Prostate Cancer Risk and Serologic Evidence of Human Papilloma Virus Infection: A Population-based Case-Control Study[1]

Hans-Olov Adami, Hannah Kuper,[2] Swen-Olof Andersson, Reinhold Bergström,[3] and Joakim Dillner

Department of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden [H-O. A.]; Clinical Research Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom [H. K.]; Department of Urology, Örebro University Hospital, Örebro, Sweden [S-O. A.]; Department of Statistics, University of Uppsala, Uppsala, Sweden [R. B.]; and Deparment of Medical Microbiology, University Hospital, Malmö, Sweden [J. D.]

Abstract

Epidemiological evidence is accumulating that sexual history may be associated with prostate cancer, and some studies have suggested a relation between human papilloma virus (HPV) infections and prostate cancer. We measured the presence of antibodies to the major oncogenic HPV types 16, 18, and 33 among 238 subjects with untreated prostate cancer and 210 population-based control subjects. Odds ratios (ORs) were estimated from multivariate logistic regression models, controlling for age and HPV types 16, 18, and 33, simultaneously. HPV types 16 and 18 were not associated with prostate cancer [OR, 0.7; 95% confidence interval (CI), 0.4–1.3 for HPV 16; OR, 0.9; 95% CI, 0.5–1.9 for HPV 18]. There was a possible association between HPV 33 and prostate cancer (OR, 1.6; 95% CI, 1.0–2.7), and there was a significant excess risk for subjects with high antibody levels against HPV 33 (OR when the difference in absorbance exceeded 0.2, 2.3; 95% CI, 1.2–4.1). When HPV antibody levels were modeled as continuous variables, the results were qualitatively similar. The data do not support previous studies that have suggested an association with HPV 16 or 18 and prostate cancer risk. Inconsistent associations with different HPV types seen in different studies suggest that the association may be because of chance, bias, or confounding by some unknown risk factor that may associate with different HPV infections in different populations. Additional studies of the relationship between prostate cancer and other HPV types, notably HPV 33, could be helpful for clarifying the possible role of sexual risk factors.

Introduction

There has been substantial progress in epidemiological research on prostate cancer over the last decade (1). An area of increasing interest is the possible role of number of sexual partners and history of sexually transmitted infections as a risk factor for prostate cancer (2–7). However, accurate information on sexual behavior is difficult to obtain, and the association between sexual history and exposure to specific infectious agents may be weak and will vary across populations. Studies of prostate cancer risk in relation to features of sexual life have obtained some evidence for an effect of indicators of high sexual activity, such as early intercourse, and many sexual partners (2, 4–7). We have previously reported tentative evidence from the current study population that marital status, early first intercourse, and a larger number of sexual partners are associated with increased prostate cancer risk (3). Specific sexually transmitted infections have been associated inconsistently with prostate cancer, with positive associations being reported with syphilis, gonorrhea and HPV[4] infection in various studies (2, 4, 7–9).

There has been particular attention given to HPV infections as possible prostate cancer risk factors, as these are definite causes of several other forms of cancer, particularly cervical cancer (10). HPV, especially HPV type 18, have tropism for the grandular epithelium and can immortalize prostate epithelial cells (11). Several studies have reported that HPV DNA was detectable in prostate cancer cells (12–17), although other studies have not reproduced this finding (12, 18–20). These inconsistencies in results may be because of technical difficulties in HPV DNA detection. There are several possible reasons for false-positive or false-negative results, most notably PCR contamination, degradation, or cross-linking of DNA and tumor samples not being representative. In addition, control samples from the target tissue cannot be readily obtained from nondiseased persons.

Therefore, serological studies offer an attractive alternative, as they provide an integrated, readily standardized measure of long-term HPV exposure on a biological sample that can be easily obtained from both cases and healthy controls. Indeed, serological studies have contributed substantially to establishing the causal relationship between HPVs and several cancers, such as cervical, vulvar, and oropharyngeal cancers in women and men (21–23). They have also generated hypotheses in relation to other tumor sites (24). With regard to prostate cancer, a prospective study with >20 years of follow-up reported a highly significant increased risk associated with HPV type 18 seropositivity, although the proportion of exposed cases was small (8). Tentative evidence suggesting an association with HPV type 16 was reported in one serological case-control study (4) but not in others (8, 19).

