services to over 6 million members, representing approximately 30% of insured Californians.[20] All members have access to primary care, including routine cancer screening, and specialty services, including referral to urology and oncology. The study population was the subset of men from a previously described cohort.[6] Briefly, HIV-positive men were identified from HIV registries that included all known HIV/AIDS cases among KPNC members since the early 1980s and KPSC members since 2000, with HIV-positive status confirmed by chart review or provider review of case lists. Men not included in the registries were considered HIV-negative. Among HIV-positive men, we did not include person-time before diagnosis in the HIV-negative group because HIV infection may have predated diagnosis for several years.

HIV-negative men were then frequency-matched 10:1 to HIV-positive men by year of start of follow-up, age at start of follow-up (5-year age groups), and medical center. The start of follow-up for HIV-positive subjects was the earliest date after January 01, 1996 (KPNC), or January 01, 2000 (KPSC), when they met the following criteria: KP member, ≥18 years of age, known to be HIV positive, and in HIV care, defined as the first CD4 T-cell count measurement recorded in the health care system. The start of follow-up for HIV-negative subjects was the earliest date during the year selected in frequency matching when they met the following criteria: KP member and ≥18 years of age. Subjects were followed until the earliest of prostate cancer diagnosis, loss to follow-up (i.e., left the health plan, defined as a gap in membership of ≥3 months), or December 31, 2007.

The institutional review boards at KPNC and KPSC approved this study, providing waivers of informed written consent.

Study Measurements

HIV Registries

The primary exposure of interest was HIV status, obtained from the KP HIV registries. Additional data elements obtained from the HIV registries included race/ethnicity, HIV-transmission risk factor, previous AIDS diagnosis as defined by Centers for Disease Control criteria,[21] and duration of known HIV infection.

Cancer Registries

The primary outcome was an incident invasive prostate cancer diagnosis ascertained from the KP cancer registries, which are contributing sites to the Surveillance, Epidemiology, and End Results (SEER) program registry. KP cancer registries use rigorous standardized methods for verifying and coding all new reportable cancers to ensure accuracy and completeness for reporting to SEER-affiliated regional registries. Individuals with prostate cancer diagnoses in the 2 years before study entry were considered prevalent cases and excluded from analysis. In addition, cancer stage at diagnosis was obtained, including SEER summary stage and tumor, nodes, metastasis (TNM) stage. TNM stage incorporated Gleason score for all cancers according to the American Joint Committee on Cancer Sixth Edition Staging Manual,[22] and was available for descriptive analysis for the KPNC subset. Given previously published data on the distribution of TNM stage for prostate cancer,[23,24] we expected to observe few stage I cases.

Electronic Medical Record

Data obtained from the clinical and administrative databases constituting KP's electronic medical record (EMR) included laboratory test results (CD4 cell counts and HIV RNA levels); pharmacy prescription fills (ART use); age; health plan enrollment periods; dates of death from hospital records, California death certificates, and Social Security Administration data sets; and inpatient and outpatient clinical diagnoses, including overweight/obesity [International Classification of Disease codes, version 9 (ICD-9): 278, 259.9, V85; internal weight/height codes], smoking/tobacco use (ICD-9: 305.1, V15, V65, 649, internal social history codes), drug/alcohol abuse (ICD-9: 291, 292, 303–305.0, 305.2–305.5), and diabetes (ICD-9: 250.0–250.9 for KPSC and from the Diabetes Registry for KPNC[25]). For the KPNC subset, additional data were available on documented testosterone deficiency, based on diagnosis of hypogonadism/hypotestosterone (ICD-9: 257.2) or a pharmacy fill for exogenous testosterone therapy. Subjects without a recorded clinical

diagnosis in the EMR were considered unexposed for that risk factor; thus, there were no missing data on these variables.

PSA Testing

Data on PSA tests and levels were available only for the KPNC subset. Laboratory databases do not distinguish PSA tests used for screening from those used to monitor progression of disease or after a previously abnormal PSA test. To address this limitation, we considered the first PSA test during the follow-up period as a presumptive PSA screening test if it was ordered by a primary care physician and did not follow a prostate biopsy. This definition is similar to that used in a previous KPNC study of prostate cancer in the general population.[26]

Statistical Analysis

Variables considered in the analysis included age (<40, 40–49, 50–64, 65+ years), race/ethnicity (white, black/African-American, Hispanic/Latino, Asian/Pacific Islander, other), smoking (ever/never), overweight/obesity (ever/never), diabetes (ever/never), and drug or alcohol abuse (ever/never). Among HIV-positive subjects only, we considered any previous ART use, years known to be HIV positive (≥10, 5–9.9, <5 years), HIV-transmission risk factor [men who have sex with men (MSM), heterosexual sex, injection drug use, unknown], recent (i.e., within the previous 6 months) and nadir (i.e., lowest recorded in KP) CD4 counts (<200, 200–499, ≥500 cells/μL), and recent HIV RNA levels (≥10,000, 500–9,999, <500 copies/mL). Time-dependent variables included age, previous ART use, years known to be HIV positive, and recent CD4 counts and HIV RNA levels. Time-dependent variables were updated continuously except for CD4 counts and HIV RNA levels, which were updated at 6-month intervals.

