INTRODUCTION

The International Centre for Infectious Diseases (ICID) is a Canadian not-for-profit organization that brings people and resources together to find new ways to fight infectious diseases worldwide. The Canadian Network on HPV Prevention is a program of ICID committed to optimizing disease prevention strategies and technologies and improving evidence-based decision-making in public health. The HPV Research Priorities Abstract Summary 2005-2008 was produced to update Canada’s HPV community about HPV research priorities identified at the National HPV Vaccine Research Priorities Workshop (2005) and Master Class (2006).

Human papillomavirus research and knowledge continues to advance our understanding of the role and impact of HPV infections worldwide. HPVs represent the most common infectious agents that are transmitted sexually throughout the world. The 2009-2010 HPV Abstract Summaries and Research Priorities provides an update on HPV research published in scholarly journals between January 2009 and September 2010. More than 2,000 articles were reviewed to identify the final 245 abstract summaries contained in this document. Each section of the Abstract Summary contains a brief synopsis of the relevant literature. Interesting areas for further HPV exploration have been identified in certain sections.

The 2009-2010 HPV Abstract Summaries and Research Priorities organizes the most current literature into major HPV topics beginning with the Epidemiology of HPV by disease site followed by Primary Interventions, Immunization, Screening, Data Management, Therapeutic Use of Vaccine, and HPV Testing Technology. The contents of this pdf document can be reviewed in whole, by section of interest, or searched by subject matter of interest.

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This document will continue to be updated on a regular basis and made available in electronic form through the International Centre for Infectious Diseases.

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Key Findings

- HPV 16 and 18 remained the most frequent HPV type identified in cervical cancer (53-84%), in situ cervical cancer (56-73%), and high grade cervical lesions (52–62%).
- HPV 18 and 45 were underrepresented in patients with cervical dysplasia development.
- Bimodal peaks of cervical HPV infection were evident in younger populations and women over the age of 40.
- Current and past smoking behaviors were independent predictors of HPV persistence and risk of developing cervical lesions.
- Early onset of sexual activity was an independent risk factor for HPV infection.
- Ethnic and racial disparities remain a significant factor among women diagnosed with genital cancers.
- HPV 16 and 18 are prevalent in anal precancerous and cancerous lesions.
- Anal HPV infections follow a similar pattern of duration and clearance as cervical HPV infection.
- HPV 16 is the most common HPV type in posterior naso/oropharyngeal tumors.
- Risk factors for head and neck cancers associated with HPV infections included oral sex and number of sex partners.
- Non-smokers and non-drinkers who developed oral cancers were six times more likely to have a high risk HPV infection than those who did not develop oral cancer.
- A strong association with index and second primary anogenital cancer and oropharyngeal cancers, specifically tonsillar cancer following anal cancer, has been demonstrated.
- HPV related oropharyngeal tumors in several studies appeared to frequently metastasize to lymph nodes with prognosis about the same or improved using current treatment regimens.
- Studies have confirmed that HIV infection increased HPV infection incidence after controlling for confounders.
- HPV 6 and 11 are confirmed as the etiologic factor for most recurrent respiratory papillomatosis.
- Lifetime number of sex partners, oral or vaginal sex partners, and current partner HPV infection were significant risk factors for HPV infection in men and couples in new relationships.
- HPV 16 was more common and had a longer duration among uncircumcised men.
- Clinical trial data have shown moderate impacts of HPV vaccination on non-vaccine oncogenic HPV types 31, 33, 45, 52, and 58.
• Reductions in genital warts have occurred among vaccinated Australian women under the age of 25.
• Factors impeding maximal HPV vaccination uptake have been identified as short notice for vaccine program implementation, negative media, and lack of general practitioner encouragement to eligible females.
• HPV vaccination cost effectiveness and modeling studies using current vaccine efficacy data, vaccine costs, and cervical cancer screening rates have not demonstrated value for women over the age of 30 who continue to be screened at least every two years.
• Ethnic, cultural, and socio-economic differences impact HPV knowledge and vaccination intention.
• Joint decision-making between school aged girls and their parents improved immunization uptake rates.
• Cost of vaccination, physician recommendation, and perceived social norms from family and friends impacted HPV vaccination intention and decision-making.
• Common characteristics among physicians and nurses related to likelihood to recommend HPV vaccination included individual beliefs, knowledge, support from colleagues, and patient’s insurance coverage.
• HPV testing improved disease detection rates in screening and follow up treatment, was more cost-effective, and was a more sensitive test for women over the age of 30 in many studies.
• Primary HPV DNA screening with cytology triage in women over the age of 30 was found to be more specific than conventional screening and resulted in decreased rates of colposcopy referral and follow up.
• HPV testing offered opportunities to reach high risk populations through HPV self-sampling, bypassing traditional access issues to cervical cancer screening services.
• HPV DNA testing technology continued to be evaluated demonstrating clinical utility of Hybrid Capture II and other developing HPV test methods.
Section 1
Epidemiology and Burden of Disease
1.1 FEMALE GENITAL CANCERS AND DISEASE

What have we learned about HPV distribution among different female populations and diseases?

1.1.1 Epidemiology

SUMMARY

Studies in Europe, China, and United States confirmed HPV 16 and 18 as the most frequent HPV type identified in cervical cancer (53-85%), in situ cervical cancer (56-73%), and high grade cervical lesions (52-62%). HPV 16 occurred more frequently (>75%) and HPV 18 less frequently (<10%) in vulvar, vaginal, and anal cancers than in cervical cancer.

Research continued to extend from original HPV testing triage studies to identify underrepresented HPV types in cervical dysplasia development (HPV 18 and 45). Multiple HPV infections were found to impact development of cervical dysplasia (OR 2.2 for any high risk HPV, 4.3 for HPV 16/18 infection). Persistent infection with HPV 16 and 18 was a strong predictor of cervical lesion development (RR 66.2 for CIN development following incident HPV 16/18 infection). Exposure to HPV with development of antibody response could be protective.

HPV type distribution varied by geographic area, ethnicity, HPV testing technology, and changes in distribution and prevalence over time and within cohorts. Bimodal peaks of cervical HPV infection were evident in younger populations and women over the age of 40. These data, while providing valuable information about the epidemiology of HPV, are difficult to interpret in relation to next generation vaccine developments and reinforce the importance of screening program outreach strategies for women over 50 years of age.

Priority Research

1. Studies evaluating and predicting the impact of HPV vaccination on all female genital lesions is important to expand our understanding of the potential impact of HPV 16 and 18 vaccination on a broader range of female cancers.

2. Analysis of the relationship between incident HPV infection, persistence, and natural antibody responses among both vaccinated and unvaccinated women will guide future public health strategies.

1.1.1.1. Incidence and Prevalence


ABSTRACT: In order to estimate the impact of primary cervical cancer screening with human papillomavirus (HPV) testing, and implementation of the current HPV vaccines, we have summarised the most recent and largest HPV studies in Europe. Eighteen studies including between 897 and 46,900 women from 14, mostly Northern and Western
European, countries were included. Everywhere, high-risk (HR) HPV prevalence peaked before age 25 or 30 years with steady declines thereafter. For women in the 30-64-year age-range, for whom primary HPV testing is considered, age-adjusted HR HPV prevalence ranged from 2% in Spain to approximately 12% in Belgium and France, where sustained elevated levels were found in women aged ≥35 years. HPV16 and 18, the two HR types prevented by current HPV vaccines, accounted for 30% (range 19-43%) and 12% (range 0-22%) of all HR HPV positives, respectively, and varied according to the presence of cervical lesions. Based on an updated meta-analysis of HPV type distribution in the whole of Europe, HPV16 and/or 18 are estimated to be present in 52%, 61% and 76% of cytologically detected high-grade squamous intraepithelial lesions, histologically confirmed cervical intraepithelial neoplasia grade 2/3, and invasive cervical carcinoma, respectively. © 2009 Elsevier Ltd. DOI: 10.1016/j.ejca.2009.07.019


ABSTRACT: Prophylactic vaccination against HPV 16 and 18 has the potential for effective prevention of high-grade precancer (cervical intraepithelial neoplasia [CIN]) 2/3 and ICC caused by these viruses (globally 50 and 70%, respectively) when employed in women prior to starting sexual activity. To provide data for decisions on HPV vaccination in China, we determined HPV type-distribution in ICC and CIN 2/3 from women of different regions within China. A multicenter study was conducted by randomized sampling of paraffin blocks of 664 ICC (630 squamous cell carcinoma [SCC]; 34 adenocarcinoma [ADC]), 569 CIN 2/3 cases from seven regions of China. Histological diagnosis was confirmed in 1,233 cases by consensus review. HPV DNA was detected using the SPF10 LiPA25 version 1 assay. HPV prevalence was 97.6% in SCC, 85.3% in adenocarcinoma, and 98.9% in CIN 2/3. HPV 16 (76.7%) and HPV 18 (7.8%) were the most common, together accounting for 84.5% of SCC, followed by HPV 31 (3.2%), HPV 52 (2.2%), and HPV 58 (2.2%). HPV positivity in SCC did not differ notably by region. However, SCC cases from women 34 years had higher HPV 16 positivity than women over 50 years, among whom HPV 52, 58, and 39 were more common. HPV 16 and 18 were under-represented, whereas HPV 31, 52, and 58 were over-represented in CIN2/3 compared to SCC. The potential impact of vaccines against oncogenic HPV types 16 and 18 is estimated to be high (84.5%) against total SCC. These data are critical for China’s future evaluation of the cost-effectiveness of current cervical cancer vaccines and of HPV-based screening guidelines.

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**SECTION 1 - EPIDEMIOLOGY AND BURDEN OF DISEASE**

**ABSTRACT:** Information on HPV type distribution in cervical cancer in situ in different populations is needed for evaluation of prophylactic vaccination programs targeting HPV 16 and 18. In our study, the HPV type prevalence in 1,079 Swedish women from multicase families diagnosed with cervical cancer in situ 1965-1993 was investigated using real-time PCR and archival tissue material. HPV type information was obtained for 974 samples. Among these, HPV 16 (61%) was the dominant type followed by HPV 33/52/58 (24%), HPV 31 (13%) and HPV 18/45 (12%). The detected prevalence of HPV 16 among cancer in situ decreased by 13% over the study period while the group of low frequency high-risk types increased. Related women were not prone to infection by the same type. These data suggest that the prevalence of individual HPV types has changed over time in Swedish patients with cervical cancer in situ. Large-scale studies of pathology biobank materials will enable further insight into the temporal changes of individual HPV types, as baseline information to properly evaluate the effect of vaccine programs. The findings also indicate that genetic susceptibility to cervical cancer operates through general and not type specific susceptibility to HPV infection. © 2009 UICC.

DOI: 10.1002/ijc.24631


**ABSTRACT:** Objective: The objective of this study was to establish the prevalence and type distribution of human papillomavirus (HPV) in cervical cancer and cervical intraepithelial neoplasia (CIN) in Hubei, China. Methods: A total of 112 patients with cervical cancer and 60 CIN II-III samples were obtained from women undergoing biopsy or surgery. HPV and typing were examined by the polymerase chain reaction (PCR) and sequencing. Results: HPV DNA was detected in 105 patients with cervical cancer (93.75%), HPV 16 being detected in 91 (81.25%) cases, and HPV 58 in 7 (6.25%) cases. HPV DNA was detected in 50 patients with CIN II-III (83.33%), HPV 16 being detected in 37 (61.67%) cases, HPV 58 in 5 cases (8.33%). HPV 18 was not common in this study. About 11% cervical cancer and 8.33% CIN II-III specimens exhibited multiple infections (p = 0.79). Conclusion: The high prevalence of HPV 16 in Hubei, China, deserves attention as it has important implications for the usefulness of vaccine and the choice of diagnostic methods. Copyright © 2009 S. Karger AG.

DOI: 10.1159/000195885


Distribution of human papillomavirus types in cervical cancers in Hong Kong: Current situation and changes over the last decades. *International Journal of Cancer, 125* (7), pp. 1671-1677.

**ABSTRACT:** Human papillomavirus (HPV) type distribution among cervical cancers and its possible changes over time are key issues that determine the cost-effectiveness of HPV vaccines. Cervical cancers diagnosed during 3 periods (1997-2007, N = 280; 1984-1986, N = 74; 1972-1973, N = 81) in Hong Kong were examined for HPV type distribution using sensitive broad-catching methods. The results showed a variation in HPV distribution...
between histological groups. Among cervical squamous cell carcinoma (SCC) cases diagnosed over the past 10 years, HPV16 was most commonly found (61.2%), followed by HPV18 (17.7%), HPV52 (14.7%) and HPV58 (9.9%), whereas adeno/adenosquamous cell carcinoma was dominated by HPV18 (56.3%) and HPV16 (50.0%). The proportion of HPV16-positive SCC showed a significant linear trend of increase with time (45.2% for 1972-1973, 58.8% for 1984-1986, 61.2% for 1997-2007; \( P_{\text{Trend}} = 0.023 \)), whereas HPV52-positive SCC decreased with time (30.1% for 1972-1973; 29.4% for 1984-1986, 14.7% for 1997-2007; \( P_{\text{Trend}} = 0.001 \)). Vaccines comprising HPV16/18 cover 62.6% of SCC and 93.8% of adeno/ adenosquamous carcinoma in Hong Kong, and inclusion of HPV52 and HPV58 can increase the coverage by 18.4% for SCC and 4.1% for adeno/adenosquamous cell carcinoma. HPV type distribution may change over time. Further investigations to reveal the determinants for such changes and continuous monitoring for possible type replacement as a result of widespread long-term use of HPV vaccines are warranted. Multiple infections are commonly revealed by sensitive broad-catching methods such as those used in this study. However, their implication on vaccine efficacy and cost-effective analyses should be taken cautiously. © 2009 UICC.

DOI: 10.1002/ijc.24495


**ABSTRACT:** This meta-analysis investigated human papillomavirus (HPV) prevalence in vulvar, vaginal and anal intraepithelial neoplasia (VIN, VAIN, AIN) grades 1-3 and carcinoma from 93 studies conducted in 4 continents and using PCR assays. Overall HPV prevalence was 67.8%, 85.3% and 40.4% among 90 VIN1, 1,061 VIN2/3 and 1,873 vulvar carcinomas; 100%, 90.1% and 69.9% among 107 VAIN1, 191 VAIN2/3 and 136 vaginal carcinomas; and 91.5%, 93.9% and 84.3% among 671 AIN1, 609 AIN2/3 and 955 anal carcinomas, respectively. HPV16 was found more frequently (>75%) and HPV18 less frequently (<10%) in HPV-positive vulvar, vaginal and anal carcinomas than in cervical carcinoma. HPV6 and 11 were common in VIN1 and AIN1, but not in VAIN1. HPV prevalence in vulvar carcinoma varied most by histological type (69.4% in warty-basaloid and 13.2% in keratinized type) and was also higher in women 60 years or younger and in studies carried out in North America. HPV prevalence in anal carcinoma was higher among women (90.8%) than men (74.9%), but no difference by gender emerged in North America. The majority of AIN2/3 derived from studies of HIV-positive individuals and/or men who have sex with men. Among AIN2/3, HIV infection was associated with higher HPV prevalence, more multiple-type infections and a relative under-representation of HPV16. In conclusion, 40% of vulvar, 60% of vaginal and 80% of anal carcinoma may be avoided by prophylactic vaccines against HPV16/18. This proportion would be similar for the corresponding high-grade lesions of the vagina and anus, but higher for VIN2/3 (75%) than for vulvar carcinoma. © 2008 Wiley-Liss, Inc.

DOI: 10.1002/ijc.24116

Detection of precancerous cervical lesions is differential by human papillomavirus type. 

