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HUMAN PAPILLOMAVIRUS TYPES 16, 18 AND 31 SEROSTATUS AND PROSTATE CANCER RISK IN THE PROSTATE CANCER PREVENTION TRIAL

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Short title: HPV infection and prostate cancer

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ABSTRACT

Since human papillomavirus (HPV) infection was first identified as a risk factor for cervical cancer, several seroepidemiologic and tissue-based studies have investigated HPV in relation to prostate cancer, another common genitourinary malignancy, with mixed results. To further inform this potential association, we conducted a large, prospective investigation of HPV types 16, 18, and 31 in relation to risk of prostate cancer in the Prostate Cancer Prevention Trial (PCPT). Cases were a sample of men diagnosed with prostate cancer after visit 2 or on their end-of-study biopsy (n=616). Controls were men not diagnosed with prostate cancer during the trial or on their end-of-study biopsy (n=616). Controls were frequency-matched to cases by age, treatment arm, and family history of prostate cancer. Sera from visit 2 were tested for IgG antibodies against HPV-16, -18 and -31. No associations were observed for weak or strong HPV-16 (odds ratio (OR) = 0.94, 95% confidence interval (CI): 0.53-1.64, and OR=1.07, 95% CI: 077-1.48, respectively), HPV-18 (OR=0.75, 95% CI: 0.27-2.04, and OR=0.87, 95% CI: 0.47-1.63) or HPV-31 seropositivity (OR=0.76, 95% CI: 0.45-1.28, and OR=1.15, 95% CI: 0.80-1.64) and risk of prostate cancer. Considering this finding in the context of the HPV and prostate cancer literature, HPV does not appear to be associated with risk of prostate cancer, at least by mechanisms proposed to date, and using epidemiologic designs and laboratory techniques currently available.

INTRODUCTION

Since human papillomavirus (HPV) infection was first identified as a risk factor for cervical cancer, several studies have investigated HPV in relation to prostate cancer with mixed results (1-7). When Taylor and colleagues (2) combined the results of ten of these studies, they observed a significant positive association between HPV and prostate cancer; however, subsequent investigations have observed null associations (3-6), or have detected minimal/no evidence of HPV in prostate tissue (7-12). To further inform HPV and prostate cancer, we conducted a prospective investigation of HPV types 16, 18, and 31 and prostate cancer in the Prostate Cancer Prevention Trial (PCPT, (13)). The unique design of this trial allowed us to investigate both HPV and screen-detected cancer among annually-screened men, as well as HPV and end-of-study biopsy-detected cancer to rule out differential likelihood of screening or biopsy as non-causal explanations for study findings.

MATERIAL AND METHODS

Study design

We conducted a nested case-control study among PCPT participants with adequate serum at visit 2 (14). Cases were men with a confirmed diagnosis of prostate cancer after visit 2 (n=616). Approximately equal numbers of cases diagnosed by "for-cause" and "end-of-study" biopsy were selected, as well as equal numbers with low- (Gleason sum <7) and high-grade ($\geq$7) disease. The mean time from blood draw to diagnosis was 3.4 years for "for-cause" cases and 5.0 for "end-of-study" cases. Controls were men not diagnosed with prostate cancer during the trial or on end-of-study biopsy (n=616). Controls were frequency-matched to cases by age, treatment arm, and family history of prostate cancer, and enriched for non-whites.

This study was approved by the Johns Hopkins Bloomberg School of Public Health and Fred Hutchinson Cancer Research Center Institutional Review Boards.

HPV antibody assessment

Sera were tested for IgG antibodies against HPV-16, -18 and -31 virus-like particles (VLPs) using enzyme-linked immunosorbent assays (ELISAs) specific for each HPV type (15). Samples were tested in random order, and laboratory personnel were blinded to case-control status. Each sample was tested in duplicate with repeat duplicate testing for duplicates with optical density (OD) coefficients of variation >25% and at least one value above the OD cut-off point for seropositivity. Mean OD values were calculated based on duplicate test values, or based on the mean of the three values in closest agreement for men with repeat duplicate testing. OD cut-off points of 0.080 (3 standard deviations (SDs) above the mean for control children), 0.100 (3 SDs), and 0.065 (5 SDs) were initially used to define seropositivity for HPV-16, -18, and -31, respectively.

Assay reproducibility was investigated by including 12 sets of ~6 blinded replicate samples each in the testing sequence (14). Eleven sets had 100% and one had 66.7% agreement for HPV-16; ten had 100% and two had 66.7% agreement for HPV-18; and ten had 100% and two had 83.3% agreement for HPV-31. Based on these data, we defined additional strong seropositive cut-off points to better distinguish likely seronegatives from seropositives (0.092 (>4 SD), 0.117 (>4 SD) and 0.077 (>7 SD) for HPV-16, -18 and -31, respectively).