We compared demographic and clinical characteristics of HIV-positive and HIV-negative subjects at the start of follow-up using the Pearson χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. Among subjects with a prostate cancer diagnosis, we compared demographic and tumor characteristics, including TNM stage (stage I–IV) and SEER summary stage (localized, regional, or distant),[27] by HIV status.

We computed prostate cancer incidence rates per 100,000 person-years by HIV status. Incidence rates were computed for any prostate cancer, and by TNM and SEER summary stage. Using HIV-negative subjects as the reference group, crude rate ratios (RRs) for prostate cancer were obtained from Poisson regression models. Adjusted RRs for prostate cancer incidence (any cancer and by cancer stage) were obtained from Poisson regression models that included terms for HIV infection, age, race, smoking, alcohol/drug abuse, overweight/obesity, diabetes, and KP region.

In the KPNC subset, we compared PSA testing by HIV status using Kaplan–Meier plots of the cumulative proportion with PSA testing with age as the time scale. We used Cox regression, again using age as the time scale, to obtain a race-adjusted hazard ratio for PSA testing associated with HIV status. Finally, we fit a Poisson model for prostate cancer rates by HIV status, restricting to subjects with a previous PSA test to remove the potential effect of screening, and adjusting for the same covariates included in the full cohort model.

To identify risk factors for prostate cancer among HIV-positive subjects, we obtained adjusted RRs for HIV-specific factors, in addition to factors in the full cohort model. We fit a model among HIV-positive subjects in the KPNC subset that additionally adjusted for testosterone deficiency. Finally, we fit a similar multivariable model among HIV-negative subjects to allow comparison with the type and magnitude of risk factors identified among HIV-positive subjects.

Analyses were conducted using SAS 9.1 (Cary, NC). Statistical tests were 2-sided, and statistical significance was defined as $P < 0.05$.

RESULTS

The study population included 17,424 HIV-positive and 182,799 HIV-negative men, contributing a mean value of 4.2 and 5.0 person-years/subject, respectively (Table 1). The groups were similar with respect to the matching factor of age, although small differences in all characteristics reached statistical significance due to the large sample size. The groups differed by race/ethnicity, with HIV-positive subjects more frequently white or black/African-American and HIV-negative subjects more frequently Hispanic/Latino or Asian/Pacific Islander. A higher percentage of HIV-positive subjects had a history of smoking (39.3% vs. 23.3%), alcohol abuse (12.2% vs. 6.6%), drug abuse (14.6% vs. 3.8%), and testosterone deficiency (12.8% vs. 0.6% in the KPNC subset), whereas the distributions of overweight/obesity (38.2% vs. 40.9%) and diabetes (8.3% vs. 7.5%) were similar by HIV status. Among HIV-positive subjects, MSM was the most common transmission risk factor (62.3%). Less than half (41.6%) used ART before study entry. By the end of follow-up, 76.1% had used ART, the mean CD4 count was 466 cells per microliter, and 60.5% had an HIV RNA level of <500 copies per milliliter.

Characteristics of 74 and 1195 prostate cancer cases among HIV-positive and HIV-negative men, respectively, are presented in Table 2. Similar to the overall cohort, there were no differences in age by HIV status, and HIV-positive cases were more frequently white or black/African-American ($P = 0.031$). There was a trend toward lower TNM stages among HIV-positive compared with HIV-negative cases, with 95.2% vs. 89.5% in stage II and 4.8% vs. 10.5% in stage III–IV, respectively ($P = 0.14$); there were no stage I cases. The distribution of SEER summary stage also differed by HIV status, with HIV-positive cases more frequently diagnosed with localized cancers (92.8% vs. 83.2%) and less frequently diagnosed with regional/distant cancers (7.3% vs. 16.8%) ($P = 0.036$). Finally, in the KPNC subset, recent PSA levels were lower among HIV-positive cases (9.9 vs. 17.4 ng/ml, $P = 0.019$).