**ABSTRACT:** Epidemiologic studies have reported the underrepresentation of cervical precancerous lesions caused by human papillomavirus (HPV) types 18 and 45 (HPV18/45) compared with the proportion of cervical cancers attributed to these HPV types. We investigated the timing of diagnosis of histologic cervical intraepithelial neoplasia grade 3 or worse (CIN3+) using data from the atypical squamous cells of undetermined significance-low-grade squamous intraepithelial lesion triage study (ALTS). Of the 2,725 women who underwent enrollment colposcopy, 412 of 472 (87.3%) diagnosed with histologic CIN3+ over the 2-year duration of ALTS could be assigned to a HPV type or group of types and were included in this analysis. Eighty-four percent of HPV16-positive CIN3+ were diagnosed at enrollment, compared with 57% of HPV18/45-positive C1N3+, and 58% of C1N3 positive for other carcinogenic HPV types at enrollment. In contrast, only 8% of HPV16-positive CIN3+ were diagnosed at exit, whereas 31% were HPV18/45 positive and 22% were positive for other carcinogenic types at study exit (P<0.001). These results indicate the underrepresentation of HPV18/45 in precancers, whereas HPV16-associated C1N3+ is diagnosed much earlier. Whether the underrepresentation of 18/45 may be due to occult pathology needs further investigation. © 2009 American Association for Cancer Research. DOI: 10.1158/0008-5472.CAN-08-4192


**ABSTRACT:** Background. Limited data are available describing human papillomavirus (HPV) genotype distributions in cervical cancer in the United States. Such studies are needed to predict how HPV vaccination and HPV-based screening will influence cervical cancer prevention. Methods: We used the New Mexico Surveillance, Epidemiology, and End Results Registry to ascertain cases of in situ (n = 1213) and invasive (n = 808) cervical cancer diagnosed during 1985-1999 and 1980-1999, respectively, in the state of New Mexico. HPV genotyping was performed using two polymerase chain reaction-based methods on paraffin-embedded tissues from in situ and invasive cancers and on cervical Papainiolaou test specimen from control subjects (i.e., women aged 18-40 years attending clinics for routine cervical screening [n = 4007]). Relative risks for cervical cancer were estimated, and factors associated with age at cancer diagnosis and the prevalence of HPV genotypes in cancers were examined. Results: The most common HPV genotypes detected in invasive cancers were HPV type 16 (HPV16, 53.2%), HPV18 (13.1%), and HPV45 (6.1%) and those in in situ cancers were HPV16 (56.3%), HPV31 (12.6%), and HPV33 (8.0%). Invasive cancer case subjects who were positive for HPV16 or 18 were diagnosed at younger ages than those who were positive for other carcinogenic HPV genotypes (mean age at diagnosis: 48.1 [95% confidence interval (CI) = 46.6 to 49.6 years], 45.9 [95% CI = 42.9 to 49.0 years], and 52.3 years [95% CI = 50.0 to 54.6 years], respectively). The proportion of HPV16-positive in situ and invasive cancers, but not of HPV18-positive cancers, declined with more recent calendar
year of diagnosis, whereas the proportion positive for carcinogenic HPV genotypes other than HPV18 increased. Conclusions: HPV16 and 18 caused the majority of invasive cervical cancer in this population sample of US women, but the proportion attributable to HPV16 declined over the last 20 years. The age at diagnosis of HPV16- and HPV18-related cancers was 5 years earlier than that of cancers caused by carcinogenic HPV genotypes other than HPV16 and 18, suggesting that the age at initiation of cervical screening could be delayed in HPV-vaccinated populations.

DOI: 10.1093/jnci/djn510


**ABSTRACT:** Background. A prophylactic quadrivalent human papillomavirus (HPV) vaccine could benefit adult women if they are susceptible to incident genital HPV infections and are acquiring new infections with vaccine HPV types to which they were previously not exposed. This report presents baseline and prospective data from a randomized, double-blind, placebo-controlled trial of the safety, immunogenicity, and efficacy of the quadrivalent HPV (Type 6/11/16/18) vaccine in women ages 24 to 45. METHODS: We present the results of an epidemiologic analysis of 3730 women enrolled in a quadrivalent HPV vaccine efficacy trial between June 18, 2004 and April 30, 2008. Subjects were enrolled from 7 countries (Colombia, France, Germany, Philippines, Spain, Thailand, and the United States) through community and academic health centers and primary health care providers. RESULTS: Average baseline prevalence of anogenital infection and/or seropositivity was 32.8% for ≥11 vaccine HPV types and 0.3% for all vaccine HPV types. Incidence of anogenital infection with any vaccine HPV type was ~10.5%. The rate of persistent infection was ~5% over a 30-month period among women in the placebo arm naïve to the relevant type at baseline. Predictors of incident infection included younger age, marital status other than first marriage, higher number of lifetime and recent sex partners, and Chlamydia/gonorrhea infection at baseline. CONCLUSIONS: These findings indicate that women up to age 45 are susceptible to vaccine HPV types and some are acquiring anogenital infections with vaccine HPV types. Future study concerning incident and prevalent HPV infection among women up to age 45 is warranted (Trial NCT number NCT00090220). Copyright © 2009 American Sexually Transmitted Diseases Association.

DOI: 10.1097/OLQ.0b013e3181ad25ff


**ABSTRACT:** Background. Human papillomavirus (HPV) seroprevalence data can help define the epidemiology of this common sexually transmitted pathogen. Methods. We determined the seroprevalence of HPV types 6, 11, 16, and 18 (HPV types in the quadrivalent vaccine) among 4303 persons aged 14-59 years who participated in the National Health and Nutrition Examination Survey 2003-2004. Results. The seroprevalences of HPV types 6, 11, 16, and 18
among female subjects were 17.0%, 7.1%, 15.6%, and 6.5%, respectively. Among males, the seroprevalences were lower for each type, with 6.3% observed for HPV6, 2.0% for HPV11, 5.1% for HPV16, and 1.5% for HPV18 (P < .001 for all comparisons). For any HPV vaccine type, the seroprevalence was 32.5% among females and 12.2% among males; the seroprevalence of any HPV vaccine type increased with age, reaching 42.0% among women aged 30-39 years and 18.0% among men aged 50-59 years. Antibodies to all 4 vaccine types were detected in 0.4% of females and 0% of males. Non-Hispanic blacks had a higher seroprevalence of any HPV vaccine type than that observed for non-Hispanic whites or Mexican Americans. Age and lifetime number of sex partners were factors independently associated with seroprevalence of any HPV vaccine type among both females and males, and poverty level was also a factor among females. Conclusions. This is the first population-based seroprevalence study in the United States of all 4 HPV types targeted by the quadrivalent vaccine, and its findings can inform vaccine policy.

DOI: 10.1086/604729


**ABSTRACT:** Human papillomavirus (HPV) type 16 and 18 neutralizing antibody (NAb) titers were measured in 1,020 prenatal women in British Columbia aged 15 to 39. HPV 16 and 18 NAbs were detected in 183/1,020 (17.9%) and 97/1,020 (9.5%), respectively, and 39 (3.8%) had NAbs to both types. Titers were similar across age strata. Copyright © 2009, American Society for Microbiology.

DOI: 10.1128/CVI.00238-09


**ABSTRACT:** Background. Data on the prevalence of different human papillomavirus (HPV) genotypes and the associated mucosal immune response in women with cervical ectopy are scarce. Objective: To assess the prevalence of different HPV genotypes and the mucosal anti-viral immune response in cervical ectopy. Study design: Detection and typing of HPV DNA was determined in 141 women with cervical ectopy, 272 cytologically normal controls and 98 low-grade squamous intraepithelial lesions (LSIL) by PCR and direct sequencing. Mucosal IgA antibodies to HPV16 and HPV18 were evaluated in cervical mucus by ELISA.

Results: The prevalence of HPV in cervical ectopy was higher (73.7%) than that observed in control samples (30.5% in endocervix, and 1.8% in exocervix), but similar to the prevalence in LSIL (62.2%). Typing showed that the overall distribution frequency concerned 14 different genotypes, with HPV18 being the most prevalent in cervical ectopy (53.9%), whereas HPV16 predominated in LSIL (38.7%). High-risk HPV genotypes were 2.2 times more frequent in cervical ectopy than in the normal endocervix (p < 0.0001). HPV infection in cervical ectopy patients was accompanied by a mucosal IgA-antibody response. Antibody reactivity to HPV18 was significantly higher than the response to HPV16. Conclusion:
Cervical ectopy is a risk factor for infection with high-risk HPV genotypes, in particular HPV18. Our results emphasize the need of further studies to clarify the oncogenic potential of this virus in cervical ectopy. © 2009 Elsevier B.V.

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**ABSTRACT:** Objective: To evaluate the risk of high-risk human papillomavirus (HPV) infection in women with Trichomonas vaginalis infection, and the reason remains unclear. Methods: A total of 40,000 liquid-based cytology specimens were tested from 2005 to 2008. Among these, high-risk HPV testing using the hybrid capture II assay was performed in positive cases of T. vaginalis according to the age of patients (<30 years old, between 30 and 50 years old, more than 50 years old). As controls, HPV detection was also performed in 450 normal smears. Results: T. vaginalis was found in 80 cases (0.2%). From these 80 cases, 57 were available for HPV testing (8 patients <30 years old, 42 patients between 30 and 50 years old and 7 patients more than 50 years old). As controls, high-risk HPV was tested in 150 patients with normal cytology for each of these three age categories. High-risk HPV was significantly more frequently detected in women with T. vaginalis than in women with normal smear irrespective of the categories of age (P < 0.01). Conclusion: For the first time, we demonstrated a significant prevalence of high-risk HPV in women with cytological proved T. vaginalis infection independent of the age ranges. Our data suggest a potential association between these two infectious agents by the way of a sexual intercourse and probably by a biochemical or immunological reasons. © 2009 Springer-Verlag.

DOI: 10.1007/s00404-009-1291-x


**ABSTRACT:** Objective: Most young women initiate sexual activity during adolescence; risk for sexually transmitted infections (STIs) accompanies this initiation. In this study we estimated the prevalence of the most common STIs among a representative sample of female adolescents in the United States. METHODS: Data were analyzed from 838 females who were aged 14 to 19 and participating in the nationally representative National Health and Nutrition Examination Survey 2003-2004. After interview and examination, survey participants provided biological specimens for laboratory testing. The main outcome was weighted prevalence of at least 1 of 5 STIs: Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, herpes simplex virus type 2, and human papillomavirus (HPV) (any of 23 high-risk types or type 6 or 11). RESULTS: Prevalence of any of the 5 STIs was 24.1% among all and 37.7% among sexually experienced female adolescents. HPV (23 high-risk types or type 6 or 11) was the most common STI among all female
adolescents (prevalence: 18.3%), followed by C trachomatis infection (prevalence: 3.9%). Prevalence of any of the STIs was 25.6% among those whose age was the same or 1 year greater than their age at sexual initiation and 19.7% among those who reported only 1 lifetime sex partner. CONCLUSIONS: The prevalence of STIs among female adolescents is substantial, and STIs begin to be acquired soon after sexual initiation and with few sex partners. These findings support early and comprehensive sex education, routine HPV vaccination at the age of 11 to 12 years, and C trachomatis screening of sexually active female adolescents. Copyright © 2009 by the American Academy of Pediatrics. DOI: 10.1542/peds.2009-0674

1.1.1.2 Linkage with Cervical Screening


**ABSTRACT:** In order to prevent cervical cancer, vaccines against human papilloma virus types 16 (HPV-16) and 18 (HPV-18) have been implemented worldwide. However, the HPV types that cause cancer can differ according to geographical area and ethnicity. In this new era of the HPV vaccine, it is important to elucidate the prevalent HPV types in each area. Therefore, the prevalence of HPV infection and cervical abnormalities among 369 female commercial sex workers in the Philippines were examined. HPV L1 gene was amplified by polymerase chain reaction (PCR) using modified GP5+/6+ primers, and genotyping was performed by sequencing cloned PCR products. HPV DNA was detected in 211 (57.2%) women, among whom 46 HPV types were identified. HPV-52 was most common and multiple-type infection was observed in 44.5%. Among 56 women with abnormal cervical cytology (low- and high-grade squamous intraepithelial lesions and adenocarcinoma in situ), HPV-52 was most common (23.2%), followed by HPV-16 (19.6%), -58 (10.7%), and -67 (10.7%). Only 27% of these women were positive for HPV-16 and -18. Multivariate analysis revealed that HPV-16, -39, -52, -67, and -82 were significantly associated with abnormal cytology. Repeated analysis of HPV-52 single-positive samples using the original GP5+/6+ PCR primers produced negative results in 57% of cases, suggesting that the prevalence of HPV-52 infection may have been underestimated in previous studies, and the current vaccines may not be sufficient for preventing infection and the development of premalignant lesions of the cervix in women in the Philippines. © 2009 Wiley-Liss, Inc. DOI: 10.1002/jmv.21416


**ABSTRACT:** Objective: The purpose of this study was to report type-specific prevalence and persistence of human papillomavirus (HPV) in women who underwent cytologic screening.
1.1 Female Genital Cancers and Disease

Study Design: We examined HPV prevalence in 73,371 women who had type-specific HPV testing in 1 of 23 clinical laboratories in the United States. Persistence was evaluated in 963 women who were tested within 8-16 months of their index test. Results: HPV was detected in 31% of the women, and high-risk HPV was detected in 23% of the women. HPV-16, -53, -52, and -31 were the most prevalent types. Of the 953 women with 2 tests, 39% of the women had persistent HPV infection. High-risk HPV persistence was detected in 34% of the women who were positive initially for high-risk HPV. Conclusion: Approximately one-third of our sample had HPV; of those women who were retested within 8-16 months, more than one-third had persistent infection. Among women with high-risk HPV infections, the likelihood of persistence was highest with HPV genotypes that were phylogenetically similar to HPV-16. © 2009 Mosby, Inc.
DOI: 10.1016/j.ajog.2008.10.050


ABSTRACT: Background. Human papilloma virus (HPV) prevalence studies performed in different regions and population groups across Canada would inform public health decisions regarding implementation of anti-HPV vaccines. Methods: A total of 8,700 liquid-based specimens from 8,660 women aged 13-86 from throughout British Columbia were collected. DNA was isolated from 4,980 of these samples and assessed for HPV prevalence and type distribution. HPV was detected by PCR analysis using tagged GP5+/6+ consensus primers to amplify the L1 region of HPV; typing was done by bi-directional sequencing of PCR products. Results: Overall HPV prevalence was 16.8% (age adjusted 15.5%). Prevalence of high-risk HPV was 13.9, and 10.7% of samples contained HPV16. HPV prevalence was highest in the youngest group of women (<20 years). One-third of HPV positive samples contained more than one HPV type. Percentages of low-grade (LGIL) and high-grade intraepithelial lesions (HGIL) containing high-risk HPV are 52.3 and 79.4%, respectively. Conclusions: Overall HPV prevalence in this study is within the range of estimates from other studies. The prevalence of HPV16 is higher than what is found in other Canadian and international studies. HPV16 and HPV18 compose a majority of the high-risk virus in this study. Use of current HPV vaccines could considerably reduce HPV-related conditions including cervical cancer and procedures such as colposcopy. © 2009 The Author(s). DOI: 10.1007/s10552-009-9365-4


ABSTRACT: Although a second age-related peak of human papillomavirus (HPV) infection is observed in many populations, it does not seem to have any impact on cervical screening policies. We examined the age-specific prevalence of HPV infection among 2,604 women enrolled for cervical screening and correlated the age at diagnosis of 2,491 cervical
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intraepithelial neoplasia Grade 2/3 (CIN2/3) lesions and 801 invasive cervical cancers (ICC). Two peaks of HPV infection were detected at 26-30 and 46-50 years, respectively. The first infection peak was followed by a CIN2/3 peak and an ICC peak at 5-15 and 15 years later, respectively. The second infection peak was followed by an ICC peak 20 years later, but strikingly no CIN2/3 peak was detected in between and thus eliminated an opportunity of treating the lesions at preinvasive stages. The most plausible explanation is that women at the expected second CIN2/3 peak (50-65 years) are not having Pap smears under the current opportunistic screening program. Furthermore, women of this age may have physiological retraction of the transformation zone, and CIN lesions may remain undetected if an adequate Pap smear sample is not obtained. To combat this problem, the screening program in Hong Kong needs to focus on women aged 50 years and older and a mop-up screening up to 75 years is necessary. Bimodal peaks of HPV infection and cervical cancer are seen in many countries and the analysis of population-specific age distribution of CIN2/3 should be an integral exercise in evaluating the effectiveness of a screening program. © 2009 UICC. DOI: 10.1002/ijc.24731


ABSTRACT: Objective: It is assumed that the circulation of HPV types in a population is stable over time although there are limited historical data to support this view. The existence of possible cohort effects in the circulation of HPV types has major implications for vaccination strategies and risk assessment in HPV-infected women. We analysed archival biopsy samples of cervical intraepithelial neoplasia (CIN) to study the distribution of HPV types in Northern Italy over the years 1985-2007. Methods: DNA from formalin-fixed paraffin-embedded cervical biopsies from the years 1985-87 (67 samples) and 1995-97 (92 samples) was HPV-typed by the SPF-10 Lipa assay. Cases were compared with 159 control biopsies from the years 2005-07 matched by patient age and CIN grade. Quantitative PCR was used to compare titres of HPV sequences in DNA extracted from biopsies of the three periods. Type-specific PCR was used to confirm HPV51 and 52 typing by SPF-10 Lipa. Results: HPV51, 52, 53, 56, 58, and 66 were markedly under-represented or undetectable in samples from past periods whereas they represented 5.7-30.8% of present infections. Frequency of multiple HPV infections and high-risk infections (p = 0.0001) also increased in recent years. The main changes occurred over the last decade. Infections by HPV16, 18, were three times more frequent 20 years ago than today (p = 0.012). Loss of amplifiable HPV sequences over prolonged storage was not observed. Type-specific PCR confirmed all HPV51 and 52 infections. Conclusions: Secular trends in the distribution of HPV types among women with CIN may occur in specific populations. © 2009 Elsevier Inc. DOI: 10.1016/j.ygyno.2009.07.029
1.1 Female Genital Cancers and Disease

1.1.1.3 Multiple HPV Infections

Genotype distribution of human papillomavirus (HPV) and co-infections in cervical cytologic specimens from two outpatient gynecological clinics in a region of southeast Spain. *BMC Infectious Diseases*, 9, art. no. 124.