Statistical analysis

Age-, treatment arm-, family history-, and race-standardized OD means, geometric means, and proportions were calculated by prostate cancer status. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression adjusting for age, treatment arm,

family history, and race. Confounding was investigated by adding terms for ELISA plates, other HPV types, and other variables (14) individually to the model and comparing the results to the base model. Separate analyses were performed for prostate cancer diagnosed by for-cause and end-of-study biopsy, low- and high-grade cancer, organ-confined disease, and combinations thereof. Stratified analyses were performed to evaluate effect modification.

A priori, we had ≥80% power to detect an OR≥1.6 for a control seroprevalence of 10%.

RESULTS

No differences were observed in the distribution of anti-HPV-16, -18 and -31 antibodies between cases and controls, or when the data for all three HPV types were combined (Tables 1 and 2). Generally null results were also observed after adjustment for potential confounders, and for prostate cancer diagnosed by for-cause biopsy, Gleason sum <7 cancer, and organ-confined cancer. Very slight, non-significant positive findings were observed for HPV-16 and -31 with cancer diagnosed by end-of-study biopsy, and with Gleason sum ≥7 cancer (Table 2). No effect modification was observed by treatment arm, age at cancer diagnosis, family history of prostate cancer, or race.

DISCUSSION

In this large study of older American men, no associations were observed between HPV-16, -18 and -31 and overall prostate cancer risk. Very slight, non-significant positive findings were observed for HPV-16 and -31 with prostate cancer diagnosed by end-of-study biopsy and Gleason sum ≥7 cancer, the reasons for which are unclear and could reflect chance findings. Our generally null results are consistent with those from most serologic studies conducted to date (3-6, 16-20).

As in most previous serologic studies, we assessed HPV serostatus using VLP ELISAs and serum collected before but near cancer diagnosis, raising the possibility that antibody titers could have diminished since earlier "hit and run" infection(s), or during invasive cancer development. The former possibility was suggested by Strickler and Goedert (1) based on discrepancies between observed positive associations in studies that collected serum decades before diagnosis (21, 22), and null associations in studies that collected serum at diagnosis (16, 17); while the latter was suggested by Rosenblatt and colleagues (20) based on stronger observed serologic associations for *in situ* than invasive HPV-associated cancers, which are likely closer in time to productive (capsid-expressing) HPV infections than invasive cancers. Since these studies were conducted, however, null results were observed in another study with early serum collection (3), and minimal/no evidence of HPV DNA was observed in most recent tissue-based studies (7-12), suggesting that waning capsid antibody titers are unlikely to explain null serologic results.

Thus, viewing the HPV and prostate cancer literature as a whole, HPV does not appear to be associated with prostate cancer risk, at least by mechanisms proposed to date, and using epidemiologic designs and laboratory techniques currently available.

ACKNOWLEDGMENTS

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Table 1: Human papillomavirus (HPV) types 16, 18 and 31 antibody distributions[1] for 616 prostate cancer cases and 616 frequency-matched controls in the Prostate Cancer Prevention Trial

	Cases[2]	Controls	P-value[3]
HPV-16			
Mean OD	0.06	0.06	0.60
Geometric mean OD	0.05	0.05	0.56
Serostatus (%):			
Seronegative (OD≤0.080)	81.3	81.8	
Weak seropositive (0.080<OD≤0.092)	4.1	4.5	0.90
Strong seropositive (OD>0.092)	14.5	13.7	
HPV-18			
Mean OD	0.04	0.04	0.81
Geometric mean OD	0.03	0.03	0.87
Serostatus (%):			
Seronegative (OD≤0.100)	95.6	94.8	
Weak seropositive (0.100<OD≤0.117)	1.1	1.5	0.78
Strong seropositive (OD>0.117)	3.3	3.7	
HPV-31			
Mean OD	0.05	0.05	0.48
Geometric mean OD	0.04	0.04	0.48
Serostatus (%):			
Seronegative (OD≤0.065)	83.5	83.6	
Weak seropositive (0.065<OD≤0.077)	4.3	5.6	0.41
Strong seropositive (OD>0.077)	12.3	10.8	
HPV-16, -18 and/or -31			
All seronegative (%)	70.7	70.7	
At least one weak seropositive but no strong seropositives (%)	5.9	7.7	
One strong seropositive (%)	17.7	15.9	0.75[4]
Two strong seropositives (%)	4.6	4.8	
Three strong seropositives (%)	1.0	0.9	
At least one strong seropositive (%)	23.4	21.6	0.72[5]

OD=optical density

[1] Standardized by age, treatment arm, family history of prostate cancer and race (non-white versus white) using linear regression.