The crude prostate cancer rate per 100,000 person-years was 102 for HIV-positive subjects and 131 for HIV-negative subjects, with an unadjusted RR of 0.78 [95% confidence interval (CI): 0.61 to 0.98] and an adjusted RR of 0.73 (95% CI: 0.57 to 0.92; Table 3). The adjusted association between HIV status and prostate cancer was stronger for more advanced cancers, with an RR of 0.28 (95% CI: 0.11 to

TABLE 1. Cohort Baseline Characteristics

	HIV+	HIV−	*P*
N	17,424	182,799	
KPNC	9,455	100,625	
KPSC	7,969	82,174	
Mean yrs follow-up (SD)	4.2 (3.6)	5.0 (3.6)	<0.001
Mean age at baseline (SD)	40.8 (9.6)	40.3 (9.8)	<0.001
Race/ethnicity, % among known			<0.001
White	58.1	47.8	
Black/African-American	16.0	11.1	
Hispanic/Latino	21.2	26.5	
Asian/Pacific Islander	3.9	13.4	
Other	0.7	1.2	
% Unknown race/ethnicity	7.8	45.6	<0.001
Ever smoking, %	39.3	23.3	<0.001
Ever alcohol abuse, %	12.2	6.6	<0.001
Ever drug abuse, %	14.6	3.8	<0.001
Ever overweight/obese, %	38.2	40.9	<0.001
Diabetes, %	8.3	7.5	<0.001
Ever testosterone deficiency*, %	12.8	0.6	<0.001
HIV-transmission risk factor, %			
MSM	62.3	—	
Injection drug use	5.5	—	
Heterosexual	7.2	—	
Other	1.2	—	
Unknown	23.8	—	
CD4 cells/μL at baseline, %			
<200	28.1	—	
200–349	21.2	—	
349–499	20.4	—	
≥500	30.4	—	
Mean CD4 cells/μL at baseline (SD)	389 (282)	—	
HIV RNA copies/mL at baseline, %			
≥100,000	10.0	—	
10,000–99,999	50.8	—	
500–9999	14.1	—	
<500	25.2	—	
Mean log HIV RNA at baseline (SD)	4.1 (1.0)	—	
Prior CDC AIDS baseline	40.7	—	
Previous use of ART at baseline	41.6	—	

*KPNC subjects only.
CDC, Centers for Disease Control.

TABLE 2. Prostate Cancer Case Characteristics

	HIV+	HIV−	*P*
Cases, N	74	1195	
KPNC	34	706	
KPSC	40	489	
Age, %			0.63
<50	5.4	8.1	
50–64	64.9	65.4	
≥65	29.7	26.4	
Mean age at diagnosis (SD)	60.5 (7.1)	60.2 (7.7)	0.6
Race/ethnicity, %			0.031
White	63.5	51.6	
Black/African-American	28.4	22.5	
Hispanic/Latino	5.4	11.8	
Asian/Pacific Islander	1.4	7.2	
Other	0	2	
Unknown	1.4	4.9	
TNM stage, % among known			0.14
I	0	0	
II	95.2	89.5	
III–IV	4.8	10.5	
% Unknown TNM stage	14.9	14.1	
SEER summary stage, % among known			0.036
Localized	92.8	83.2	
Regional	2.9	13.6	
Distant	4.4	3.2	
% Unknown SEER summary stage	6.8	4.4	
Gleason score, % among known*			0.52
2–4	0.0	1.4	
5–6	83.3	71.3	
7–9	16.7	26.8	
10	0.0	0.4	
% Unknown Gleason score	11.8	1.7	
Recent previous PSA >4 ng/mL, %†	97.0	91.6	0.27
Recent previous mean PSA levels†	9.9 (5.9)	17.4 (74.4)	0.019
Mean CD4 cells/μL at diagnosis (SD)	503 (285)	—	
Mean log HIV RNA at diagnosis (SD)	3.0 (0.6)	—	

*Gleason score reported separately for Kaiser Permanente Northern California subjects only. Gleason score was incorporated into TNM staging for cancers diagnosed during 2004–2007 for both KPNC and KPSC.
†Kaiser Permanente Northern California subjects only; most recent test within 1 year before diagnosis.

0.68) for regional/distant cancers compared with 0.81 (95% CI: 0.63 to 1.05) for localized cancers, and an RR of 0.28 (95% CI: 0.09 to 0.90) for stage III/IV cancers compared with 0.77 (0.60 to 1.01) for stage II cancers.

The cumulative proportion with PSA testing by HIV status is shown in the Figure 1. Compared with HIV-negative men, a higher proportion of HIV-positive men received a PSA test by age 55 (90.8% vs. 86.1%) ($P < 0.001$), with a race-adjusted hazard ratio of 1.18 (95% CI: 1.13 to 1.23). In the KPNC subset, after restricting to those with previous PSA testing, and with additional adjustment for testosterone deficiency, HIV-positive subjects continued to have lower incidence of prostate cancer compared with HIV-negative subjects, with an adjusted RR of 0.55 (95% CI: 0.39 to 0.80; Table 3).