**ABSTRACT:** Background. Human Papillomavirus (HPV) genotype distribution and co-infection occurrence was studied in cervical cytologic specimens from Murcia Region, (southeast Spain), to obtain information regarding the possible effect of the ongoing vaccination campaign against HPV16 and HPV18. Methods: A total of 458 cytologic specimens were obtained from two outpatient gynecological clinics. These included 288 normal benign (N/B) specimens, 56 atypical squamous cell of undetermined significance (ASC-US), 75 low-grade squamous intraepithelial lesions (LSIL) and 39 high-grade squamous intraepithelial lesions (HSIL). HPV genotyping was performed using PCR and tube array hybridization. Results: The most frequent genotype found was HPV16 (14.9% in N/B; 17.9% in ASC-US; 29.3% in LSIL and 33.3% HSIL). Distribution of other genotypes was heavily dependent on the cytologic diagnoses. Co-infections were found in 15.3% of N/B, 10.7% of ASC-US, 48% of LSIL and 25.6% of HSIL cases (significantly different at p < 0.001). Strikingly, in N/B diagnoses, genotypes from A5 species were found as coinfecting in all cases. Genotypes from A7 or A9 species appeared in co-infections in 56.5% and 54% respectively whereas genotypes from A6 species appeared in 25.1% of cases. Conclusion: HPV vaccination might prevent 34.6% and 35.8% of LSIL and HSIL, respectively. Co-infection rate is dependent on both cytologic diagnosis and HPV genotype. Moreover, genotypes belonging to A5, A7 and A9 species are more often found as co-infections than genotype pertaining to A6 species. This suggests that phylogenetically related genotypes might have in common similar grades of dependency for cervical epithelium colonization.

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DOI: 10.1186/1471-2334-9-124

Multiple human papillomavirus infection and high grade cervical intraepithelial neoplasia among women with cytological diagnosis of atypical squamous cell of undetermined significance or low grade squamous intraepithelial lesions. *Gynecologic Oncology*, 113(1), pp. 115-119.

**ABSTRACT:** Objective: To evaluate the effect of multiple human papillomavirus (HPV) infection on the prevalence of cervical intraepithelial neoplasia (CIN) among women undergoing colposcopy following a cytological diagnosis of atypical squamous cells of undetermined significance (ASCUS) or low grade squamous intraepithelial lesions (LSIL). Methods: HPV type-specific sequences of 15 high-risk and 10 low risk types were detected by the line probe, INNO-LiPA HPV genotyping assay before colposcopic examination and targeted biopsies. Multinomial logistic regression was used to evaluate the effect of multiple infection on pathologic outcome adjusting for confounders. Results: The prevalence of HPV infection in the 1218 women enrolled was 69.9% (851/1218). HPV 16 (37.4%), 31 (26.1%), 51 (17.4%), 52
(15.7%) and 18 (14%) were the commonest viral types identified. Overall, the rates of multiple infection were 22.5% (153/680) among subjects with negative colposcopy/biopsy, 63.6% (218/343) and 79.5% (155/195) among those with CIN 1 and CIN ≥ 2, respectively (p for trend < .001). The corresponding rates among subjects uninfected by HPV 16 or 18 were 13.5% (77/572), 57.4% (112/195) and 62% (48/77), respectively (p for trend < .001). In multinomial logistic regression, the odds ratio of CIN ≥ 2 in multiple high risk as compared to single high risk HPV infection was 4.33 (95% confidence intervals = 2.32-7.14) in the overall population and 2.76 (95% confidence intervals = 1.36-5.59) among women uninfected by HPV 16 or 18. Conclusions: Multiple HPV infection is a significant risk factor for CIN ≥ 2 among women undergoing colposcopy because of ASCUS/LSIL. © 2009 Elsevier Inc.

1.1.1.4 HPV Persistence


Persistent antibodies to HPV virus-like particles following natural infection are protective against subsequent cervicovaginal infection with related and unrelated HPV. *Viral Immunology*, 22(6), pp. 445-449.

**ABSTRACT:** Whether persistent human papillomavirus (HPV) IgG antibodies following natural infection are protective against subsequent infection is unknown. In a cohort of 508 college women followed for 3y, persistent seropositivity was defined as the presence of type-specific HPV virus-like particle (VLP) antibodies at ≥ 2 consecutive visits 1y apart. Protection from incident infection with any HPV was conferred by persistent antibodies to HPV16 (p=0.02), HPV31 (p<0.001), HPV33 (p=0.03), HPV35 (p=0.002), HPV52 (p=0.007), HPV45 (p=0.003), and HPV53 (p=0.01). The risk of incident infection with species-specific HPV types was also decreased in women with persistent antibodies to any HPV type in that group, suggesting that exposure to HPV with persistent development of antibody response can be protective, and may explain the decreased efficacy of HPV vaccine in women with prior exposure. © 2009, Mary Ann Liebert, Inc.

DOI: 10.1089/vim.2009.0055


**ABSTRACT:** Background. We analyzed data from a cohort of 553 women enrolled in the placebo arm of a randomized controlled trial of the human papillomavirus (HPV) 16/18 vaccine to study the timing of the occurrence of squamous intraepithelial lesions (SIL) or cervical intraepithelial neoplasia (CIN) following incident HPV infection and its relation to persistence of the infection. Methods: At entry, women were cytologically negative, HPV 16/18 seronegative, and high-risk HPV (HR-HPV) DNA negative. Cervicovaginal samples were initially collected at 3-month and cervical samples at 6-month intervals. We estimated the mean time to SIL/CIN, relative risks of SIL/CIN following incident
HPV, and odds ratios between persistent HPV and SIL/CIN. Results: The mean time for SIL/CIN detection was 43.3 (95% confidence interval (95% CI), 36.4-50.1) and 46.4 (95% CI, 42.0-50.7) months from first infection with HPV 16/18 and other HR-HPVs, respectively. Relative risks of SIL/CIN following incident HPV infection were 66.2 (95% CI, 14.9-295.1) for HPV 16/18 and 50.9 (95% CI, 11.5-225.4) for other HR-HPVs. The odds ratios of SIL/CIN for persistent HPV 16/18 infection, defined as a minimum of two and three (6 monthly) visits, were, respectively, 169.0 (95% CI, 37.2-768.6) and 169.1 (95% CI, 31.5-907.4). The majority of women with cervical infection with HPV 16/18 lasting >6 months (33 of 51, 65%) developed SIL and/or CIN. Conclusions: These analyses provide the first actuarial estimate of mean time between incident HR-HPV infection in previously uninfected women and onset of cervical lesion development. Persistent HR-HPV infection, particularly HPV 16/18, is a strong predictor of cervical lesion risk and potentially a reliable end point for clinical HPV research. Copyright © 2009 American Association for Cancer Research. DOI: 10.1158/1055-9965.EPI-08-1012


ABSTRACT: The objective of this study was to analyse the prevalence, infection pattern, duration and outcome of long-term, type-specific, persistent human papillomavirus (HPV) infections in a routine cytology-based cervical screening population of West German women followed up for 7.5 years. From a screening population of 31,000 women, a strictly selected cohort of 100 patients with ≥18-month persistent, type-specific HPV infection were prospectively followed up for a mean of 35.52 months (±13.0). HPV type prevalence and odds ratios for regression, progression and steady state were analysed, as well as the influence of age and HPV coinfection on outcome. Altogether, 21 different genotypes were detected. Seventy-two percent of women were infected with high-risk HPVs, 24% with low-risk and 4% with unknown risk HPV types; 44% of cases had coinfections with multiple HPV types. The risk of progression in low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions was the highest for infections with high-risk HPVs [odds ratio: 2.2 (0.79-6.11, 95% confidence interval)], whereas cases with low-risk and unknown risk HPVs tended to regress or remained unchanged during follow-up. The mean duration of infections showed considerable variation among the different HPV types and risk groups detected and ranged between 19.7 and 54.3 months. Age was not significantly associated with disease progression and infection duration, and histology had a poor sensitivity for detecting high-grade dysplasia. In conclusion, detecting long-term persistent HPV infections by genotyping may help to identify women with cervical intraepithelial lesions who are at lower and higher risk of developing high-grade precancer and cancer. This may influence future screening strategies and therapy decisions. © 2009 Lippincott Williams & Wilkins, Inc. DOI: 10.1097/CEJ.0b013e328324061a

**ABSTRACT:** We investigated short-term persistence of human papillomavirus (HPV) infection among 2,408 women with low-grade or equivocal cytological abnormalities followed for 24 months. Odds ratios (ORs) for persistence to the next 6-month visit were estimated by a discrete time survival model. Prevalent HPV infections persisted longer in older women, but no association with age was found for incident HPV infections. Increased likelihood of persistence was found among current smokers of >20 cigarettes per day compared with smokers of ≤10 cigarettes per day (OR51.43; 95% confidence interval [CI]: 1.02-2.01) and among current injectable contraceptive users (OR51.15; 95% CI: 1.01-1.32). Persistence was more likely among infections with higher viral load (OR52.05; 95% CI: 1.65-2.53) or with concurrent cytological abnormalities (OR51.19; 95% CI: 1.03-1.39 and 1.29; 95% CI: 0.99-1.70 for ASCUS/LSIL and ASC-H/HSIL, respectively). We conclude that new HPV infections in older women are not riskier by the metric of viral persistence than those in younger women. Other risk factors such as oral contraceptive use and multiparity that have been associated with cervical cancer or cervical intraepithelial neoplasia grade 3 were not associated with short-term HPV persistence. © 2009 UICC.

DOI: 10.1002/ijc.24752

1.1.2 Burden of Disease

**SUMMARY**
A retrospective study of Ontario administrative databases demonstrated an increase in squamous cell anal cancer (OR 10.5) among women previously diagnosed with cervical, vaginal, or vulvar cancer. A retrospective survey of Finish databases calculated higher annual new incident cases of HPV 6 and 11 clinical lesions versus HPV 16 and 18 associated clinical lesions (13,066 vs. 8,316). A high rate of HPV 6 and 11 were found in vulvar intraepithelial lesions (64.5% VIN 1 and 29% of VIN 2/3) adding to the disease burden of HPV. Significant racial disparities remain in the United States among American women diagnosed with genital cancers (cervical, vaginal, and vulvar).

**Priority Research**

1. Studies are required to evaluate the burden of HPV related illnesses in vaccinated and non-vaccinated cohorts as well as populations from different cultures and risk profiles to identify the temporal changes in HPV types, the cost implication of HPV vaccination, and the priority for additional HPV types in the next generation vaccines.

2. More investigation into the relationship among HPV related neoplasms is needed to better understand the impact from preventative HPV strategies to reduce the burden of disease.
1.1 Female Genital Cancers and Disease


**ABSTRACT:** Objective: The oncogenic HPV subtypes responsible for gynecologic malignancies have also been implicated in the development of squamous cell cancer of the anus (SCAC). SCAC is more common in women, typically presenting at an older age than gynecologic cancers. The aim of this study was to determine whether women diagnosed with anal cancer are more likely to have a history of HPV-related gynecological cancer as compared to a matched control group. Methods: We performed a population-based, case-control study at the Institute for Clinical Evaluative Sciences (ICES) which houses the administrative databases for all residents of the province of Ontario, Canada. All women diagnosed with SCAC between 1992 and 2005, identified using ICD-9 codes (154.2, 154.3, 154.8) for anatomic site and ICD-O codes (8070-8075, 8120, 8123, 8124) for histologic subtype, were included as cases. Up to 5 female controls, matched for age, socioeconomic status, health region and number of years enrolled in the provincial health plan, were selected for each case. The exposure of interest was previous HPV-related gynecologic cancer, specifically cervical cancer, vulvar cancer and vaginal cancer. Conditional logistic regression was performed to assess the relationship between this exposure and SCAC. Results: A total of 674 women with SCAC were identified whose median age was 61. Amongst the cases, there were 7 cervical, 3 vulvar and 1 vaginal cancers compared with 5 cervical, 0 vulvar and vaginal cancers in the 3264 controls. Previous HPV-related gynecological cancer (cervical, vaginal or vulvar cancer) was significantly associated with SCAC (OR: 10.5, 95% C.I.: 3.6 to 30.3). The median time between the diagnosis of anal cancer and previous cervical cancer was 20 years. Conclusions: Previous HPV-related gynecological cancers are strongly associated with anal cancer and may occur decades before the anal cancer. © 2009 Elsevier Inc.