Received 1/17/03; revised 5/2/03; accepted 5/14/03.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] Supported by grants from the Swedish Cancer Society.
[2] To whom requests for reprints should be addressed, at Clinical Research Unit, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom. Phone: 44-20-7958-8335; Fax: 44-20-7958-8338; E-mail: hannah.kuper@lshtm.ac.uk.
[3] Deceased.

[4] The abbreviations used are: HPV, human papilloma virus; OR, odds ratio; CI, confidence interval.

We report here results from a population-based case-control study of prostate cancer, in which serological evidence of infection to three major oncogenic HPV types (16, 18, 33) has been evaluated. Serum samples from the same study have been used previously in analyses of steroid hormones (25) and insulin-like growth factor I (26).

Materials and Methods

Cases and Controls. The patients and controls were participating in a population-based case-control interview study described in detail elsewhere (25, 26). All of the men under the age of 80 years, born in Sweden and living in the Örebro County, Sweden, at any time from January 1989 through September 1991, formed the study base. Patients in this population with newly diagnosed prostate cancers, cytologically or histologically confirmed, were eligible to participate in the study. Clinical records from the three participating hospitals and the Department of Pathology at Örebro University Hospital allowed complete case ascertainment, confirmed through cross-checking the clinical records of case subjects with the regional cancer registry. All of the tumors were staged clinically in accordance with the tumor-node-metastasis classification system (27); among them, 26.6% were surgically staged.

Control subjects were identified contemporaneously with case subjects. Selected every third month from the county population register, control subjects were frequency-matched to case subjects in 10-year age groups. All of the potential control subjects underwent a digital rectal examination by one of us (S-O. A.) and a prostate-specific antigen test. Men with a palpable nodule and/or elevated prostate-specific antigen serum levels (>10 ng/ml) underwent additional diagnostic testing through ultrasound-guided biopsy (four to six random samples), and were eligible as controls only if their biopsy specimens showed no evidence of cancer.

In the initial study, participation in the face-to-face interview and collection of blood samples (see below) was obtained from 240 case-subjects (86% of those eligible to participate in the study) and 235 control-subjects (82% of those eligible). Blood samples were drawn at any given day between 8:00 a.m., and 10:00 a.m. from case and control subjects, before digital rectal examination was performed or any treatment to the case subjects was given. Most of the blood samples from case subjects were collected within 4–6 weeks after diagnosis (none collected later than 3 months), but this should not affect validity because the likelihood of seroconversion after diagnosis is low. Potential control subjects who did not provide blood were generally similar (age and body mass index) to those control subjects who did. Blood samples were centrifuged at $1200 \times g$ for 10 min at room temperature and stored as serum at −70°C. For the purposes of this study, serum was still available for 238 case-subjects and 210 control-subjects. The mean ages were 69.8 and 69.9 years, respectively.

Laboratory Methods. Serum samples, packed in dry ice, were shipped from the Örebro University Hospital to the Karolinska Institutet. They were analyzed by experienced laboratory personnel under the supervision of J. D. No one in the analyzing laboratory was aware of the case-control status of the samples.

Seropositivity for HPV was determined by the standard ELISA assay, using baculovirus-expressed capsids (28), with disrupted capsids of bovine papillomavirus as negative control (29, 30). The HPV 16 capsids were obtained from Dr. John T. Schiller, National Cancer Institute (Bethesda, MD), whereas the HPV 18 and 33 capsids were obtained from Dr. Martin Sapp, University of Mainz (Mainz, Germany). To ensure that the cutoff levels used to assign positivity from continuous values were representative, the evaluation was based on cutoff levels already established from previous work. For HPV16, previous work had determined that a cutoff level of 100 absorbance units was able to distinguish HPV16-infected and virgin women (31). However, patients with cervical cancer and normal subjects were more clearly distinguished using a higher cutoff level (which, relative to internal standards, corresponds to 0.292 in the present study; Ref. 29), presumably because rapidly cleared (transient) infections induced lower levels of antibodies than do persistent infections (32). The specificity of the serology for the sexually transmitted HPV types was high, because no antibodies could be found in panels of serum samples from virginal women analyzed in parallel with sera of the present study (31).