Prostate cancer risk factors in HIV-positive subjects are presented in Table 4. There were no HIV-specific factors independently associated with prostate cancer incidence. Significant risk factors included increasing age ($P < 0.001$), black/African-American race compared with other race/ethnicities (RR, 2.5; 95% CI: 1.5 to 4.2), and smoking (RR, 2.1; 1.3 to 3.4). In the KPNC subset, testosterone deficiency was not associated with prostate cancer incidence (see **Table, Supplemental Digital Content 1,** http://links.lww.com/QAI/A528, which shows testosterone deficiency results).

Among HIV-negative subjects, several risk factors of comparable magnitude to HIV-positive subjects were observed. Prostate cancer incidence was higher with increasing age ($P < 0.001$), among individuals of black/African-American race compared with other racial/ethnicities (RR, 2.7; 95% CI: 2.4

TABLE 3. Prostate Cancer Incidence Rates and RRs by HIV Status

	All Prostate Cancer	By SEER Summary Stage		By TNM Stage		Among PSA Tested (KPNC Only)
		Localized	Regional/Distant	Stage II	Stage III/IV	
HIV+ n (rate)*	74 (102)	69 (88)	5 (7)	71 (83)	3 (4)	33 (237)
HIV− n (rate)	1195 (131)	1003 (105)	192 (21)	1087 (101)	108 (12)	680 (410)
Unadjusted RR†	0.78	0.85	0.33	0.82	0.35	0.58
95% CI	0.61 to 0.98	0.66 to 1.09	0.13 to 0.79	0.63 to 1.07	0.11 to 1.10	0.41 to 0.82
P	0.036	0.19	0.014	0.14	0.072	0.002
Adjusted RR‡	0.73	0.81	0.28	0.77	0.28	0.55
95% CI	0.57 to 0.92	0.63 to 1.05	0.11 to 0.68	0.60 to 1.01	0.09 to 0.90	0.39 to 0.80
P	0.008	0.11	0.005	0.057	0.032	0.001

*Rates per 100,000 person-years.
†Poisson regression model included term for HIV status.
‡Poisson regression model included terms for HIV status, age, black/African-American race, smoking, alcohol/drug abuse, overweight/obesity, diabetes, and Kaiser Permanente region. For KPNC subset, model additionally included testosterone deficiency.

to 3.1), and among individuals with a history of smoking (RR, 1.5; 95% CI: 1.3 to 1.7; see **Table, Supplemental Digital Content 2,** http://links.lww.com/QAI/A528, which shows risk factors in HIV-negative subjects). In contrast to HIV-positive subjects, overweight/obesity was associated with increased incidence (RR, 1.6; 95% CI: 1.4 to 1.8), and incidence was lower among those with drug abuse (RR, 0.7; 95% CI: 0.5 to 0.9) and diabetes (RR, 0.8; 95% CI: 0.6 to 0.9).

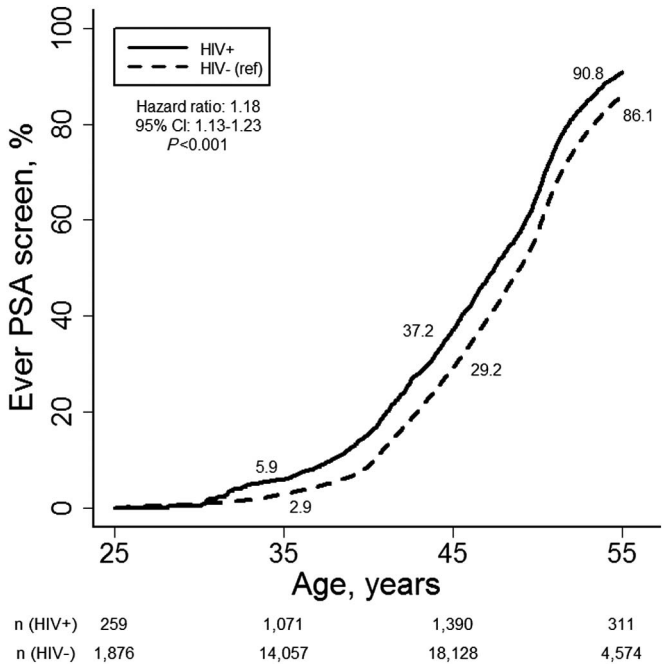

FIGURE 1. Kaplan–Meier plots show cumulative proportion with a PSA test by HIV infection status in the KPNC subset. Plots include numbers at risk by age, and the percentage tested by HIV status at age 35, 45, and 55. Overall, 8,402 HIV+ and 90,799 HIV− individuals aged 20–60 years contributed to the plots. The hazard ratio for HIV status (HIV-negative reference) was obtained from a Cox regression model adjusting for black/African-American race with age as the time scale.