DOI: 10.1016/j.ygyno.2009.05.006


**ABSTRACT:** Apart from cancers of the lower female genital tract, human papillomaviruses (HPV) are associated with a large number of benign, premalignant and malignant lesions at different anatomic sites in both genders. Malignant tumours and their precursors are usually attributed to the oncogenic (high-risk, HR) HPV types, whereas benign lesions (mostly papillomas) are ascribed to the low-risk (LR) HPV types, most notably HPV6 and HPV11. To date, the main interest has been focused on HR-HPV types and their associated pathology, and much less attention has been paid to the lesions caused by the LR-HPV types. The recent licensing of an effective prophylactic vaccine against the 2 most important LR-HPV types (HPV6 and HPV11) has resulted in considerably increased interest in these LR-HPV types as well. This author recently conducted a systematic survey of the annual disease burden due to HPV6/11 infections in Finland. As a rational continuation, the present survey was conducted...
to estimate the annual disease burden due to HPV16 and HPV18 infections in our country. Together, these 2 documents form the foundation for calculations of the annual costs needed to treat the diseases caused by these 2 most common LR and HR HPV types. Similar to HPV6/11, accurate estimates of disease burden are also mandatory for all modelling of the cost-effectiveness of prophylactic HPV16/18 vaccines. In the first step, the published HPV literature was used to create a list of benign, premalignant and malignant lesions associated with this virus at different anatomic sites. The GLOBOCAN 2004 (IARC; International Agency for Research on Cancer) database was used to derive the global numbers of incident cases for each of these malignancies in 2002, and the Finnish Cancer Registry (FCR) website was used to obtain these numbers for Finland (y 2005). The evidence linking HPV to each individual tumour category was classified as: (1) established, (2) emerging, and (3) controversial. All published evidence was weighted for each individual malignant, premalignant and benign lesion, anatomic region-by-region, while assessing the attributable fraction of HPV16/18 genotypes in each lesion. Because benign and most of the precancer lesions are not registered by the FCR or GLOBOCAN, different approaches had to be used to derive the estimates for their incidence, based on published literature or other registries. In cases with no reasonable consensus, a lower and an upper boundary was set for the range of these estimates. Where well established, the different incidence rates among males and females were used to calculate the numbers of incident cases by gender. The present survey implicates that a minimum of 7859 to 8316 new cases of HPV16- or HPV18-associated clinical lesions would be detected each y in Finland, if all were registered. In other words, these numbers represent the annual disease burden due to these 2 most common HR-HPV genotypes. In the Finnish population, these lower and upper limits translate to the crude annual incidence rates of 147/100,000 and 156/100,000, respectively. When adjusted for the European Standard Population, the respective age-adjusted incidence rates are 137/100,000 and 145/100,000. As compared with the annual disease burden of HPV6/11 in this country (12,666 to 13,066 new cases), these numbers for HPV16/18 are significantly smaller. Another major difference between HPV6/11 and HPV16/18 is that the disease burden due to the former is much more evenly distributed among the genders, with only a slight female preponderance (approximately 7500 vs 5500 cases). This is in sharp contrast to HPV16/18 disease burden, of which by far the major proportion is contributed by females (approximately 7000 vs 1300 cases). Of note, these clinical lesions counted in this report for HPV16/18 only represent a small minority of the total viral burden due to the infections by these 2 HR-HPV genotypes. This is because the vast majority of these HR-HPV infections are transient and spontaneously resolve within a few months, without ever developing a clinical disease. However, this spontaneous clearance does not make these latent infections less important, because as long as the virus reservoir exists, it serves as the source of viral transmission to susceptible individuals, with a multitude of HPV16/18-associated pathologies as a potential outcome. The implications of these data in the era of effective prophylactic HPV vaccination should be straightforward. However, the 2 impending challenges for designers of future HPV vaccines and vaccination programmes are: (1) the marked imbalance of HPV16/18 disease burden between the genders, and (2) the fact that HPV6/11 annual disease burden far exceeds that of HPV16/18 and it is also more evenly contributed by both genders. © 2009 Informa UK Ltd.

DOI: 10.3109/00365540903331985

ABSTRACT: In addition to cancer of the lower female genital tract, human papillomaviruses (HPV) are associated with a large number of benign, precancer and cancer lesions at different anatomic sites in both genders. Malignant tumours and their precursors are usually attributed to the oncogenic (high-risk, HR) HPV types, whereas benign lesions (papillomas) are associated with the low-risk (LR) HPV types, most notably with HPV6 and HPV11. Until recently, the main interest in HPV research has been focused on HR-HPV types and their associated pathology, and much less attention has been paid to the lesions caused by the LR-HPV types. With the recent licensing of an effective prophylactic vaccine against the 2 most important LR-HPV types (HPV6 and HPV11), it has become timely to make a systematic survey on the annual disease burden due to these 2 HPV genotypes in our country. These types of data should form the foundation for all calculations of the annual costs needed to treat these diseases by conventional means. Accurate estimates of disease burden are also mandatory for all modeling of the cost-effectiveness of prophylactic HPV6 and HPV11 vaccines. If proven useful for any of these purposes, this document will have fulfilled its purpose. In the first step, published HPV literature was used to create a list of benign, premalignant and malignant lesions associated with this virus at different anatomic sites. GLOBOCAN 2004 (IARC) database was used to derive the global numbers of incident cases for each of these malignancies in 2002, and the Finnish Cancer Registry (FCR) website for obtaining these (y 2005) numbers in Finland. The evidence linking HPV to each individual tumour category was classified as: 1) established, 2) emerging, and 3) controversial. All published evidence was weighted for each individual malignant, premalignant and benign lesion, anatomic region by region, while assessing the attributable fraction of HPV6/11 genotypes in each lesion. Because benign and most of the precancer lesions are not registered by FCR or GLOBOCAN, different approaches had to be used to derive the best estimates for their incidence, based on published literature or other registries (e.g. genital wart registry of the UK and Wales, and mass screening registry of FCR). With a lack of reasonable consensus, a lower and an upper limit was set for the range of estimates. In cases with different age-specific incidence (e.g. genital warts), the population pyramid of Finland was used to calculate the incident cases. Where well established, the different incidence rates among males and females were used to calculate the numbers of incident cases by gender. The malignant neoplasms with established or emerging evidence on the causal role of HPV are listed by their ICD-10 codes in Table I. Included in this list are also 2 controversial malignancies (colorectal cancer and endometrial cancer), of which the contradictory HPV data are critically discussed. The third major cancer in this same category (prostate cancer) was not included in the list, because the data are clearly insufficient to categorize this entity even among the emerging HPV associated malignancies. Estimated disease burden due to HPV6/11 in Finland, calculated as numbers of annual new cases by anatomic region and tumour type is given in Table II, and summarized in Figure 1. The present analysis implicates that a minimum of 12,666 to 13,066 new cases of HPV6- or HPV11-associated clinical lesions would be detected each year in Finland, if all were registered.
Notably, these numbers represent the disease burden due to these 2 HPV types. However, these clinical lesions only represent a small minority of the total viral burden due to the infections by these 2 HPV genotypes. This is because the vast majority of all infections by these ubiquitous viruses are latent, being transient in nature and spontaneously resolving within a few months (up to 1 year), without ever developing a clinically detectable disease. This spontaneous clearance does not make these latent infections less important, however, because as long as the virus reservoir exists, it serves as the source of viral transmission to susceptible individuals, with a multitude of HPV6/11 associated pathologies as a potential outcome, as described in this document. The implications of these data in the era of effective prophylactic HPV vaccination against HPV6 and HPV11 should be clear.

DOI: 10.1080/00365540902887730


ABSTRACT: In 2008, CDC published a supplement to the journal Cancer describing incidence patterns of human papillomavirus (HPV)-associated cancers prior to availability of an HPV vaccine. This report updates the information on HPV-associated female genital cancer incidence with more recent data, adds information on trends, and includes American Indian/Alaska Native (AI/AN) populations. We used combined data from two federal cancer surveillance programs, CDC’s National Program of Cancer Registries (NPCR) and NCI’s Surveillance, Epidemiology, and End Results (SEER) Program, covering 92% of the U.S. population from 1999 to 2004, to examine recent trends and incidence of invasive cervical carcinoma and vaginal and vulvar squamous cell carcinoma (SCC). Incidence of in situ vaginal and vulvar SCC are also presented. The average annual age-adjusted rate of cervical cancer among women of all races/ethnicities was 8.5/100,000. Annual cervical cancer incidence rates were highest but declined more rapidly among Hispanic and black women compared with non-Hispanic and white women. The rate of vulvar cancer among all women was 1.7/100,000 and was higher among white women than other racial groups. Vulvar cancer rates rose among black women (+2.9% per year) and were relatively stable among all other racial and ethnic groups over the 6-year period. Vaginal cancer was rare (rate 0.5/100,000); the rate was higher among black women than other racial and higher among Hispanic women than among non-Hispanic women. A significant decline of vaginal cancer was observed only among black women (+6.2% per year). This article confirms previous findings on racial disparities in HPV-associated female genital cancers. Any post-HPV vaccine declines in these cancers should be interpreted in light of current declines. Enhancing current cancer surveillance systems, combined with special studies to collect data on in situ or precancerous lesions of these cancers, will provide important information in determining the potential impact of the HPV vaccine. © 2009, Mary Ann Liebert, Inc. DOI: 10.1089/jwh.2009.1570


ABSTRACT: Background. We describe the prevalence of 14 common types [human papillomavirus (HPV)-6/11/16/18/31/33/35/39/45/51/52/56/58/59] in vulvar intraepithelial...
1.1 Female Genital Cancers and Disease

neoplasia grades 1 to 3 (VIN 1-3) and HPV genotype-specific infection in relation to the development of VIN 1-3. Methods: Data were analyzed from women enrolled in the placebo arms of three randomized double-blind trials. Anogenital examinations, including collection of labial/vulvar/perineal/perianal swabs, occurred at day 1 and every 6 to 12 months through 48 months. Lesions that were possibly, probably, or definitely HPV related or of unknown etiology were biopsied. Biopsies and swabs were HPV typed. Biopsies were read for endpoint determination (VIN 1-3) by up to four pathologists. Results: Incident infection with HPV-16 was the most common (6.0/100 person-years). The mean time from incident infection to the development of VIN 1-3 was 18.5 months (95% confidence interval, 13.4-23.6). HPV-6 or -11 was observed in 64.5% of VIN 1 and 29.0% of VIN 2/3, whereas HPV-16 was observed in 6.5% of VIN 1 and 64.5% of VIN 2/3. Conclusion: A vaccine that includes both low- and high-risk types could prevent more than half of VIN 1-3 lesions, including the precursor lesions to HPV-related vulvar carcinoma. Understanding the incidence and duration of vulvar HPV infection and risk for progression to VIN 1-3 may inform therapeutic decisions for vulvar disease and mathematical models that assess the cost-effectiveness of vaccination. Copyright © 2009 American Association for Cancer Research. DOI: 10.1158/1055-9965.EPI-09-0067

1.1.3 Risk Factors

SUMMARY

Studies assessing the correlation of current and past smoking on incident HPV infection, persistent infection and invasive cervical cancer evaluated smoking from serum samples and self reported smoking behavior. Current heavy smoking was an independent risk factor for squamous cell cervical cancer (OR 3.2), baseline HPV 16 and 18 viral load was significantly greater with current smokers (P=0.03; P=0.02), and a higher prevalence of high risk HPV was found in current smokers (OR 1.6). Current and past smoking behaviors were independent predictors of HPV persistence and risk of developing cervical lesions. A low level of education did not account for an increased cervical cancer risk and was not an independent risk factor for HPV prevalence. A large study of 20,000 women confirmed early onset of sexual activity as a risk factor for HPV infection. A study of sexually experienced, low income young women demonstrated independent associations between HPV infection and Black race (OR 2.03) and lifetime number of male sexual partners (OR 4.79).


ABSTRACT: The strong correlation between smoking and exposure to oncogenic human papillomaviruses (HPVs) has made it difficult to verify the independent role of smoking in cervical carcinogenesis. Thus, the authors evaluated this role. Five large Nordic serum banks containing samples from more than 1,000,000 subjects were linked with nationwide cancer registries (1973-2003). Serum samples were retrieved from 588 women who developed invasive cervical cancer and 2,861 matched controls. The samples were analyzed for
cotinine (a biomarker of tobacco exposure) and antibodies to HPV types 16 and 18, herpes simplex virus type 2, and Chlamydia trachomatis. Smoking was associated with the risk of squamous cell carcinoma (SCC) among HPV16- and/or HPV18-seropositive heavy smokers (odds ratio = 2.7, 95% confidence interval: 1.7, 4.3). A similar risk of SCC (odds ratio = 3.2, 95% confidence interval: 2.6, 4.0) was found in heavy smokers after adjustment for HPV16/18 antibodies. The point estimates increased with increasing age at diagnosis and increasing cotinine level. This study confirms that smoking is an independent risk factor for cervical cancer/SCC in women infected with oncogenic HPVs. These findings emphasize the importance of cervical cancer prevention among women exposed to tobacco smoke. © The Author 2008. Published by the Johns Hopkins Bloomberg School of Public Health.


Relationship between cigarette smoking and human papilloma virus types 16 and 18 DNA load. *Cancer Epidemiology Biomarkers and Prevention, 18*(12), pp. 3490-3496.

**ABSTRACT:** Background. Although cigarette smoking has been associated with increased human papilloma virus (HPV) detection, its impact on HPV DNA load is unknown. Methods: The study subjects were women who were positive for HPV16 and/or HPV18 at enrollment into the Atypical Squamous Cells of Undetermined Significance - Low-grade Squamous Intraepithelial Lesion Triage Study. Assessments of exposure to smoke and sexual behavior were based on self-report. Viral genome copies per nanogram of cellular DNA were measured by multiplex real-time PCR. Linear or logistic regression models were used to assess the relationship between cigarette smoking and baseline viral load. Results: Of the 1,050 women (752 with HPV16, 258 with HPV18, and 40 with both HPV16 and HPV18), 452 (43.0%) were current smokers and 101 (9.6%) were former smokers at enrollment. The baseline viral load was statistically significantly greater for current compared with never smokers (P = 0.03 for HPV16; P = 0.02 for HPV18) but not for former smokers. Among current smokers, neither HPV16 nor HPV18 DNA load seemed to vary appreciably by age at smoking initiation, smoking intensity, or smoking duration. The results remained similar when the analysis of smoking-related HPV16 DNA load was restricted to women without detectable cervical abnormality. Conclusion: Higher baseline HPV16 and HPV18 DNA load was associated with status as a current but not former smoker. A lack of dose-response relationship between cigarette smoking and viral load may indicate a low threshold for the effect of smoking on HPV DNA load. Copyright © 2009 American Association for Cancer Research.

DOI: 10.1158/1055-9965.EPI-09-0763


ABSTRACT: Background. The purpose of this study was to assess the effect of smoking on the prevalence and incidence of high-risk human papillomavirus (hr-HPV) infection and cervical intraepithelial neoplasia (CIN) in a large sample of Latin American women. METHODS: The study examines baseline data on over 12,000 women included in the Latin American Screening Study (Brazil and Argentina), and over 1000 women followed-up for a period of 36 months. Three groups were formed: never smokers, current, and past smokers. The prevalence of hr-HPV infection and CIN were compared between the study groups. In the prospective analysis, women were controlled at 6-month intervals to assess the cumulative risk of incident hr-HPV infection, smear abnormalities, and CIN. RESULTS: A higher prevalence (21.7%) of hr-HPV infection was found among current smokers as compared to never smokers (16.5%) or past smokers (13.5%). Being a current smoker was significantly (P <0.01) associated with hr-HPV detection (OR = 1.6; 95% CI = 1.2-2.1). Being a current smoker was a significant predictor of incident hr-HPV during the follow-up [Hazards ratio (HR) = 1.4; 95% CI 1.0-1.9]. For incident CIN2+, being a past smoker (HR = 3.6; 95% CI 1.6-9.8) or current smoker (HR = 3.6; 95% CI 1.5-8.6) were the significant independent predictors. Current and past smokers had a significantly increased risk of incident CIN2+ (P <0.01). CONCLUSIONS: Smoking increases the risk of contracting hr-HPV infection and modifies the effect of a persistent hr-HPV infection by further increasing the risk of developing CIN2+. It seems that this effect modification persists over several years after smoking cessation. Copyright © 2009 American Sexually Transmitted Diseases Association. DOI: 10.1097/OLQ.0b013e3181935a7d


ABSTRACT: Background. Cervical cancer risk is associated with low education even in an unscreened population, but it is not clear whether human papillomavirus (HPV) infection follows the same pattern. Methods: Two large multicentric studies (case-control studies of cervical cancer and HPV prevalence survey) including nearly 20 000 women. GP5/GP6 PCR was used to detect HPV. Results: Education level was consistently associated with cervical cancer risk (odds ratio (OR) for 0 and 5 years vs 1-5 years1.50, 95% confidence interval (CI): 1.25-1.80 and 0.69, 95% CI: 0.57-0.82, respectively, P for trend 0.0001). In contrast, no association emerged between education level and HPV infection in either of the two IARC studies. A majority of the women studied had never had a Pap smear. The association between low education level and cervical cancer was most strongly attenuated by adjustment for age at first sexual intercourse and first pregnancy. Parity and screening history (but not lifetime number of sexual partners, husband’s extramarital sexual relationships, and smoking) also seemed to be important confounding factors. Conclusion: The excess of cervical cancer found in women with a low socio-economic status seems, therefore, not to be explained by a concomitant excess of HPV prevalence, but rather by early events in a woman's sexually active life that may modify the cancer-causing potential of HPV infection. © 2009 Cancer Research UK. DOI: 10.1038/sj.bjc.6605224


**ABSTRACT:** Background. Two HPV vaccines prevent infection with HPV-16 and HPV-18, high-risk (cancer-associated) HPV types which together cause approximately 70% of cervical cancers; one vaccine also prevents HPV-6 and HPV-11, which together cause approximately 90% of anogenital warts. Defining type-specific HPV epidemiology in sexually experienced women will help estimate the potential clinical benefits of vaccinating this population.