Table 1 Distribution of serologic measurements (absorbance units) of HPV infection among 238 cases and 210 controls

HPV type	Mean (SD)		Wilcoxon test
	Cases	Controls	*P*
HPV 16	54.7 (104.8)	61.6 (133.9)	0.95
HPV 18	52.0 (97.3)	60.6 (102.6)	0.14
HPV 33	121.6 (213.6)	84.6 (169.3)	0.13

Statistical Methods. In the first analytic step, cases and controls were compared using univariate methods. As the HPV antibody levels were heavily skewed, we used both *t* tests (with and without assumption of equal variances) and nonparametric two-sample Wilcoxon tests. Because many samples had no detectable antibody (zero absorbance), we decided not to present analyses based on logarithmically transformed variables. In the multivariate modeling, the logistic regression model was used. Estimates were obtained by the maximum likelihood method and these were then converted to ORs as estimates of relative risk with 95% CI. In the testing Wald, likelihood ratio and score tests were used. The variables were used both in their continuous and categorized form. Because the controls were matched for age, adjustment for age was made in the logistic regression estimation.

Results

The mean value for serological measurement of HPV 16 and 18 was lower for cases than for controls, whereas cases had higher mean values for HPV 33. The distributions for all three of the HPV types were strongly skewed. In simple unadjusted comparisons between groups, the difference between cases and controls with regard to HPV 16, and HPV 18 was not statistically significant. For HPV 33, the difference was also not statistically significant, although the absorbance units were ~50% higher in cases than in controls (Table 1).

The proportion of subjects who were seropositive for HPV 16 and HPV 18 (absorbances exceeding the cutoff value of 0.1) was small, in the range of 11–15%, without any appreciable differences between cases and controls. For HPV 33, the seropositive proportion was 29% among cases and 23% among controls (Table 2). Because the age distribution among cases and controls was similar (mean values 69.9 and 69.8 years), age-adjusted logistic regression analyses produced essentially the same results as univariate analyses. With the antibody measurements in their original untransformed form, we found no association between HPV 16 or HPV 18 and risk of prostate cancer in the age-adjusted analyses. However, for HPV 33 there was some evidence of a positive association, which was addi-

Table 2 ORs with 95% CIs for the association between serum titers of HPV type 16, 18, and 33, and prostate cancer

Serum titers analyzed as categorical and continuous variables with and without mutual adjustment[a].

HPV type	Serum titer	Cases/controls	Age-adjusted		Mutually adjusted[a]	
			OR	95% CI	OR	95% CI
HPV 16	≤100	207/178	1.0	Referent	1.0	Referent
	>100	31/32	0.8	(0.5–1.4)	0.7	(0.4–1.3)
	Continuous per 200 units		0.91	(0.66–1.24)	0.90	(0.60–1.34)
HPV 18	≤100	210/185	1.0	Referent	1.0	Referent
	>100	28/25	1.0	(0.6–1.8)	0.9	(0.5–1.9)
	Continuous per 200 units		0.84	(0.58–1.23)	0.52	(0.29–0.93)
HPV 33	≤100	168/162	1.0	Referent	1.0	Referent
	>100	70/48	1.4	(0.9–2.2)	1.6	(1.0–2.7)
	Continuous per 200 units		1.54	(1.00–2.36)	2.69	(1.39–5.21)

[a] Adjusted simultaneously for HPV 16, HPV 18, HPV 33, and age.

tionally strengthened after mutual adjustment between the three different HPV types (Table 2).