DISCUSSION

In this large cohort of HIV-positive and HIV-negative men receiving care in the same health care system, we found a 27% reduced risk of prostate cancer among HIV-positive men after adjustment for age, race, smoking, alcohol/drug abuse, overweight/obesity, and diabetes, and a 45% reduced risk when restricted to previously PSA-tested individuals and with additional adjustment for testosterone deficiency. HIV-positive men were more likely to be tested and were diagnosed with lower-stage cancers and lower PSA levels. Furthermore, we observed a stronger protective association between HIV infection and prostate cancer among higher-stage cancers, a result that is less likely to be biased by differences in screening than an association among lower-stage cancers. Our results suggest that the observed lower incidence of prostate cancer among HIV-positive men in this setting is attributable to factors other than differences in PSA screening or the risk factors evaluated.

Our finding of a lower incidence of prostate cancer in HIV-positive men is consistent with several previous studies exploring this association.[3–8] While others have observed a higher risk[28–30] of prostate cancer among HIV-positive men or no difference by HIV status,[31–34] most were based on registry data without adjustment for prostate cancer risk factors. Only 2 studies directly compared risk by HIV status using an internal HIV-negative comparison group,[30,32] with both adjusting for basic demographic characteristics and 1 additionally adjusting for a family history of prostate cancer[30]; neither adjusted for testosterone deficiency, diabetes, or other risk factors. The discrepant results across studies may also have resulted from differences in screening rates, access to health care, or health behaviors across study populations. We observed a reduced incidence of prostate cancer among HIV-positive men after controlling for prostate cancer risk factors and restricting to those with a previous PSA test.

Our finding that PSA testing is more common among HIV-positive men is in contrast to a previous study by Shiels et al[8] that identified a lower rate of PSA testing in a cohort of low-income men with AIDS compared with the general population. Our results suggest that in settings of equal access to

TABLE 4. Multivariable Analysis of Prostate Cancer Risk in HIV-Positive Subjects

	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Age ≥65 vs. <50 yrs	104.5 (36.0 to 303.1)	<0.001	81.6 (27.6 to 241.2)	<0.001
Age 50–64 vs. <50 yrs	29.7 (10.7 to 82.3)	<0.001	24.7 (8.8 to 69.0)	<0.001
Black/African-American vs. other race/ethnicities	2.4 (1.4 to 3.9)	<0.001	2.5 (1.5 to 4.2)	<0.001
MSM	0.8 (0.5 to 1.2)	0.245	1.0 (0.6 to 1.7)	0.938
Known HIV+ ≥5 yrs	1.6 (1.0 to 2.6)	0.059	1.2 (0.7 to 2.0)	0.536
AIDS diagnosis (CDC criteria)	1.3 (0.8 to 2.1)	0.30	1.3 (0.7 to 2.4)	0.322
ART use	1.9 (1.0 to 3.6)	0.067	1.1 (0.5 to 2.4)	0.728
Recent CD4 <200 vs. ≥200 cells/μL	0.5 (0.2 to 1.2)	0.105	0.7 (0.3 to 1.7)	0.378
Nadir CD4 <200 vs. ≥200 cells/μL	0.8 (0.5 to 1.3)	0.393	0.6 (0.3 to 1.2)	0.147
HIV RNA >500 vs. ≤500 copies/mL	0.6 (0.3 to 0.9)	0.023	0.7 (0.4 to 1.2)	0.221
Ever smoking	2.4 (1.5 to 3.9)	<0.001	2.1 (1.3 to 3.4)	0.004
Ever overweight/obese	0.9 (0.6 to 1.4)	0.709	0.8 (0.5 to 1.3)	0.350
Ever alcohol abuse	0.6 (0.3 to 1.3)	0.205	0.6 (0.3 to 1.3)	0.204
Ever drug abuse	0.5 (0.2 to 1.1)	0.099	0.7 (0.3 to 1.6)	0.444
Diabetes	3.2 (1.8 to 5.7)	<0.001	1.2 (0.7 to 2.2)	0.537
KPNC vs. KPSC region	0.6 (0.4 to 0.9)	0.017	0.6 (0.4 to 1.1)	0.087

CDC, Centers for Disease Control.

care, HIV-positive patients are not screened less often, and in fact may be more likely to be screened. This finding is supported by the lower PSA levels and earlier-stage cancers observed among HIV-positive cases, and by the stronger association observed for HIV infection among higher-stage cancers. Thus, it is possible that our results were biased toward the null, such that the reduced incidence of prostate cancer we observed among HIV-positive men would have been even more pronounced if HIV-negative men were tested as frequently.