Objectives: To examine HPV epidemiology in a diverse sample of sexually experienced women, and to determine factors associated with high-risk HPV and vaccine-type HPV (HPV-6, HPV-11, HPV-16 and HPV-18). Study design: Cross-sectional study of 13-26-year-old women (N = 409) who completed a questionnaire and provided a cervicovaginal swab. Swabs were genotyped for HPV using PCR amplification. Logistic regression models were used to determine whether participant characteristics, knowledge, and behaviors were associated with high-risk and vaccine-type HPV. Results: Most women (68.4%) were positive for ≥1 HPV type, 59.5% were positive for ≥1 high-risk type, 33.1% were positive for ≥1 vaccine-type HPV, and 3.5% were positive for both HPV-16 and HPV-18: none was positive for all four vaccine types. In adjusted logistic regression models, Black race (OR 2.03, 95% CI 1.21-3.41) and lifetime number of male sexual partners (OR 4.79, 95% CI 2.04-11.23 for ≥10 partner vs. ≤1 partner) were independently associated with high-risk HPV infection. Conclusions: HPV prevalence was very high in this sample of sexually active young women, but <5% were positive for both HPV-16 and HPV-18, suggesting that vaccination could be beneficial for many individual women who are sexually experienced. © 2009 Elsevier B.V.

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1.2 ANAL CANCER AND DISEASE

1.2.1 Epidemiology

**SUMMARY**

HPV typing of anal cancers has demonstrated the high prevalence of HPV 16 and 18 in anogenital precancerous and cancerous lesions. Two studies have demonstrated high prevalence of HPV in anal cancer; type 16/18 and HPV 16 only prevalence increased from 27% in low grade lesions and 69% in high grade lesions to 89% in invasive anal cancers. The biological mechanisms related to the natural history of HPV infection and progression are still not understood. One recent study of healthy women and anal HPV infection duration and clearance demonstrated similar clearance patterns to cervical HPV infection. The majority of HPV infections cleared in less than 12 months with HPV 59 and 58 taking longer to clear than HPV 16 and 18 (median clearance: 350 days, 252 days, 132 days, and 212 days respectively). Clearance of HPV 16 in anal lesions in HIV positive men having sex with men demonstrated the lowest clearance rate with a retention time of 36 months.
1.2 Anal Cancer and Disease


ABSTRACT: A systematic review was conducted of HPV type distribution in anal cancer and anal high-grade and low-grade squamous intraepithelial lesions (HSIL and LSIL). A Medline search of studies using PCR or hybrid capture for HPV DNA detection was completed. A total of 1,824 cases were included: 992 invasive anal cancers, 472 HSIL cases and 360 LSIL cases. Crude HPV prevalence in anal cancer, HSIL, and LSIL was 71, 91 and 88%, respectively. HPV16/18 prevalence was 72% in invasive anal cancer, 69% in HSIL and 27% in LSIL. The HPV 16 and/or 18 prevalence in invasive anal cancer cases was similar to that reported in invasive cervical cancer. If ongoing clinical trials show efficacy in preventing anal HPV infection and associated anal lesions, prophylactic HPV vaccines may play an important role for the primary prevention of these cancers in both genders. © 2008 Wiley-Liss, Inc.
DOI: 10.1002/ijc.24215

Human papillomavirus genotypes in anal intraepithelial neoplasia and anal carcinoma as detected in tissue biopsies. *Modern Pathology, 23*(1), pp. 144-150.

ABSTRACT: Human papillomavirus (HPV) infection strongly correlates with the development of anal intraepithelial neoplasias and carcinomas; however, few studies have characterized the distribution of the specific subtypes of the virus in the varying grades of dysplasia. This report characterizes the distribution of HPV 16/18 in surgical specimens with anal intraepithelial neoplasia (AIN) I-III and histological variants of anal carcinoma. A total of 111 anal surgical specimens with no dysplasia (10), AIN I-III (53), and anal carcinomas (48) were evaluated for the presence of high-risk HPV infection and subtyped by nested PCR or the Invader Assay. High-risk virus types were detected in progressively greater number of anal intraepithelial lesions from 56% in low grade to 88% in high grade. Type 16 was the prevalent subtype and was noted in 28% of low grade and 68% of high-grade lesions. Moderate dysplasias showed type 16 in 20%, a prevalence similar to that in low-grade lesions. The non-16/18 subtypes of the virus predominated and were present in 50% of the cases. Most (89%) squamous carcinomas were associated with high-risk viruses, 68% with type 16, a prevalence similar to that noted in high-grade dysplasia. Most (89%) squamous carcinomas were associated with high-risk viruses, 68% with type 16, a prevalence similar to that noted in high-grade dysplasia. Most (89%) squamous carcinomas were associated with high-risk viruses, 68% with type 16, a prevalence similar to that noted in high-grade dysplasia. Non-16/18 subtypes were encountered more frequently in squamous carcinomas from immunodeficient individuals (57% cases) as compared with immunocompetent individuals (18% cases). The similarity in the prevalence of type 16 in high-grade dysplasia and squamous carcinomas suggests that anal intraepithelial lesion III is the true precursor of squamous carcinoma and warrants aggressive management. Anal intraepithelial lesions II showed a virus distribution that was similar to low-grade dysplasia. In addition, a subset of these that were associated with type 16 or 18 showed progression, whereas those associated with non-16/18 subtypes regressed, thereby raising the possibility of conservative management for these lesions. © 2010 USCAP, Inc.
DOI: 10.1038/modpathol.2009.143


**ABSTRACT:** Objectives: To study anal intraepithelial neoplasia and its associations with anal and cervical human papillomavirus (HPV), cervical neoplasia, host immune status, and demographic and behavioral risk factors in women with and at risk for HIV infection. Design: Point-prevalence analysis nested within a prospective study of women seen at three clinical centers of the Women's Interagency HIV Study. Methods: In 2001-2003 participants were interviewed, received a gynecological examination, anal and cervical cytology testing and, if abnormal, colposcopy-guided or anoscopy-guided biopsy of visible lesions. Exfoliated cervical and anal specimens were assessed for HPV using PCR and type-specific HPV probing. Logistic regression analyses were performed, and odds ratios (ORs) estimated risks for anal intraepithelial neoplasia. Results: Four hundred and seventy HIV-infected and 185 HIV-uninfected women were enrolled. Low-grade anal intraepithelial neoplasia was present in 12% of HIV-infected and 5% of HIV-uninfected women. High-grade anal intraepithelial neoplasia was present in 9% of HIV-infected and 1% of HIV-uninfected women. In adjusted analyses among HIV-infected women, the risk factors for low-grade anal intraepithelial neoplasia were younger age [OR = 0.59, 95% confidence interval (CI) = 0.36-0.97], history of receptive anal intercourse (OR = 3.2, 95% CI = 1.5-6.8), anal HPV (oncogenic types only OR = 11, 95% CI = 1.2-103; oncogenic and nononcogenic types OR = 11, 95% CI = 1.3-96), and cervical HPV (oncogenic and nononcogenic types OR = 3.5, 95% CI = 1.1-11). In multivariable analyses among HIV-infected women, the only significant risk factor for high-grade anal intraepithelial neoplasia was anal HPV infection (oncogenic and nononcogenic types OR = 76, 95% CI = 1.5-38). Conclusion: Even in the era of highly active antiviral therapy, the prevalence of anal intraepithelial neoplasia was 16% in HIV-infected women. After controlling for potential confounders, several risk factors for low-grade anal intraepithelial neoplasia differed from risk factors for high-grade anal intraepithelial neoplasia. © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins. DOI: 10.1097/QAD.0b013e32831cc101

1.2.1.2 HPV Duration and Clearance


**ABSTRACT:** Background. The association of anal cancer with human papillomavirus (HPV) infection is well established; however, little is known about the epidemiology of anal HPV in healthy women. We investigated patterns of duration and clearance of anal HPV infection in a cohort of healthy women in Hawaii. Methods. Viral and nonviral determinants of anal HPV clearance were examined in a longitudinal cohort study of 431 sexually active women. At baseline and at 4-month intervals, interviews were conducted and cervical and anal cell
3.4

1.2 Anal Cancer and Disease

Specimens were obtained for detection of HPV DNA. Results. Of the 431 women, 50% experienced a total of 414 incident anal HPV infections, reported at ≥1 clinic visits from baseline through a follow-up period of average duration of 1.2 years. Of these infections, 58% cleared during follow-up. The clearance rate for a high-risk anal infection was 9.2 per 100 woman-months (95% confidence interval [CI], 6.9-11.9 per 100 woman-months), with a median duration of 150 days (95% CI, 132-243 days). The slowest clearing high-risk HPV types were HPV-59 (median clearance time, 350 days) and HPV-58 (median clearance time, 252 days). The median clearance times for HPV-16 and HPV-18, the predominant types associated with anal cancer, were 132 days and 212 days, respectively. Nonviral factors that delayed clearance of anal HPV included douching, long-term tobacco smoking, and anal sex.

Conclusions. The majority of anal HPV infections resolve in a relatively short time. Although anal HPV is commonly acquired in healthy women, its rapid clearance suggests limited efficacy of HPV testing as an anal cancer screening tool. © 2009 by the Infectious Diseases Society of America.

DOI: 10.1086/596758


ABSTRACT: Background. Human immunodeficiency virus (HIV)-seropositive men who have sex with men (MSM) are at higher risk of human papillomavirus (HPV) infection. This study was conducted to better understand the natural history of type-specific HPV infection in the anus. Methods. A cohort study was conducted among HIV-seropositive MSM in Montreal to investigate acquisition and loss of anal HPV infection. Participants were followed up every 6 months for 3 years for risk behaviors, HIV related parameters, and HPV testing. Results. HPV DNA was detected in 97.9% of the 247 participants at baseline (median, 5 HPV types). The most common types were HPV-16 (38.2%) and HPV-6 (35.3%). Prevalent HPV-16 infections had the lowest clearance rate (12.2 cleared episodes per 1000 person-months [95% confidence interval (CI), 8.5-17.7]) and a mean retention time of 36 months (95% CI, 32.7-38.8). The highest incidence rates were found for HPV-16 (10.8 new cases per 1000 person-months [95% CI, 8.0-14.7]), HPV-52 (10.8 new cases per 1000 person-months [95% CI, 8.2-14.1]), and HPV-53 (9.8 new cases per 1000 person-months [95% CI, 7.4-13.0]), with cumulative incidences at 36 months of 30%. Conclusions. Multiple HPV types were common in the anal canals of HIV-seropositive MSM. Incidence and clearance rates were not similar among HPV types. Ongoing surveillance of this cohort will help our understanding of the determinants of HPV persistence and progression to lesions. © 2009 by the Infectious Diseases Society of America.

DOI: 10.1086/597207
1.2.2 Burden of Disease


**ABSTRACT:** Objectives: To determine the prevalence and risk factors for anal human papillomavirus (HPV) infection in community-based cohorts of homosexual men in Sydney, Australia. Methods: A cross-sectional study in consecutively presenting participants in the positive Health and Health in Men cohorts in 2005. HPV testing was performed on anal PreservCyt specimens collected from 316 homosexual men (193 HIV-negative, 123 HIV-positive) using the Digene Hybrid Capture 2 (HC-2) assay for detection of low-risk (LR) and high-risk (HR) genotypes. HPV genotype testing was also performed on a subset of 133 men (93 HIV-negative, 36 HIV-positive) using Roche Linear Array (LA) assay. Results: HC-2 detected HPV infection in 79% of men (LR 55%, HR 69%). HIV-positive men were more likely than HIV-negative men to have LR-HPV (OR 3.5, 95% CI 2.1 to 5.7) and HR-HPV (OR 5.5, 95% CI 3.0 to 10.2). LA detected HPV infection in 95% of men (LR 85%, HR 77%). HIV-positive men had a mean of 7.1 HPV types compared to 4.2 in HIV-negative men; the difference was significant for both LR-HPV (p<0.001) and HR-HPV (p<0.001). HPV-16 was detected in 36% of HIV-positive and 27% of HIV-negative men. There was no consistent trend in HPV prevalence with increasing age. HR-HPV detection was associated with anal bleeding for HIV-positive men and anal warts for HIV-negative men. Conclusions: Anal HPV infection was nearly universal in this community-based sample of homosexual men. A wide variety of HPV genotypes were detected, and coinfection with multiple genotypes was common. Anal HPV infection is more prevalent and more diverse in HIV-positive than HIV-negative homosexual men.

DOI: 10.1136/sti.2008.034744


**ABSTRACT:** Purpose: The incidence of anal high-grade dysplasia in men who have sex with men is increasing. Anal cytology that shows atypical squamous cells of undetermined significance is common, nonspecific, and rarely predicts high-grade squamous intraepithelial lesion. We want to know whether Hybrid-Capture II® testing for oncogenic human papillomavirus (human papillomavirus+) in men who have sex with men with atypical squamous cells of undetermined significance is beneficial and whether other predictors of high-grade squamous intraepithelial lesion exist. METHODS: We performed a retrospective chart review of men who have sex with men undergoing anal screening with atypical squamous cells of undetermined significance cytology, Hybrid-Capture® II testing, and biopsy. Records were analyzed for all screenings. RESULTS: A total of 597 men who have sex with men enrolled and had 1,015 atypical squamous cells of undetermined
significance cytology results: 185 (18.2 percent) had high-grade squamous intraepithelial lesion and 156 (84 percent) were human papillomavirus+. The rates for sensitivity, specificity, positive predictive value, and negative predictive value were 84, 53, 29, and 94 percent, respectively. Of 390 low-grade squamous intraepithelial lesion cytology results, high-grade squamous intraepithelial lesion was found in 141 and 127 (90 percent) were human papillomavirus+. Those with previous high-grade squamous intraepithelial lesions or human immunodeficiency virus had increased risk of high-grade squamous intraepithelial lesion (hazard ratio = 2.2 and hazard ratio = 1.95, respectively). Age was not a factor. CONCLUSIONS: Hybrid-Capture II® testing is useful in men who have sex with men with atypical squamous cells of undetermined significance. Referring only those with oncogenic human papillomavirus for biopsy reduces the number requiring this by almost half but some high-grade squamous intraepithelial lesions are missed. History of high-grade squamous intraepithelial lesion and human immunodeficiency virus are predictors of high-grade squamous intraepithelial lesion while screening intervals might be lengthened absent oncogenic human papillomavirus or in those free of high-grade squamous intraepithelial lesion for long periods.

DOI: 10.1007/DCR.0b013e31819736aa

1.3  HEAD AND NECK CANCER

SUMMARY

The association between HPV oncogenic types and posterior naso/oropharyngeal/laryngeal tumors has been substantiated in many studies from multiple countries. HPV 16 was identified as the most common HPV type, detected in 70-90% of tumors. Head and neck cancer occurred more frequently in young populations, incidence rates increased in females, and tumors were more localized to tonsillar crypts in the pharynx. Risk factors included oral sex and numbers of partners.

HPV related tumors in several studies appeared to frequently metastasize to lymph nodes with prognosis about the same or improved using current treatment regimens. High risk HPV was detected in a small case control study of 18 oral squamous cell carcinomas of non-smokers and non-drinkers. Non-smokers and non-drinkers who developed oral cancer were 6.1 times more likely to have an HPV infection than those who did not develop oral cancer. One study among women with known cervical HPV infections found no relationship with concurrent development of oral HPV infections. However, a large study of primary and secondary HPV related cancers in men found a strong association with index and second primary anogenital cancer and oropharyngeal cancers (Standardized Incidence Ratio 1.9 and 3.0), specifically tonsillar cancer following anal cancer (SIR 13.0).