Additional exploratory analyses of HPV 33 indicated an excess risk confined to high values. Indeed, in the antibody measurement interval of absorbances 0.101–0.2 we found an OR, 0.9 (95% CI, 0.5–1.6) for age-adjusted analyses and OR, 1.0 (95% CI, 0.6–1.9) after mutual adjustment. Substantially higher relative risks were obtained for serum titers exceeding 0.2, namely OR, 2.3 (95% CI, 1.2–4.1) in age-adjusted analyses and OR, 3.2 (95% CI, 1.6–6.4) after mutual adjustment.

When HPV antibody levels were analyzed as continuous variables, there was no convincing positive association between HPV 16 or HPV 18 and risk of prostate cancer; indeed, after mutual adjustment, there was some evidence of a negative association in relation to HPV 18. In contrast, significant positive associations were found for HPV 33 both in age-adjusted and, even more convincingly, in mutually adjusted analyses.

Discussion

The results of this population-based case-control study show an association between serological evidence for HPV 33 infection and risk for prostate cancer. The risk was significantly elevated for subjects with high antibody levels against HPV 33. In contrast, no association between the presence of antibodies for HPV 16 or HPV 18 and risk of prostate cancer was apparent.

Most of the earlier studies on the effect of HPV infection on prostate cancer risk have been case series using PCR methods to detect the presence of HPV DNA. Because of the difficulty in obtaining suitable control samples in most of these studies the prevalence of HPV DNA in prostate cancer specimens was compared with that in benign prostatic hyperplasia (BPH) specimens. The results have been inconsistent, with some reports showing no relationship between HPV 16, 18, or 33 with prostate cancer (15, 18, 33, 34) and others reporting a potential effect of HPV 16 (17, 35), HPV 18, or HPV 33 (35). Several studies also failed to detect HPV DNA sequences in any of the specimens, whether cases or controls (19, 20, 36).

Discrepancies between these studies may be attributable to the use of different techniques for HPV DNA detection, including the use of different primer sets (16). The use of paraffin-embedded archival samples, compared with fresh frozen samples, may also cause inconsistency and nonreproducibility in results (37). In addition, disagreement between studies may be the result of sampling errors. A lack of association between the presence of HPV DNA and prostate cancer does not definitely exclude a role for HPV infection in prostate cancer, because the presence of HPV DNA does not reflect past exposure (only present exposure), and for carcinogenesis past exposure is likely to be more important.

The detection of HPV immune response in the serum, as was used in the present study, indicates both past and present infection and overcomes many of the limitations of the studies using HPV DNA detection. Our data reported here are consistent with a case-control study comparing prostate cancer cases to BPH controls, which found no evidence for an association between HPV 16 (or HPV 11), whether measured through antibody responses or HPV DNA from prostate specimens, and risk of prostate cancer (19). Our results are also consistent with a survey of HPV 16 antibodies in patients with epithelial cancer, which found a low prevalence of HPV 16 seropositive prostate cancer cases, both in comparison with other cancer types and to the noncancer study group (38). However, our data are not consistent with two nested case-control studies, which found a weak positive association between prostate cancer and presence of antibodies to HPV 16 (4, 8), a significant positive association with HPV 18 antibodies (8) and a nonsignificant inverse association between HPV 33 antibodies and prostate cancer (8).

An important strength of this study is that this is the largest study that has been conducted, up until now, investigating the association between HPV infection and prostate cancer. We measured HPV infection using serological, rather than PCR data, and we investigated the independent effects of HPV 16, 18, and 33 on prostate cancer risk. We used a population-based case-control study design, limiting many of the problems associated with hospital-based case-control studies, and we used healthy male controls, rather than controls with BPH.

There are also limitations to our study. It would have been preferable to use a nested case-control design, rather than a case-control design, because we cannot exclude the possibility that our results are produced by virus reactivation by the cancer, or an increased susceptibility for infection caused by prostate cancer. However, this is unlikely to have explained our results, because the association with prostate cancer was specific for HPV 33, whereas no effect was found for either HPV 16 or 18. Because not all of the eligible cases and controls participated in our study, there is room for selection bias. However, the proportion of refusals was low, and earlier reports from this study are in line with current knowledge about prostate cancer (25, 26). We cannot exclude the possibility that the association between HPV 33 and prostate cancer risk was produced by chance, and the association appeared to be driven by a few high values. This highlights the need to replicate these findings in other settings.