[2] Cases were a sample of men diagnosed with prostate cancer on any biopsy after visit 2 or on their end-of-study biopsy (1996-2003).

[3] P-values were calculated by linear regression for continuous variables, and by generalized logit models for categorical variables.

[4] P-value for the comparison of all seronegatives, at least one weak seropositive but no strong seropositives, one strong seropositive, two strong seropositives, and three strong seropositives.

[5] P-value for the comparison of all seronegatives, at least one weak seropositive but no strong seropositives, and at least one strong seropositive.

Table 2: Odds ratios (ORs) and 95% confidence intervals (CIs) of prostate cancer by human papillomavirus (HPV) type 16, 18 and 31 serostatus in 616 prostate cancer cases[1] and 616 frequency-matched controls in the Prostate Cancer Prevention Trial

	HPV-16		HPV-18		HPV-31	
	Cases/controls	OR[2] (95% CI)	Cases/controls	OR[2] (95% CI)	Cases/controls	OR[2] (95% CI)
Total prostate cancer:						
Seronegative[3]	503/502	1.00	590/583	1.00	516/513	1.00
Weak seropositive[4]	25/28	0.94 (0.53-1.64)	7/9	0.75 (0.27, 2.04)	27/34	0.76 (0.45, 1.28)
Strong seropositive[5]	88/86	1.07 (0.77-1.48)	19/24	0.87 (0.47, 1.63)	73/69	1.15 (0.80, 1.64)
Prostate cancer diagnosed by for-cause biopsy[3]:						
Seronegative[3]	272/502	1.00	313/583	1.00	274/513	1.00
Weak seropositive[4]	13/28	0.89 (0.45, 1.76)	6/9	1.21 (0.42, 3.45)	16/34	0.82 (0.44, 1.52)
Strong seropositive[5]	42/86	0.92 (0.62, 1.37)	8/24	0.69 (0.31, 1.58)	37/69	1.05 (0.68, 1.62)
Prostate cancer diagnosed by end-of-study biopsy[4]:						
Seronegative[3]	231/502	1.00	277/583	1.00	242/513	1.00
Weak seropositive[4]	12/28	1.01 (0.50, 2.06)	1/9	0.22 (0.03, 1.72)	11/34	0.65 (0.32, 1.31)
Strong seropositive[5]	46/86	1.25 (0.84, 1.86)	11/24	1.08 (0.51, 2.28)	36/69	1.27 (0.82, 1.99)
Gleason sum <7 prostate cancer:						
Seronegative[3]	261/502	1.00	299/583	1.00	269/513	1.00
Weak seropositive[4]	16/28	1.24 (0.65, 2.38)	5/9	1.11 (0.36, 3.42)	14/34	0.72 (0.38, 1.38)
Strong seropositive[5]	36/86	0.82 (0.54, 1.26)	9/24	0.83 (0.37, 1.86)	30/69	0.94 (0.59, 1.50)
Gleason sum ≥7 prostate cancer:						
Seronegative[3]	242/502	1.00	291/583	1.00	247/513	1.00
Weak seropositive[4]	9/28	0.69 (0.32, 1.49)	2/9	0.41 (0.09, 1.91)	13/34	0.77 (0.40, 1.49)
Strong seropositive[5]	52/86	1.31 (0.89, 1.91)	10/24	0.90 (0.42, 1.92)	43/69	1.33 (0.88, 2.03)
Organ-confined (≤T2N0M0) prostate cancer:						
Seronegative[3]	459/502	1.00	540/583	1.00	473/513	1.00
Weak seropositive[4]	24/28	0.98 (0.56, 1.74)	7/9	0.83 (0.30, 2.25)	26/34	0.79 (0.47, 1.35)
Strong seropositive[5]	83/86	1.10 (0.79, 1.53)	19/24	0.95 (0.51, 1.77)	67/69	1.16 (0.80, 1.67)

[1] Cases were a sample of men diagnosed with prostate cancer on any biopsy after visit 2 or on their end-of-study biopsy (1996-2003).

[2] Calculated by unconditional logistic regression, including terms for age (continuous), treatment arm, family history of prostate cancer and non-white race.

[3] HPV-16: OD≤0.080; HPV-18: OD≤0.100; HPV-31: OD≤0.065.

[4] HPV-16: 0.080<OD≤0.092; HPV-18: 0.100<OD≤0.117; HPV-31: 0.065<OD≤0.077.

[5] HPV-16: OD>0.092; HPV-18: OD>0.117; HPV-31: OD>0.077.

[6] Refers to a biopsy performed because of an elevated prostate specific antigen concentration or an abnormal digital rectal examination.

[7] Refers to a biopsy performed without indication after seven years of participation in the study as part of the study protocol.