1.3.1 Epidemiology

ABSTRACT: Objectives: We sought to identify the prevalence of human papillomavirus (HPV) in tonsillar squamous cell carcinoma, and to examine the relationship of HPV to prognosis and tumor morphology. Methods: We performed in situ hybridization for HPV and retrospective clinical outcome analysis. Results: Of the 48 patients with tonsillar carcinoma, in situ hybridization identified 35% as HPV-positive tumors. Age matched controls had no evidence of HPV. There was no significant difference between HPV-positive and HPV-negative patients regarding age (p = 0.34), tobacco consumption (p = 0.59), alcohol consumption (p = 0.91), or treatment method (p = 0.39). Forty-four patients were eligible for outcome analysis. The overall rate of recurrence in this population was 25%, and the disease-specific survival rate was 84%. There was no significant difference between the two groups either in the incidence of recurrence (p = 0.14) or in the disease-specific survival rate (p = 0.19). HPV-associated tumors developed from the tonsillar crypts significantly more frequently than did HPV-negative tumors (p = 0.01). Conclusions: As previously described, HPV is significantly associated with squamous cell carcinoma of the tonsil; however, HPV status in our series did not correlate with clinical outcome. Morphologically, we found that HPV-positive tumors had their origin in the tonsillar crypts, whereas HPV-negative tumors arose from the surface epithelium. © 2009 Annals Publishing Company.


ABSTRACT: In the county of Stockholm, between 1970 and 2002, we have previously reported a 3-fold parallel increase in the incidence of tonsillar squamous cell carcinoma (SCC) and the proportion of human papillomavirus (HPV) positive tonsillar SCC. Here, we have followed the above parameters in all patients (n = 120) diagnosed with tonsillar SCC during 2003-2007 in the same area, and also in correlation to our previous data. Ninety-eight pretreatment biopsies were available and presence of HPV DNA and HPV-16 E6 and E7 RNA were tested by polymerase chain reaction (PCR) and RT-PCR. Incidence data were obtained from the Swedish Cancer Registry. Data reported from 1970 to 2002 were also obtained for comparison. HPV DNA was present in 83 of 98 (85%) of the tonsillar SCC biopsies from 2003 to 2007 and 77 of these were HPV-16 positive. HPV-16 E6 and E7 RNA were found in 98% of 52 analyzed HPV-16 positive cases. The proportion of HPV-positive cancers had significantly increased both from 1970 to 2007 (p < 0.0001) as well from 2000 to 2007 (p < 0.01), with 68% (95% confidence interval (CI), 53-81) 2000-2002; 77% (95% CI, 63-87) 2003-2005; and 93% (95% CI, 82-99) 2006-2007. The incidence rate of HPV-positive tumors almost doubled each decade between 1970 and 2007, in parallel with a decline of HPV-negative tumors. In conclusion, the incidence of HPV-positive cancers is still increasing in the County of Stockholm, suggesting an epidemic of a virus-induced carcinoma, with soon practically all tonsillar SCC being HPV positive, as in cervical cancer. © 2009 UICC. DOI: 10.1002/ijc.24339


**ABSTRACT:** Background. The risk of head and neck squamous cell carcinoma (HNSCC) associated with common human papillomavirus types has not been well defined. Methods: We conducted a case-control study of 1034 individuals (486 incident cases diagnosed with HNSCC and 548 population-based controls matched to cases by age, gender, and town of residence) in Greater Boston, MA. Sera were tested for antibodies to human papillomavirus (HPV)6, HPV11, HPV16, and HPV18 L1. Results: HPV6 antibodies were associated with an increased risk of pharyngeal cancer [odds ratio (OR) = 1.6, 1.0-2.5], controlling for smoking, drinking, and HPV16 seropositivity. In HPV16-seronegative subjects, high HPV6 titer was associated with an increased risk of pharyngeal cancer (OR = 2.3, 1.1-4.8) and oral cancer (OR = 1.9, 1.0-3.6), suggesting that the cancer risk associated with HPV6 is independent of HPV16. There was no association between smoking and alcohol use and HPV6 serostatus. Further, the risk of pharyngeal cancer associated with heavy smoking was different among HPV6-seronegative (OR 3.1, 2.0-4.8) and HPV6-seropositive subjects (OR = 1.6, 0.7-3.5), while heavy drinking also appears to confer differing risk among HPV6-negative (OR 2.3, 1.5-3.7) and -positive subjects (OR = 1.3, 0.6-2.9). Conclusions: There may be interactions between positive serology and drinking and smoking, suggesting that the pathogenesis of human papillomavirus in HNSCC involves complex interactions with tobacco and alcohol exposure. © The Author 2008. Published by Oxford University Press on behalf of the European Society for Medical Oncology.

DOI: 10.1093/annonc/mdn643

46. **Jo, V.Y., Mills, S.E., Stoler, M.H., Stelow, E.B. (2009).**


**ABSTRACT:** Papillary squamous cell carcinoma (SCC) is an uncommon variant of SCC in the upper aerodigestive tract. It is most frequently located in the larynx, oropharynx, and sinonasal tract, and is more common in older men. Because of its complex exophytic papillary architecture, histologic assessment of underlying invasion can be challenging. Risk factors and pathogenesis are unclear. We reviewed 31 papillary SCCs of the upper aerodigestive tract seen at our institution over a 17-year period with respect to p16 immunoreactivity and human papillomavirus (HPV) status. Twelve papillary SCCs were associated with invasive SCC in their disease course. In our study, more than two-thirds of papillary SCCs in the upper aerodigestive tract were immunoreactive with antibody to p16 and 68% of those lesions had identifiable high-risk HPV by in situ hybridization. As with other HPV-associated SCCs of the upper aerodigestive tract, the majority of HPV-associated papillary SCCs are oropharyngeal (base of tongue and palatine tonsils), although both sinonasal and laryngeal tumors were also associated with infection (67% and 33% of cases,
respectively). Given the better prognosis of HPV-associated SCCs of the upper aerodigestive tract, it may be prudent to report the p16 and HPV status of these tumors when they are encountered. Copyright © 2009 by Lippincott Williams & Wilkins.

DOI: 10.1097/PAS.0b013e3181b6d8e6


Human papillomaviruses are identified in a subgroup of sinonasal squamous cell carcinomas with favorable outcome. Cancer, 115(12), pp. 2701-2709.

ABSTRACT: Background. The role of human papillomavirus (HPV) in the pathogenesis of squamous cell carcinomas (SCCs) of the sinonasal tract and its clinicopathological implications were evaluated. METHODS: All SCCs of the sinonasal tract diagnosed in the Hospital Clinic of Barcelona from 1981 to 2006 were retrospectively evaluated (N = 60). Clinical and pathological data were reviewed. HPV infection was determined and typed by amplification of HPV DNA by polymerase chain reaction using the SPF-10 primers. p16 INK4a expression was determined by immunohistochemistry. Overall and progression-free survival for HPV-positive and -negative patients was estimated by Kaplan-Meier analysis and by the use of a multivariate Cox proportional hazards model. RESULTS: HPV DNA was detected in tumor tissue of 12 of 60 (20%) patients. HPV16 was identified in 11 tumors and HPV35 in 1. Immunohistochemistry for p16 INK4a stained all HPV-positive and no HPV-negative tumors (P<.001). No differences were observed in terms of site and histological grade or stage at presentation between HPV-positive and -negative tumors. However, HPV-positive patients had a significantly better 5-year progression-free survival (62%; 95% confidence interval [CI], 23%-86% vs 20%; 95% CI, 9%-34%; P = .0043, log-rank test) and overall survival (80%; 95% CI, 20%-96% vs 31%; 95% CI, 15%-47%; P = .036, log-rank test) than patients with HPV-negative tumors. In multivariate analysis, HPV-positive tumors were associated with improved progression-free survival (hazard ratio, 0.21; 95% CI, 0.17-0.98; P = .012). CONCLUSIONS: A subgroup of sinonasal SCCs is associated with HPV infection. These tumors have a significantly better prognosis. © 2009 American Cancer Society.

DOI: 10.1002/cncr.24309


ABSTRACT: Objectives/Hypothesis: To examine the role of HPV status in the etiology, prognosis, and treatment of head and neck squamous cell carcinoma in early larynx malignancies. Study Design: Retrospective. Methods Thirty-eight cases of T1 or carcinoma in situ (CIS) laryngeal lesions were examined for the presence of human papilloma virus (HPV) using an inclusive polymerase chain reaction (PCR)/hybridization technique capable of identifying 37 HPV subtypes. Results: HPV DNA was detected in 6 (16%) of the 38 lesions, representing HPV types 16, 26, 31, 39, and 52, and p16 tumor suppressor protein expression was confirmed in 10 representative cases. This HPV prevalence is higher than that noted in many previous laryngeal cancer studies, possibly due to the relatively large
panel of subtypes screened for in this study. Identification of HPV-26, which has been associated with uterine cervical cancer, in an early laryngeal cancer specimen represents the first evidence of this subtype in a laryngeal carcinoma. Consistent with reports focusing on head and neck squamous cell carcinoma (HNSCC) arising from other subsites within the upper aerodigestive tract, patients with HPV-positive laryngeal carcinomas were of younger age and were somewhat less likely to have a history of tobacco use, although the latter of the two findings did not reach statistical significance. Conclusions: Our findings emphasize the presence of a broad spectrum of HPV types in a relevant proportion of early laryngeal cancers, and together with evidence of an association of HPV tumor status with a more favorable clinical course, provide a rationale for the routine HPV testing of small larynx lesions. © 2009 The American Laryngological. DOI: 10.1002/lary.20509

49. **Bleyer, A. (2009).**


**ABSTRACT:** From 1975 to the mid 1990s, the incidence of cancer in the oral cavity and pharynx (OC/P) declined substantively, in large part because of successful educational and medical campaigns to reduce cigarette smoking and tobacco chewing. Recent data, however, suggest that the incidence trend in young adults has reversed. The current study investigated National Cancer Institute Surveillance, Epidemiology and End Results databases for changes in the incidence of and survival from OC/P cancer. Since the mid 1990s, females in the United States, between 10 and 40 years of age, have had a steady, apparently accelerating, increase in the incidence of these cancers, particularly in females 15-34 years of age. Most of the increase occurred in the salivary glands and tongue, and were of squamous, acinar, and mucoepidermoid morphologic types. All racial/ethnic groups evaluated have shown the incidence trend pattern, with the increase most prominent in non-Hispanic whites. Five-year survival rates for females 15-39 years of age, when diagnosed to have OC/P cancer, show no improvement since 1975. In contrast, older females and males of all ages continue to demonstrate a reduction in incidence and improvement in survival. The observed patterns are consistent with changing sexual mores and increasing orogenital sexual practices in the United States, with transmission of human papillomavirus and potentially other sexually transmitted carcinogenic vectors. If so, the human papillomavirus vaccines will have cancer prevention benefits beyond cervical carcinoma and will be needed increasingly as the incidence of head and neck cancer is projected to continue to rise in young women. © 2009 Elsevier Inc. DOI: 10.1053/j.seminoncol.2009.07.005


ABSTRACT: The association between human papillomavirus (HPV) infection and the development of head and neck cancer has been documented recently. In this study on 86 head and neck cancer patients and 124 controls, data regarding demographics, behavioral risk factors, and risks related to HPV exposure were collected. HPV detection was carried out using polymerase chain reaction in the tumors and in oral exfoliated cells, and HPV typing by a reverse line blot assay specific for 37 HPV types. Sera were tested by an enzyme-linked immunoabsorbent assay specific for HPV proteins. Head and neck cancer cases report significantly more oral-anal contact (P=0.02) and tobacco and alcohol use than controls (P=0.001; P=0.02, respectively). High-risk HPV DNA was detected in 43% of oral washings of cases and 4% of controls (P<0.0001). The association between the presence of high-risk HPV DNA in oral exfoliated cells and in tumor tissues was statistically significant (adjusted P<0.0001). The prevalence of HPV-specific antibodies was significantly higher in cases than in controls (adjusted P<0.0001). These results provide epidemiological and immunological evidence for HR HPV as a strong risk factor (OR=44.3, P<0.0001) for head and neck cancer, even after controlling for age, tobacco and alcohol use. The detection of high-risk HPV DNA in oral exfoliated cells and HPV-specific antibodies in serum can be considered as clinically relevant surrogate markers for the presence of a HPV-associated head and neck cancer, with a high sensitivity (83%) and specificity (88%). © 2009 Wiley-Liss, Inc.

DOI: 10.1002/jmv.21470


ABSTRACT: Background. Evidence is accumulating for the aetiological role of human papillomavirus (HPV) in the pathogenesis of potentially malignant oral mucosal lesions and squamous cell carcinomas. Methods: Paraffin tissue sections from 49 patients with ‘white patches’ of the oral mucosa were investigated histologically, by broad-spectrum PCR followed by genotyping and chromogenic in situ hybridisation (CISH). Results: Histologically, 33 flat hyperplasias and 16 papillary hyperplasias were diagnosed. Twenty-two of 28 samples studied (78.6%) were positive for HPV DNA by PCR and six were negative. The following HPV types were detected in decreasing order of prevalence: HPV 35, HPV 6, HPV16, HPV 53, HPV 18, HPV 51 and HPV 55. Seventeen samples (60.7%) contained high-risk HPV DNA. Using CISH, ≥ 1 HPV signals were detected at least in a few epithelial cells in 95% of cases studied. All but one case were positive with the high-risk HPV probe and all HPV infections contained low viral load. Concordant positive results both by PCR and CISH were detected in 14 of 19 cases (73.7%) analysed. Conclusions: The high prevalence of HPV infection in hyperplastic ‘white patches’ of the oral mucosa supports the putative role of HPV at an early stage of oral carcinogenesis. These results further indicate that the majority of white oral mucosal lesions - flat, exophytic, wart-like or papillary proliferations - could be considered as the clinical manifestations of oral HPV infection. This finding has clinical relevance regarding therapy and patient management and may help in elucidating the role of HPV infection in oral carcinogenesis. © 2008 John Wiley & Sons A/S.

DOI: 10.1111/j.1600-0714.2008.00723.x

Low rate of oral human papillomavirus (HPV) infection in women screened for cervical HPV infection in Southern Italy: A cross-sectional study of 140 immunocompetent subjects. *Journal of Medical Virology, 81*(8), pp. 1438-1443.

**ABSTRACT:** Even though the natural history of cervical and oral human papillomavirus (HPV) infection has been investigated intensely, the possibility that HPV may infect both sites in the same subject is not well documented. This study investigated the frequency of concurrent oral and cervical HPV infection in southern Italian women, in the light of some selected socio-behavioral variables. One hundred forty women (mean age: 36 years), with known cervical HPV status, were analyzed for oral HPV. Age, smoking/drinking habits, clinical and socio-behavioral history were assessed by personal interviews. Oral mucosal cells were collected by oral brushing and HPV DNA was sought by the use of nested PCR amplification followed by direct DNA sequencing and the commercial assay INNOLiPA HPV Genotyping (Innogenetics N.V., Ghent, Belgium). The data were analyzed by using the chi-square test and a logistic regression (logit) model (P<0.05 statistically significant). Oral HPV infection was detected in 2/140 (1.4%) cases, being present in 2/76 (2.6%) women with cervical HPV infection and 0/64 uninfected women (P = 0.19). A lack of type-specific concordance in the two patients with concurrent infection was observed. In the sample of population examined, HPV cervical infection does not seem to predispose to oral transmission, even in the presence of oral-genital sexual habits, thus suggesting the independence of infection at the two mucosal sites. © 2009 Wiley-Liss, Inc.