Inconsistent associations of prostate cancer with seropositivity for different HPV types in different studies could be the result of chance or publication bias, but also because of confounding by some unknown risk factor that may associate with different HPV infections in different populations. Specifically, the spread of the HPV infection is dependent on the contact rates and mixing patterns in the population. These factors vary between different populations and may also vary over calendar time in the same population. Additional studies of the relationship between prostate cancer and other HPV types, notably HPV 33, and their relationship with sexual behavior, could help clarify the possible role of sexual risk factors. Despite the inconsistent epidemiological data, a direct role for HPV 33 in prostate carcinogenesis is biologically plausible because it can be isolated from prostate tissue (12), and HPV33 is a known oncogenic infection, causally involved in the development of cervical cancer (10).

References

1. Signorello, L. B., and Adami, H-O. Prostate cancer. *In*: H-O. Adami, D. Hunter, and D. Trichopoulos (eds.). Textbook of Cancer Epidemiology, pp. 400–428. New York: Oxford University Press, 2002.

2. Key, T. Risk factors for prostate cancer. Cancer Surv., *23:* 63–77, 1995.

3. Andersson, S. O., Baron, J., Bergström, R., Lindgren, C., Wolk, A., and Adami, H. O. Lifestyle factors and prostate cancer risk: a case-control study in Sweden. Cancer Epidemiol. Biomark. Prev., *5:* 509–513, 1996.

4. Hisada, M., Rabkin, C. S., Strickler, H. D., Wright, W. E., Christianson, R. E., and van den Berg, B. J. Human papillomavirus antibody and risk of prostate cancer. JAMA, *283:* 340–341, 2000.

5. Rosenblatt, K. A., Wicklund, K. G., and Stanford, J. L. Sexual factors and the risk of prostate cancer. Am. J. Epidemiol., *153:* 1152–1158, 2001.

6. Strickler, H. D., and Goedert, J. J. Sexual behavior and evidence for an infectious cause of prostate cancer. Epidemiol. Rev., *23:* 144–151, 2001.

7. Dennis, L. K., and Dawson, D. V. Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology, *13:* 72–79, 2002.

8. Dillner, J., Knekt, P., Boman, J., Lehtinen, M., A. F., Geijersstam, V., Sapp, M., Schiller, J., Maatela, J., and Aromaa, A. Sero-epidemiological association between human-papillomavirus infection and risk of prostate cancer. Int. J. Cancer, *75:* 564–567, 1998.

9. Hayes, R. B., Pottern, L. M., Strickler, H., Rabkin, C., Pope, V., Swanson, G. M., Greenberg, R. S., Schoenberg, J. B., Liff, J., Schwartz, A. G., Hoover, R. N., and Fraumeni, J. F., Jr. Sexual behaviour, STDs and risks for prostate cancer. Br. J. Cancer, *82:* 718–725, 2000.

10. IARC. Human papillomaviruses. Monographs on the Evaluation of Carcinogenic Risks to Humans no. 64. Lyon, France: IARC Scientific Publishers, 1995.

11. Weijerman, P. C., van Drunen, E., Konig, J. J., Teubel, W., Romijn, J. C., Schroder, F. H., and Hagemeijer, A. Specific cytogenetic aberrations in two novel human prostatic cell lines immortalized by human papillomavirus type 18 DNA. Cancer Genet. Cytogenet., *99:* 108–115, 1997.

12. Cuzick, J. Human papillomavirus infection of the prostate. Cancer Surv., *23:* 91–95, 1995.

13. Moyret-Lalle, C., Marcais, C., Jacquemier, J., Moles, J. P., Daver, A., Soret, J. Y., Jeanteur, P., Ozturk, M., and Theillet, C. ras, p53 and HPV status in benign and malignant prostate tumors. Int. J. Cancer, *64:* 124–129, 1995.