The reason for the reduced risk in HIV-positive individuals remains unclear. One viable explanation may be that ART use, specifically PIs, protects against the development of prostate cancer. A study by Chao et al[35] from the same population studied here noted that duration of PI use was associated with a decreased incidence of prostate cancer. This finding was consistent with studies demonstrating that PIs have direct antitumor effects on prostate cancer cells by inducing apoptosis and sensitizing them to the cytotoxic effects of cancer treatments.[36,37] It may also be that MSM, who comprise a substantial proportion of the HIV-positive men in industrialized countries, have more favorable nutrition, weight, or exercise patterns, which can reduce the risk of cancer.[38] Although we did not see a difference in incidence by sexual orientation, the prevalence of heterosexual men was low, and we did not have data to identify contributing factors among MSM. Prostate cancer risk among HIV-positive and HIV-negative MSM should be further explored in settings where detailed behavioral data are collected.

There are some limitations of this study. First, it is possible that some PSA tests were performed to evaluate alterations in urologic function or as a result of an abnormal digital rectal exam. However, we minimized this possibility by excluding PSA tests ordered by a urologist or subsequent to a prostate biopsy, similar to a method previously used in a study of prostate cancer in the general population.[26] In a previous study conducted in KPSC during 1997–2008, a chart review found that few of the men with PSA testing had abnormal findings during a physical examination, lending further confidence to our use of PSA testing as a proxy for screening.[39] Among men with PSA testing in our study, we found that the proportion with PSA >4 ng/mL was 1.3% among HIV-negative and 1.2% among HIV-positive men younger than 50 years, 4.1% among HIV-negative and 4.2% among HIV-positive men aged 50–59 years, and 15.3% among HIV-negative and 15.1% among HIV-positive men aged 60 years or older. These percentages were similar to those reported in the general population (1.5% for age 40–49, 5.3% for age 50–59, and 5.7% for age 60–69),[40] suggesting that most of the men with PSA tests in our study were not tested as a result of symptoms. While the cumulative incidence of PSA screening in the general population during 2003–2008 was lower than what we observed in our cohort—with 25% of men aged 40–49 years reporting previous PSA screening, 56% of those aged 50–59 years, and 72% of those aged 60–69 years—screening rates were nearly 3 times higher among men with health insurance compared with those without health insurance.[41] Finally, we expect that any misclassification of PSA tests as screening would have occurred in both HIV-negative and HIV-positive men.

A second limitation is that men with undiagnosed HIV infection may have been misclassified as HIV negative; however, correctly classifying them as HIV positive would likely have yielded an even stronger protective association. Third, there were some missing data on race/ethnicity, but multiple imputation of missing race/ethnicity data did not previously impact findings regarding prostate cancer risk in this cohort.[42] Fourth, among subjects diagnosed with hypogonadism/hypotestosterone, we were not able to differentiate in our analysis between those who were or were not treated.

Furthermore, there may have been differential misclassification of testosterone deficiency if HIV-positive men were more likely to be tested or receive testosterone therapy for reasons other than testosterone deficiency, such as wasting or fatigue. Fifth, prescription fills for ART and testosterone therapy obtained outside KP were not captured; however, pharmacy databases capture over 90% of prescriptions.[43] Sixth, KPSC data on PSA testing and testosterone deficiency were not available; however, age and race/ethnicity distributions were similar between regions, suggesting generalizability to KPSC. Seventh, data were not available on some risk factors, including a family history of prostate or other cancers, or could not be analyzed with a high level of detail, such as smoking. We would not expect family history of prostate cancer to differ by HIV status; however, clinical diagnoses such as smoking may have been differentially diagnosed among cancer cases, thus inducing or strengthening the observed associations. Finally, there was a small number of HIV-positive cancer cases, particularly at higher stages. Nevertheless, the study was adequately powered to detect modest differences in cancer incidence by HIV status.

Our study also has several key strengths. First, we used a large, well-characterized cohort from the same health care system, thus minimizing the selection biases that can be introduced by using an external HIV-negative comparison group and allowing adjustment for patient-level factors. Second, HIV and cancer registries allowed for near-perfect case ascertainment for HIV infection and prostate cancer, whereas clinical, laboratory, pharmacy, and administrative databases allowed for the identification of important covariates for analysis. Third, because information from the disease registries and EMR were collected for clinical purposes, the data were comprehensive with respect to care received at KP facilities, and billing claims databases captured information on non-KP facilities. Fourth, we collected data on PSA testing as a proxy for screening, which has not been previously examined in a cohort of HIV-positive and HIV-negative men. Finally, the KP membership mirrors the age, sex, and race/ethnicity distributions of the California population,[20] and the demographics of HIV-positive KP members are comparable to those of AIDS cases in California.[44] Thus, our results are likely to be generalizable to other individuals with access to health care.