DOI: 10.1002/jmv.21509


**ABSTRACT:** Objective: To test the hypothesis of a bidirectional association of anogenital and oral cavity/pharyngeal human papillomavirus (HPV)-associated cancers in men. Design: Population-based epidemiological study using the Surveillance, Epidemiology, and End Results cancer database. Setting: Population-based cancer study involving patients receiving care in the United States. Participants: The study included 47,308 men 20 years and older with an index oral cavity/pharyngeal or anogenital cancer. Main Outcome Measure: Second primary HPV-associated cancers (anogenital or oral cavity/pharyngeal) or HPV-unrelated cancers (prostate, bladder, or colon). Results: The standardized incidence ratio (SIR) was elevated for both anogenital cancer following oral cavity/pharyngeal cancer (SIR, 1.9; 95% confidence interval [CI], 1.2-2.7) and oral cavity/pharyngeal cancer following anogenital cancer (SIR, 3.0; 95% CI, 2.1-4.2). The increase in SIR was most pronounced for tonsillar cancer following anal cancer (SIR, 8.4; 95% CI, 2.7-19.6). The risk of second primary HPV-associated cancers did not vary significantly by age, race, year of diagnosis, or geographic location but was greater among never-married men, particularly for anal cancer following oral cavity/pharyngeal cancer (SIR, 6.5; 95% CI, 1.8-16.7 in never-married men, but SIR, 1.6; 95% CI, 0.7-3.1 in ever-married men) and for tonsillar cancer following anogenital cancer (SIR, 13.0; 95% CI, 3.5-33.2 in never-married men, but SIR, 3.8; 95% CI, 1.0-9.7 in ever-married men). Other than a slightly increased risk of
tongue cancer following colon cancer (SIR, 1.3; 95% CI, 1.1-1.6), there was no increased risk of oral cavity/pharyngeal or anogenital cancer following HPV-unrelated cancers or vice versa. Conclusion: The association between index and second primary anogenital and oral cavity/pharyngeal cancers, strongest in never-married men, supports the influence of sexual behavior on the risk of HPV-associated head and neck cancers. © 2009 American Medical Association. DOI: 10.1001/archoto.2009.19

Oropharyngeal carcinoma in non-smokers and non-drinkers: A role for HPV. *Oral Oncology, 45*(6), pp. 486-491.

**ABSTRACT:** Incidence of oropharyngeal squamous cell carcinoma (OSCC) increased 3% annually from 1973 to 2001. OSCC’s can be attributed to tobacco and alcohol, but 25% are unlinked to typical risks. Case-control studies on HPV detection in non-smoking/non-drinking (NS/ND) OSCC patients have not previously been performed. The primary objective of this study was to determine whether high-risk HPV infection was significantly associated with development of oral squamous malignancy in non-smokers/non-drinkers. A chart review of 802 OSCC patients from the UNC Pathology Archives (1995-2006) yielded 40 non-smoker/non-drinker subjects. Utilizing a case-control design, 18 cancer cases and 22 benign biopsy controls were consecutively identified. Biopsy tissue was subjected to (i) HPV-L1 consensus PCR and sequencing (ii) real-time PCR. Chi-square and logistic regression analysis was employed. Logistic regression analysis determined that cases were 6.1 (OR 95% CI, 1.3-28) times more likely to have HPV infection in their tumors than controls. High-risk HPV-DNA was readily detected in the tonsils and base of tongue (oropharynx) of 14/18 cases and 6/22 controls by both consensus and real-time PCR. Of high-risk HPV containing lesions, 85% (17/20) originated in the oropharynx (chi-square, p = 0.03). High risk HPV was also detected in benign biopsies of the oropharynx in 30% (3/10) of individuals who had a previous oral cancer (chi-square, p = 0.006). The infectious nature of OSCC in NS/ND was revealed by consistent detection of HPV, suggesting HPV’s potential role in transforming oral epithelium, providing further evidence of the need to screen the oropharynx for HPV in NS/ND. © 2008. DOI: 10.1016/j.oraloncology.2008.07.008

1.3.2 Burden of Disease


**ABSTRACT:** Objectives: We sought to determine whether the primary tumor burden in oropharyngeal squamous cell carcinoma is lower in tumors positive for human papillomavirus (HPV) or in tumors with a smoking- or alcohol-related cause. Methods: We retrospectively reviewed medical records of patients at our institution who had squamous cell carcinoma of the palatine tonsils, base of tongue, soft palate, or pharynx from 1996 through 2006. The patients underwent primary surgical therapy. The main outcome measures were the HPV status of tumors and nodes and the survival rates (categorized by HPV status). Results: Of
102 treated patients, 48 (47.1%) had HPV-positive carcinomas. Primary tumor size was not significantly different between HPV-positive and HPV-negative tumors (median, 2.5 versus 2.0 cm; p = 0.43.). Patients with HPV had a higher prevalence of neck nodal metastases (35% versus 11%; p = 0.003) and high-grade lesions (83% versus 64%; p = 0.03). Conclusions: Primary tumor burden was not associated with HPV status. Patients with HPV-positive oropharyngeal squamous cell carcinomas had a higher prevalence of neck nodal metastases and high-grade lesions. © 2009 Annals Publishing Company.

1.4 PENILE CANCER

SUMMARY

One systematic review of the literature (30 studies) and one histological analysis of penile tumor tissues (N=145) confirmed the presence of high risk HPV in half of penile cancer cases (47.9-52%) with HPV 16 the most prevalent type.

1.4.1 Epidemiology


ABSTRACT: Objective: Type-specific prevalence data of human papillomavirus (HPV) DNA in penile carcinoma are needed to determine the potential impact of HPV prophylactic vaccines, assuming demonstrated efficacy in men. Methods: A review was conducted using search terms including HPV and penile cancer. Studies using polymerase chain reaction (PCR) assays for HPV DNA detection in invasive penile carcinoma were included. Results: A total of 1,266 squamous cell carcinoma (SCC) cases contributed data from 30 studies. The number of SCC was similar in Europe (28.2%), North America (27.6%), South America (23.9%) and Asia (20.4%). All SCC were histologically confirmed with biopsies for DNA detection. Most commonly used PCR primers were type-specific (35.2%), and combination PCR (18.2%). HPV prevalence was 47.9%, ranging from 22.4% in verrucous SCC to 66.3% for the basaloid/warty subtypes. HPV16 (30.8%), HPV6 (6.7%) and HPV18 (6.6%) were the most prevalent types. HPV16 and/or HPV 18 prevalence was 36.7%. Conclusions: HPV DNA was detected in half of SCC, with HPV16 being the most common type. If proven efficacious in men, prophylactic vaccines targeting carcinogenic types HPV16 and 18 could potentially reduce approximately one-third of incident SCC. © 2008 Springer Science+Business Media B.V. DOI: 10.1007/s10552-008-9276-9


ABSTRACT: A high prevalence of cervical cancer associated high-risk types of human papillomavirus (hrHPV) has been demonstrated in premalignant and invasive squamous cell lesions of the penis, but large studies correlating histological characteristics with HPV status.
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are few in number. Tumour tissues from 145 patients with invasive (n = 116) or in situ (n = 29) penile squamous cell carcinoma were subjected to systematic histological evaluation and were PCR-tested for 14 hrHPV types and 23 low-risk HPV types. Around half (52%) of invasive and nine-tenths (90%) of in situ lesions were positive for a hrHPV type, of which HPV 16 was by far the predominant type (91% of hrHPV-positive lesions). In relation to histological characteristics, hrHPV positivity was statistically significantly more common in high-grade tumours, lesions dominated by small tumour cells, lesions with a high number of multinucleated cells and mitoses, and lesions with a small amount of parakeratosis. In conclusion, about half of invasive penile squamous carcinomas in this study were hrHPV-positive, most notably to HPV 16, and probably arose through in situ lesions whereas the other half of invasive penile lesions appeared to be unrelated to hrHPV. A number of histological characteristics differed significantly between hrHPV-positive and -negative invasive penile carcinomas. © 2009 Blackwell Publishing Ltd.
DOI: 10.1111/j.1365-2613.2008.00636.x

1.5 OTHER POSSIBLE CANCERS

1.5.1. Lung Cancer

SUMMARY
A literature review of HPV and lung cancer articles indicated that HPV was detected in lung cancer (mean incidence 24.5%), association was not restricted to squamous cell carcinomas, and low and high risk HPV types were present (HPV 6, 11, 16, 18, 31, 33).

ABSTRACT: HPV has been identified not only in gynaecological carcinomas but also in tumors of other organs, especially of the oropharynx and upper aero-digestive tract. In this study we focused on the available literature on HPV in lung carcinomas. In total, 53 publications reporting on 4508 cases were reviewed and assessed for the following parameters: continent and region of the study, number of cases, detection method, material type, HPV type, histological subtype and number of the HPV-positive cases. Overall, the mean incidence of HPV in lung cancer was 24.5%. While in Europe and the America the average reported frequencies were 17% and 15%, respectively, the mean number of HPV in asian lung cancer samples was 35.7%. There was a considerable heterogeneity between certain countries and regions. Particular high frequencies of up to 80% were seen in Okinawa (Japan) and Taichung (Taiwan). However, there were also discrepant results within the same region pointing to methodological differences and the need for validation. All lung cancer subtypes were affected and especially the high risk types 16, 18, 31 and 33 as well as the low risk types 6 and 11 were found, the later mainly in association with squamous cell carcinomas. The data suggest that HPV is the second most important cause of lung cancer after cigarette smoking and strongly argues for additional research on this issue. © 2008 Elsevier Ireland Ltd.
DOI: 10.1016/j.lungcan.2008.10.003
1.5 Other Possible Cancers

1.5.2. Breast Cancer

**SUMMARY**

Two retrospective Australian studies found oncogenic HPV in breast carcinoma. Investigation into the role of HPV in breast cancer should continue.


**ABSTRACT:** Background. High-risk human papilloma viruses (HPVs) are candidates as causal viruses in breast cancer. The scientific challenge is to determine whether HPVs are causal and not merely passengers or parasites. Studies of HPV-related koilocytes in breast cancer offer an opportunity to address this crucial issue. Koilocytes are epithelial cells characterised by perinuclear haloes surrounding condensed nuclei and are commonly present in cervical intraepithelial neoplasia. Koilocytosis is accepted as pathognomonic (characteristic of a particular disease) of HPV infection. The aim of this investigation is to determine whether putative koilocytes in normal and malignant breast tissues are because of HPV infection.

Methods: Archival formalin-fixed normal and malignant breast specimens were investigated by histology, in situ PCR with confirmation of the findings by standard PCR and sequencing of the products, plus immunohistochemistry to identify HPV E6 oncoproteins.

Results: Human papilloma virus-associated koilocytes were present in normal breast skin and lobules and in the breast skin and cancer tissue of patients with ductal carcinoma in situ (DCIS) and invasive ductal carcinomas (IDCs).

Interpretation: As koilocytes are known to be the precursors of some HPV-associated cervical cancer, it follows that HPVs may be causally associated with breast cancer. © 2009 Cancer Research UK.

DOI: 10.1038/sj.bjc.6605328

60. **Heng, B., Glenn, W.K., Ye, Y., Tran, B., Delprado, W., Lutze-Mann, L., Whitaker, N.J., Lawson, J.S. (2009).**


**ABSTRACT:** Background. There is increasing evidence that high-risk human papilloma virus (HPV) is involved in cancers in addition to cervical cancer. For example, it is generally accepted that HPV has a role in a significant proportion of head and neck tumours, and it has long been hypothesised that hormone dependent oncogenic viruses, such as HPV may have causal roles in some human breast cancers. A number of reports have identified HPV DNA in breast tissue and breast cancer specimens, but these rely on standard polymerase chain reaction (PCR), which is criticised for its propensity for contamination.

Methods: We have used two different technologies, in situ and standard PCR (with sequencing), and histology based on light microscopy.

Results: We unambiguously demonstrate the presence of high-risk HPV in the cells of breast cancer specimens and breast cancer cell lines. In addition, we also show that the oncogenic characteristics of HPV associated breast cancer are very similar to HPV-associated cervical cancer. Specifically, that putative koilocytes are present in some HPV associated breast cancers.

Interpretation: The above observations indicate a likely causal role...
for high-risk HPV in human breast cancer and offer the possibility of primary prevention of some breast cancers by vaccination against HPV. © 2009 Cancer Research UK. DOI: 10.1038/sj.bjc.6605282

1.6 HIV AND HPV – EPIDEMIOLOGY AND PROGNOSTIC LINKAGES

WHAT ARE THE KNOWN INTERACTIONS BETWEEN INFECTIONS WITH HIV AND HPV?

Since early in the HIV epidemic the increased incidence/prevalence of cervical and anal neoplasia has been noted. Past studies have not been definitive with regard to specific risk factors, natural history, effective interventions, or outcomes. Recent studies have addressed confounders, confirmed that HIV infection increased HPV infection incidence, identified that progression to neoplasia was more rapid, and screening programs were effective in identifying atypical cells/HPV oncogenic serotypes. Questions regarding interventions and screening programs that could be effective to reduce anal HPV infections remain outstanding due to the lack of screening program access by more than 80% of women globally. These women are at greatest risk of cervical cancer due to concomitant HIV infection initiating discussions about the role of HPV immunization in HIV infected individuals.

New data on HIV acquisition in HPV infected individuals has been compared to controls without HPV. High prevalence of HPV infections and cervical dysplasia has been documented in HIV seropositive women. High prevalence of HPV infections and high grade anal dysplasia has been documented in HIV seropositive men. HIV infections in one or both sexually active partners increased high risk HPV prevalence among couples. Risk of HPV associated cancers was elevated among men and women. Among HIV positive women cervical cancer incidence has not decreased and anal cancer incidence has increased in both HIV positive men and women. Odds ratios suggested a 40-50% increased probability of HPV transmission from females to males; two studies have found increased HIV transmission from women to men if the male is HPV infected. These studies need rapid confirmation, presumably from existing data banks, mathematical modeling and large intervention trials with HPV immunization. If proven, HPV immunization could reduce HIV incidence in heterosexual partnerships.

Priority Research

1. HPV immunization studies including antibody response in HIV infected populations with varying immunocompromised levels.

2. Identifying populations at risk of HIV and confirming the possible enhancing role of HPV for transmission of HIV followed by well designed studies to determine if HPV immunization reduces HIV infection.

1.6.1 Epidemiology


Human papillomavirus prevalence, viral load and pre-cancerous lesions of the cervix in women initiating highly active antiretroviral therapy in South Africa: A cross-sectional study. 
BMC Cancer, 9, 275.
ABSTRACT: Background. Cervical cancer and infection with human immunodeficiency virus (HIV) are both important public health problems in South Africa (SA). The aim of this study was to determine the prevalence of cervical squamous intraepithelial lesions (SILs), high-risk human papillomavirus (HR-HPV), HPV viral load and HPV genotypes in HIV positive women initiating anti-retroviral (ARV) therapy. Methods: A cross-sectional survey was conducted at an anti-retroviral (ARV) treatment clinic in Cape Town, SA in 2007. Cervical specimens were taken for cytological analysis and HPV testing. The Digene Hybrid Capture 2 (HC2) test was used to detect HR-HPV. Relative light units (RLU) were used as a measure of HPV viral load. HPV types were determined using the Roche Linear Array HPV Genotyping test. Crude associations with abnormal cytology were tested and multiple logistic regression was used to determine independent risk factors for abnormal cytology. Results: The median age of the 109 participants was 31 years, the median CD4 count was 125/mm$^3$, 66.3% had an abnormal Pap smear, the HR-HPV prevalence was 78.9% (Digene), the median HPV viral load was 181.1 RLU (HC2 positive samples only) and 78.4% had multiple genotypes. Among women with abnormal smears the most prevalent HR-HPV types were HPV types 16, 58 and 51, all with a prevalence of 28.5%. On univariate analysis HR-HPV, multiple HPV types and HPV viral load were significantly associated with the presence of low and high-grade SILs (LSIL/HSIL). The multivariate logistic regression showed that HPV viral load was associated with an increased odds of LSIL/HSIL, odds ratio of 10.7 (95% CI 2.0 - 57.7) for those that were HC2 positive and had a viral load of $\leq$ 181.1 RLU (the median HPV viral load), and 33.8 (95% CI 6.4 - 178.9) for those that were HC2 positive with a HPV viral load $>$181.1 RLU. Conclusion: Women initiating ARVs have a high prevalence of abnormal Pap smears and HR-HPV. Our results underscore the need for locally relevant, rigorous screening protocols for the increasing numbers of women accessing ARV therapy so that the benefits of ARVs are not partially offset by an excess risk in cervical cancer. © 2009 Moodley et al; licensee BioMed Central Ltd.