14. Suzuki, H., Komiya, A., Aida, S., Ito, H., Yatani, R., and Shimazaki, J. Detection of human papillomavirus DNA and p53 gene mutations in human prostate cancer. Prostate, *28:* 318–324, 1996.

15. Wideroff, L., Schottenfeld, D., Carey, T. E., Beals, T., Fu, G., Sakr, W., Sarkar, F., Schork, A., Grossman, H. B., and Shaw, M. W. Human papillomavirus DNA in malignant and hyperplastic prostate tissue of black and white males. Prostate, *28:* 117–123, 1996.

16. Terris, M. K., and Peehl, D. M. Human papillomavirus detection by polymerase chain reaction in benign and malignant prostate tissue is dependent on the primer set utilized. Urology, *50:* 150–156, 1997.

17. Serth, J., Panitz, F., Paeslack, U., Kuczyk, M. A., and Jonas, U. Increased levels of human papillomavirus type 16 DNA in a subset of prostate cancers. Cancer Res., *59:* 823–825, 1999.

18. Noda, T., Sasagawa, T., Dong, Y., Fuse, H., Namiki, M., and Inoue, M. Detection of human papillomavirus (HPV) DNA in archival specimens of benign prostatic hyperplasia and prostatic cancer using a highly sensitive nested PCR method. Urol. Res., *26:* 165–169, 1998.

19. Strickler, H. D., Burk, R., Shah, K., Viscidi, R., Jackson, A., Pizza, G., Bertoni, F., Schiller, J. T., Manns, A., Metcalf, R., Qu, W., and Goedert, J. J. A multifaceted study of human papillomavirus and prostate carcinoma. Cancer (Phila.), *82:* 1118–1125, 1998.

20. Saad, F., Gu, K., Jean-Baptiste, J., Gauthier, J., and MesMasson, A. M. Absence of human papillomavirus sequences in early stage prostate cancer. Can. J. Urol., *6:* 834–838, 1999.

21. Lehtinen, M., Dillner, J., Knekt, P., Luostarinen, T., Aromaa, A., Kirnbauer, R., Koskela, P., Paavonen, J., Peto, R., Schiller, J. T., and Hakama, M. Serologically diagnosed infection with human papillomavirus type 16 and risk for subsequent development of cervical carcinoma: nested case-control study. BMJ, *312:* 537–539, 1996.

22. Hildesheim, A., Han, C. L., Brinton, L. A., Kurman, R. J., and Schiller, J. T. Human papillomavirus type 16 and risk of preinvasive and invasive vulvar cancer: results from a seroepidemiological case-control study. Obstet. Gynecol., *90:* 748–754, 1997.

23. Mork, J., Lie, A. K., Glattre, E., Hallmans, G., Jellum, E., Koskela, P., Moller, B., Pukkala, E., Schiller, J. T., Youngman, L., Lehtinen, M., and Dillner, J. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N. Engl. J. Med., *344:* 1125–1131, 2001.

24. Bjorge, T., Hakulinen, T., Engeland, A., Jellum, E., Koskela, P., Lehtinen, M., Luostarinen, T., Paavonen, J., Sapp, M., Schiller, J., Thoresen, S., Wang, Z., Youngman, L., and Dillner, J. A prospective, seroepidemiological study of the role of human papillomavirus in esophageal cancer in Norway. Cancer Res., *57:* 3989–3992, 1997.

25. Andersson, S. O., Adami, H. O., Bergstrom, R., and Wide, L. Serum pituitary and sex steroid hormone levels in the etiology of prostatic cancer-a population-based case-control study. Br. J. Cancer, *68:* 97–102, 1993.

26. Wolk, A., Mantzoros, C. S., Andersson, S. O., Bergström, R., Signorello, L. B., Lagiou, P., Adami, H. O., and Trichopoulos, D. Insulin-like factor 1 and prostate cancer risk: a population-based, case-control study. J. Natl. Cancer Inst., *90:* 911–915, 1998.