To the best of our knowledge, this is the first large-scale study to investigate prostate cancer incidence and PSA testing among HIV-positive men using an internal HIV-negative comparison group and adjusting for several risk factors. We observed a decreased incidence of prostate cancer in HIV-positive men, especially advanced stage cancers, independent of PSA testing or the risk factors evaluated. This finding is particularly germane given the 2012 US Preventive Services Task Force recommendation against the use of PSA testing for prostate cancer screening.[45] This guideline has not been universally adopted, including by KP,[46] and may be implemented in practice on the basis of perceived risk,[47,48] although our data suggest that decisions regarding PSA testing should not differ by HIV status. In summary, while the cause of the decreased risk of prostate cancer in HIV-positive men remains unclear, we found that it is not attributable to a disparity in PSA testing or the risk factors evaluated; this suggests an as-yet-unidentified biological effect that should be explored in future studies, in particular the role of PIs or other antiretroviral therapies.

REFERENCES

1. Effros RB, Fletcher CV, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis.* 2008;47:542–553.
2. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst.* 2011;103:753–762.
3. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS*. 2006;20:1645–1654.
4. Mbulaiteye SM, Biggar RJ, Goedert JJ, et al. Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immune Defic Syndr.* 2003;32:527–533.
5. Biggar RJ, Kirby KA, Atkinson J, et al. Cancer risk in elderly persons with HIV/AIDS. *J Acquir Immune Defic Syndr.* 2004;36:861–868.
6. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev.* 2011;20:2551–2559.
7. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Ann Intern Med.* 2008;148:728–736.
8. Shiels MS, Goedert JJ, Moore RD, et al. Reduced risk of prostate cancer in U.S. men with AIDS. *Cancer Epidemiol Biomarkers Prev.* 2010;19:2910–2915.
9. Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? *JAMA*. 2003;289:1414–1420.
10. Sofikerim M, Eskicorapci S, Oruc O, et al. Hormonal predictors of prostate cancer. *Urol Int.* 2007;79:13–18.
11. Rochira V, Zirilli L, Orlando G, et al. Premature decline of serum total testosterone in HIV-infected men in the HAART-era. *PLoS One.* 2011;6:e28512.
12. Wunder DM, Bersinger NA, Fux CA, et al. Hypogonadism in HIV-1-infected men is common and does not resolve during antiretroviral therapy. *Antivir Ther.* 2007;12:261–265.
13. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *Diabetes Care.* 2008;31:1224–1229.
14. Ledergerber B, Furrer H, Rickenbach M, et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis.* 2007;45:111–119.
15. Waters KM, Henderson BE, Stram DO, et al. Association of diabetes with prostate cancer risk in the multiethnic cohort. *Am J Epidemiol.* 2009;169:937–945.
16. Kasper JS, Liu Y, Giovannucci E. Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. *Int J Cancer.* 2009;124:1398–1403.
17. Atchison EA, Gridley G, Carreon JD, et al. Risk of cancer in a large cohort of U.S. veterans with diabetes. *Int J Cancer.* 2011;128:635–643.
18. Turner EL, Lane JA, Donovan JL, et al. Association of diabetes mellitus with prostate cancer: nested case-control study (Prostate testing for cancer and treatment study). *Int J Cancer.* 2011;128:440–446.
19. Barbosa-Desongles A, Hernandez C, De Torres I, et al. Diabetes protects from prostate cancer by downregulating androgen receptor: new insights from LNCaP cells and PAC120 mouse model. *PLoS One.* 2013;8:e74179.
20. Gordon NP. *How Does the Adult Kaiser Permanente Membership in Northern California Compare with the Larger Community?* 2006. Available at: http://www.dor.kaiser.org/external/uploadedFiles/content/research/mhs/_2011_Revised_Site/Documents_Special_Reports/comparison_kaiser_vs_nonKaiser_adults_kpnc(1).pdf. Accessed May 21, 2013.
21. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years–United States, 2008. *MMWR Recomm Rep.* 2008;57:1–12.

22. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 2002. Available at: https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC6thEdCancerStagingManualPart2.pdf. Accessed April 4, 2014.
23. Andriole GL, Crawford ED, Grubb RL III, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360:1310–1319.
24. Cross T, McPhail S. *Prostate Cancer: Diagnosis and Treatment (Supplement): An Assessment of Need*. Cardiff, UK: National Collaborating Centre for Cancer (UK); 2008.
25. Karter AJ, Ferrara A, Liu JY, et al. Ethnic disparities in diabetic complications in an insured population. *JAMA*. 2002;287:2519–2527.
26. Haque R, Van Den Eeden SK, Jacobsen SJ, et al. Correlates of prostate-specific antigen testing in a large multiethnic cohort. *Am J Manag Care.* 2009;15:793–799.
27. Young JL, Roffers SD, Ries LAG, et al. Male Genital System: Prostate Gland. *SEER Summary Staging Manual—2000: Codes and Coding Instructions*. In: Institute NC, ed. Bethesda, MD: NIH Pub. No. 01–4969; 2001.
28. Burgi A, Brodine S, Wegner S, et al. Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. *Cancer*. 2005;104:1505–1511.
29. Hessol NA, Pipkin S, Schwarcz S, et al. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol.* 2007;165:1143–1153.
30. Hsiao W, Anastasia K, Hall J, et al. Association between HIV status and positive prostate biopsy in a study of US veterans. *ScientificWorldJournal.* 2009;9:102–108.
31. Serraino D, Boschini A, Carrieri P, et al. Cancer risk among men with, or at risk of, HIV infection in southern Europe. *AIDS*.2000;14:553–559.
32. Bedimo RJ, McGinnis KA, Dunlap M, et al. Incidence of non-AIDS-defining malignancies in HIV-infected versus noninfected patients in the HAART era: impact of immunosuppression. *J Acquir Immune Defic Syndr.* 2009;52:203–208.
33. Grulich AE, Li Y, McDonald A, et al. Rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis. *AIDS*. 2002;16:1155–1161.
34. Frisch M, Biggar RJ, Engels EA, et al. Association of cancer with AIDS-related immunosuppression in adults. *JAMA*. 2001;285:1736–1745.
35. Chao C, Leyden WA, Xu L, et al. Exposure to antiretroviral therapy and risk of cancer in HIV-infected persons. *AIDS*. 2012;26:2223–2231.
36. Ikezoe T, Hisatake Y, Takeuchi T, et al. HIV-1 protease inhibitor, ritonavir: a potent inhibitor of CYP3A4, enhanced the anticancer effects of docetaxel in androgen-independent prostate cancer cells in vitro and in vivo. *Cancer Res.* 2004;64:7426–7431.
37. Pajonk F, Himmelsbach J, Riess K, et al. The human immunodeficiency virus (HIV)-1 protease inhibitor saquinavir inhibits proteasome function and causes apoptosis and radiosensitization in non-HIV-associated human cancer cells. *Cancer Res.* 2002;62:5230–5235.
38. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. *Proc Nutr Soc.* 2008;67:253–256.
39. Wallner L, Frencher S, Hsu JW, et al. Prostate cancer screening trends in a large, integrated health care system. *Perm J.* 2012;16:4–9.
40. Welch HG, Schwartz LM, Woloshin S. Prostate-specific antigen levels in the United States: implications of various definitions for abnormal. *J Natl Cancer Inst.* 2005;97:1132–1137.
41. Allen IM, Hendrix LH, Royce TJ, et al. Prostate-specific antigen (PSA) screening in the United States: patterns of use and PSA outcomes in screened versus unscreened men. Paper presented at: Annual Meeting of the American Society of Clinical Oncology; June 3, 2012; Chicago, IL.
42. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection and the risk of cancers with and without a known infectious cause. *AIDS*. 2009;23:2337–2345.
43. Selby JV, Smith DH, Johnson ES, et al. Kaiser Permanente Medical Care Program. In: Strom BL, ed. *Pharmacoepidemiology*. 4th ed. New York, NY: Wiley; 2005:241–259.
44. California Department of Health Services, Office of AIDS. *HIV/AIDS Surveillance in California*. 2010. Available at: http://www.cdph.ca.gov/programs/aids/Documents/SSSemiAnnualRptDec2011.pdf. Accessed May 21, 2013.
45. Moyer VA. Screening for prostate cancer: U.S. preventive services task force recommendation statement. *Ann Intern Med.* 2012;157:120–134.
46. *Prostate Cancer Screening: National Guideline Summary, Kaiser Permanente*. 2012. Available at: http://www.providers.kaiserpermanente.org/info_assets/cpp_oh/oh_prostatecancerscreeningsummary_may_2013.pdf. Accessed March 28, 2014.
47. Aslani A, Minnillo BJ, Johnson B, et al. The impact of recent screening recommendations on prostate cancer screening in a large health care system. *J Urol.* 2014;191:1737–1742.
48. Cohn JA, Wang CE, Lakeman JC, et al. Primary care physician PSA screening practices before and after the final U.S. Preventive Services Task Force recommendation. *Urol Oncol.* 2014;32:41.e23–41.e30.