27. Gleason D. F. Histologic grading and clinical staging of prostatic carcinoma. *In*: M. Tannenbaum (ed). Urologic pathology: the prostate. pp. 171–97. Philadelphia, PA: Lea and Febiger, 1988.

28. Kirnbauer, R., Hubbert, N. L., Wheeler, C. M., Becker, T. M., Lowy, D. R., and Schiller, J. T. A virus-like particle ELISA detects serum antibodies in a majority of women infected with human papillomavirus type 16. J. Natl. Cancer Inst., *86:* 494–499, 1994.

29. Dillner, J., Wiklund, F., Lenner, P., Eklund, C., Fredriksson-Shanazarian, V., Schiller, J. T., Hibma, M., Hallmans, G., and Stendahl, U. Antibodies against linear and conformational epitopes of human papillomavirus type 16 that independently associate with cervical cancer. Int. J. Cancer, *60:* 377–382, 1995.

30. Heino, P., Eklund, C., Fredriksson-Shanazarian, V., Goldman, S., Schiller, J. T., and Dillner, J. Association of serum IgG antibodies against human papillomavirus type 16 capsids with anal epidermoid carcinoma. J. Natl. Cancer Inst., *87:* 437–440, 1995.

31. Andersson-Ellström, A., Dillner, J., Hagmar, B., Schiller, J., Sapp, M., Forssman, L., and Milsom, I., Comparison of development of serum antibodies to HPV16 and HPV33 and acquisition of cervical HPV DNA among sexually experienced and virginal young girls. A longitudinal cohort study. Sex. Transm. Dis., *23:* 234–238, 1996.

32. Wideroff, L., Schiffman, M. H., Nonnenmacher, B., Hubbert, N. L., Kirnbauer, R., Greer, C. E., Lowy, D., Lorincz, A. T., Manos, M. M., Glass, A. G., and Schiller, J. T. Evaluation of seroreactivity to human papillomavirus type 16 virus-like particles in an incident case-control study of cervical neoplasia. J. Infect. Dis., *172:* 425–1430, 1995.

33. Dodd, J. G., Paraskevas, M., and McNicol, P. J. Detection of human papillomavirus 16 transcription in human prostate tissue. J. Urol., *149:* 400–402, 1993.

34. Tu, H., Jacobs, S. C., Mergner, W. J., and Kyprianou, N. Rare incidence of human papillomavirus types 16 and 18 in primary and metastatic human prostate cancer. Urology, *44:* 726–731, 1994.

35. Anwar, K., Nakakuki, K., Shiraishi, T., Naiki, H., Yatani, R., and Inuzuka, M. Presence of ras oncogene mutations and human papillomavirus DNA in human prostate carcinomas. Cancer Res., *52:* 5991–5996, 1992.

36. Masood, S., Rhatigan, R. M., Powell, S., Thompson, J., and Rodenroth, N. Human papillomavirus in prostatic cancer: no evidence found by *in situ* DNA hybridization. South. Med. J., *84:* 235–236, 1991.

37. Zambrano, A., Kalantari, M., Simoneau, A., Jensen, J. L., and Villarreal, L. P. Detection of human polyomaviruses and papillomaviruses in prostatic tissue reveals the prostate as a habitat for multiple viral infections. Prostate, *53:* 263–276, 2002.

38. Strickler, H. D., Schiffman, M. H., Shah, K. V., Rabkin, C. S., Schiller, J. T., Wacholder, S., Clayman, B., and Viscidi, R. P. A survey of human papillomavirus 16 antibodies in patients with epithelial cancers. Eur. J. Cancer Prev., *7:* 305–313, 1998.

Prostate Cancer Risk and Serologic Evidence of Human Papilloma Virus Infection: A Population-based Case-Control Study

Hans-Olov Adami, Hannah Kuper, Swen-Olof Andersson, et al.

Cancer Epidemiol Biomarkers Prev 2003;12:872-875.