DOI: 10.1186/1471-2407-9-275


ABSTRACT: Objective: To examine the association between CD4 counts, HPV infection and the risk of cervical neoplasia among HIV-seropositive women. Methods: A cross-sectional observational study was conducted among 1,010 HIV-seropositive women using cytology-based Pap smears. HPV DNA testing using Linear Array genotyping assay (Roche) was carried out in a subset of 191 patients. Multivariable-adjusted prevalence ratios (mPR) and 95% confidence intervals (CIs) were estimated with log-binomial regression. Results: Among 1,010 HIV-seropositive women, the prevalence of AGC/ASCUS, LSIL and HSIL or greater was 8.3, 23.5 and 18.0%, respectively. The risk of cervical lesions was higher with CD4 $<$ 200 cells/mm$^3$ vs. CD4 levels $>$500/mm$^3$. HPV types 16 (41.7%) and HPV 56 (22.2%) were the most common types in HSIL cases. Women with CD4 levels $<$ 200/mm$^3$ had a higher prevalence of HPV types 16 (p < 0.01) and 66 (p = 0.04). No statistical relationship
between cervical lesions and HAART use was found. Conclusion: The burden of HPV infection and HSIL was high and correlated with HIV-induced immunosuppression. HPV 16 was the most common type in HSIL and increased in prevalence with greater immune suppression. Prophylactic HPV 16 vaccination could prevent approximately 40% of HSIL cases. Strengthening screening programs is imperative in this population.

DOI: 10.1007/s10552-009-9475-z


ABSTRACT: Background. HIV-positive men with a history of anal receptive intercourse are at risk for anal cancer. We determined whether human papilloma virus (HPV) biomarkers were correlated with anal pathology in these men. Methods: HPV genotype was determined by PCR/line blot assay. Real-time PCR assays were done for viral load, E6 transcripts for HPV genotypes 16, 18, and 31, and p16 transcripts. Results: The most common oncogenic HPV types were HPV 16 (38%), 18 (19%), 45 (22%), and 52 (19%). HPV types 16, 18, 31, 52, 59, and 68 were associated with high grade histology. The number of HPV genotypes per anal swab was higher for anal intraepithelial neoplasia (AIN) 2/3 than for normal or AIN 1 histology [median, 5 types (interquartile range) (IQR), 3-7 versus 3.5 (IQR), 2-6; P = 0.0005]. HPV 16 viral load was also associated with AIN 2/3 histology. There was no difference in p16 or E6 transcripts between histologic grades. In the multivariable logistic regression model, HPV genotypes 16 [odds ratio, 2.58; 95% confidence interval (95% CI), 1.31-5.08; P = 0.006] and 31 (odds ratio, 4.7; 95% CI, 2.00-11.22; P = 0.0004), baseline CD4 count < 400 cells/ mm3 (odds ratio, 2.96; 95% CI, 1.46-5.99; P = 0.0025), and Acquired Immunodeficiency Syndrome (AIDS)-defining illness (odds ratio, 2.42; 95% CI, 1.22-4.82; P = 0.01) were associated with high-grade histology after adjusting for age. Conclusions: The presence of high-grade anal pathology (AIN 2/3) in HIV-positive men was associated with multiple HPV genotypes, HPV genotypes 16 and 31, and HPV 16 viral load. Copyright © 2009 American Association for Cancer Research.

DOI: 10.1158/1055-9965.EPI-08-1141


ABSTRACT: Background. Data on human papillomavirus (HPV) prevalence are essential for developing cost-effective cervical cancer prevention programs. Methods: In 2005, 710 human immunodeficiency virus (HIV)-positive and 226 HIV-negative Rwandan women enrolled in an observational prospective cohort study. Sociodemographic data, CD4 cell counts, and cervical specimens were obtained. Cervicovaginal lavage specimens were collected, from each woman and tested, for >40 HPV types by a polymerase chain reaction
assay; HPV types 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered primary carcinogenic HPV types. Results. The prevalence of HPV was higher in HIV-positive women than in HIV-negative women in all age groups. Among HIV-infected women, 69% were positive for ≥1 HPV type, 46% for a carcinogenic HPV type, and 10% for HPV-16. HPV prevalence peaked at 75% in the HIV-positive women aged 25-34 years and then declined with age to 37.5% in those ≥55 years old (P trend<.001). A significant trend of higher prevalence of HPV and carcinogenic HPV with lower CD4 cell counts and increasing cytologic severity was seen among HIV-positive women. Conclusions: We found a higher prevalence of HPV infection in HIV-positive than in HIV-negative Rwandan women, and the prevalence of HPV and carcinogenic HPV infection decreased with age. © 2009 by the Infectious Diseases Society of America. DOI: 10.1086/599123


**ABSTRACT:** This study examined the concordance of genital human papillomavirus (HPV) infection in 254 heterosexually active couples and the impact of HIV coinfection. Genital HPV detection was significantly more common among HIV-infected women than among HIV-seronegative women (99 [68%] of 145 women vs. 33 [31%] of 107 women; P<.001); similarly, HPV detection was significantly more common among HIV-infected men than among HIV-seronegative men (67 [72%] of 93 and 65 [43%] of 150 men, respectively; P<.001). HIV-seronegative male partners of HIV-infected women had a significantly greater prevalence of HPV infection than did HIV-seronegative male partners of HIV-seronegative women (38 [58%] of 65 men vs. 27 [32%] of 85 men; P < .001), indicating that HIV coinfection in one partner has a significant impact on the prevalence of HPV genital infection in the other partner. HPV concordance between couples was associated with HIV infection status (P<.001, by Pearson’s 2 test) and was significantly higher among HIV-infected couples than among HIV-seronegative couples. Typespecific sharing of HPV was associated with HIV concordance status (P < .024). HIV-seronegative couples were more likely to share 1 HPV type and were unlikely to share >1 type, whereas HIV-infected or HIV-discordant couples were more likely to share>1 HPV type. Women with a high HPV load frequently shared HPV types with their male partners, suggesting that a high HPV load may play a role in HPV transmission between partners. In conclusion, HIV coinfection in one or both sexually active partners increased HPV prevalence and HPV type-specific concordance. © 2009 by the Infectious Diseases Society of America. DOI: 10.1086/598220


**ABSTRACT:** Background. Although risk of human papillomavirus (HPV)-associated cancers of
the anus, cervix, oropharynx, penis, vagina, and vulva is increased among persons with AIDS, the etiologic role of immunosuppression is unclear and incidence trends for these cancers over time, particularly after the introduction of highly active antiretroviral therapy in 1996, are not well described. Methods - Data on 499,230 individuals diagnosed with AIDS from January 1, 1980, through December 31, 2004, were linked with cancer registries in 15 US regions. Risk of in situ and invasive HPV-associated cancers, compared with that in the general population, was measured by use of standardized incidence ratios (SIRs) and 95% confidence intervals (CIs). We evaluated the relationship of immunosuppression with incidence during the period of 4-60 months after AIDS onset by use of CD4 T-cell counts measured at AIDS onset. Incidence during the 4-60 months after AIDS onset was compared across three periods (1980-1989, 1990-1995, and 1996-2004). All statistical tests were two-sided. Results - Among persons with AIDS, we observed statistically significantly elevated risk of all HPV-associated in situ (SIRs ranged from 8.9, 95% CI = 8.0 to 9.9, for cervical cancer to 68.6, 95% CI = 59.7 to 78.4, for anal cancer among men) and invasive (SIRs ranged from 1.6, 95% CI = 1.2 to 2.1, for oropharyngeal cancer to 34.6, 95% CI = 30.8 to 38.8, for anal cancer among men) cancers. During 1996-2004, low CD4 T-cell count was associated with statistically significantly increased risk of invasive anal cancer among men (relative risk [RR] per decline of 100 CD4 T cells per cubic millimeter = 1.34, 95% CI = 1.08 to 1.66, P = .006) and non-statistically significantly increased risk of in situ vagina or vulva cancer (RR = 1.52, 95% CI = 0.99 to 2.35, P = .055) and of invasive cervical cancer (RR = 1.32, 95% CI = 0.96 to 1.80, P = .077). Among men, incidence (per 100,000 person-years) of in situ and invasive anal cancer was statistically significantly higher during 1996-2004 than during 1990-1995 (61% increase for in situ cancers, 18.3 cases vs 29.5 cases, respectively; RR = 1.71, 95% CI = 1.24 to 2.35, P < .001; and 104% increase for invasive cancers, 20.7 cases vs 42.3 cases, respectively; RR = 2.03, 95% CI = 1.54 to 2.68, P < .001). Incidence of other cancers was stable over time. Conclusions - Risk of HPV-associated cancers was elevated among persons with AIDS and increased with increasing immunosuppression. The increasing incidence for anal cancer during 1996-2004 indicates that prolonged survival may be associated with increased risk of certain HPV-associated cancers.

DOI: 10.1093/jnci/djp205


ABSTRACT: Purpose of review: The incidence of human papillomavirus (HPV)-related cancers has increased among people with HIV infection compared with the general population. This review will describe recent findings in HPV-associated cancer incidence since the introduction of antiretroviral therapy, HPV/disease prevalence at sites other than cervix and anus, and recent data on screening and treatment of anal intraepithelial neoplasia. Recent findings: Consistent with high prevalence of anogenital HPV infection, new data on cervical intraepithelial neoplasia and anal intraepithelial neoplasia in HIV-positive men and women show that the incidence of cervical cancer has not declined since the introduction of antiretroviral therapy and that the incidence of anal cancer is rising. Several studies also highlight high rates of HPV infection and HPV-associated disease at sites other than the cervix and anus, including the penis and the mouth. Treatment methods for anal
intraepithelial neoplasia have been described and show reasonable efficacy. Summary: New data imply that the problem of HPV-related cancers will not decline among HIV-positive men and women in the antiretroviral therapy era, highlighting the need to perform studies to determine if screening and treatment of anal intraepithelial neoplasia will prevent development of anal cancer. Recent data show progress in both these areas. © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins. DOI: 10.1097/COH.0b013e32831a7246


**ABSTRACT:** Objective: Little is known about the interaction between human papillomavirus (HPV) and HIV. This study aimed to explore the association of oncogenic (high risk) and nononcogenic (low risk) HPV with HIV incidence. METHODS: We used 1683 urethral swabs collected at the last follow-up visit of a male circumcision trial conducted in Orange Farm (South Africa). Swabs analyses and HPV genotyping were performed by polymerase chain reaction. We estimated HIV adjusted incidence rate ratios (aIRRs) and 95% confidence intervals (CIs) using survival analysis. Background characteristics, male circumcision status, sexual behavior, HPV status, and other sexually transmitted infections were used as covariates. RESULTS: The prevalence of HR and LR HPV was 14.0% (95% CI: 12.4 to 15.7) and 17.3% (95% CI: 15.6 to 19.2), respectively. When controlling for HR-HPV status, LR-HPV status was not associated with HIV incidence (aIRR = 1.13, 95% CI: 0.40 to 3.16; P = 0.82). When controlling for all covariates, HIV incidence increased significantly with HR-HPV positivity (aIRR = 3.76, 95% CI: 1.83 to 7.73, P < 0.001) and with the number of HR-HPV genotypes (adjusted-P linear trend = 0.0074). CONCLUSIONS: Several explanations could account for our findings. One is that HR-HPV facilitates HIV acquisition. The association of HPV with HIV acquisition requires further investigations. Copyright © 2009 by Lippincott Williams & Wilkins. DOI: 10.1097/QAI.0b013e3181b327e7


**ABSTRACT:** Objective: To review and summarize evidence from clinical, translational and epidemiologic studies which have examined the clinically relevant aspects of HPV type prevalence and cervical dysplasia in HIV-infected women. Methods: Relevant studies were identified through a MEDLINE search. References of identified reports were also used to identify additional published articles for review. Results: HIV-infected women in different geographic regions (such as Zambia, Brazil, Rochester NY) appear to be infected with less prevalent types of HR-HPV as compared to the general population who, across all continents, are more commonly infected with types 16 and 18. Secondly, integration of HPV DNA into the host genome is no longer thought to be a necessary cause of malignant transformation of cervical cells. However, rate of integration appears to differ by the type of HPV. In fact, the types of HPV which appear to be more common in cervical dysplasia...
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of HIV-infected women are the same types which are more likely to require integration for malignant transformation. Finally, HPV types found in HIV-infected women are relatively common and likely to persist. The most common among these types belong to the alpha-9 and -7 species which are the most carcinogenic species. Conclusion: Given that current vaccines target HR-HPV-16/18, the findings from the above mentioned studies may have important implications for the design of HPV vaccines that target the types of HPV associated with disease risk in HIV-infected women. HPV typing and assessment of the physical state (whether it is integrated or episomal) appear to be two valuable parameters for the prognostic evaluation of dysplastic lesions of the uterine cervix. This, however, has not yet been assessed in HIV-infected women. Recent data about the immune response in HPV/HIV co-infection may lead to understanding potential mechanisms for less virulent HPV causing malignant transformation in HIV-infected women. © 2009 Elsevier Inc.

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Increased risk of HIV acquisition among Kenyan men with human Papillomavirus infection. Journal of Infectious Diseases, 201(11), 1677-1685.

ABSTRACT: Background. Few data on the effect of human papillomavirus (HPV) infection on human immunodeficiency virus (HIV) acquisition are available. Methods. HIV-seronegative, sexually active, 18–24-year-old Kenyan men participating in a randomized trial of male circumcision provided exfoliated penile cells from 2 anatomical sites (glans/coronal sulcus and shaft) at baseline. The GP5+/6+ polymerase chain reaction assay ascertained a wide range of HPV DNA types at the baseline visit. The risk of HIV infection was estimated using Kaplan-Meier methods and hazard ratios from proportional hazards models. Results. Of 2168 uncircumcised men with baseline HPV data, 1089 (50%) were positive for HPV DNA. The cumulative incidence of HIV infection by 42 months was 5.8% (95% confidence interval [CI], 3.6%–7.9%) among men with HPV-positive glans/coronal sulcus specimens, versus 3.7% [95% CI, 1.8%–5.6%] among men with HPV negative glans/coronal sulcus specimens (Pp.01). Controlling for subsequent circumcision status, baseline herpes simplex virus type 2 serostatus, and sexual and sociodemographic risk factors, the hazard ratio for HIV infection among men with HPV-positive glans/coronal sulcus specimens was 1.8 (95% CI, 1.1–2.9), compared with men with HPV-negative glans/coronal sulcus specimens. Conclusion. The results suggest an independent increased risk of HIV seroconversion among HPV-positive men. If this finding is confirmed in other studies, HPV prevention could be another tool for HIV prevention.

DOI: 10.1086/652408


ABSTRACT: Background. Persistent infections with oncogenic human papillomavirus
(HPV) types are causally related to cervical cancer. Little is known about the distribution of HPV types, independent risk factors of incidence and persistence, and patterns of persistence in sub-Saharan Africa. METHODS: A cohort of 2040 Zimbabwean women was enrolled in a randomized trial assessing the effect of diaphragm/gel provision on human immunodeficiency virus and HPV acquisition. Data from the study arms were pooled for this analysis because diaphragm/gel provision did not affect HPV acquisition and clearance. Clinicians collected cervical samples for HPV testing at enrollment, 12 months, and exit (median 21 months). RESULTS: HPV prevalence was 24.5% for any HPV type and 16.1% for oncogenic types. HPV incidence at 12 months was 23.3% for any HPV type and 11.4% for oncogenic types. HPV58 had the highest baseline prevalence (5.0%) and incidence (2.4%). Type-specific persistence was 29.8% among all HPV infections over a median of 21 months of follow-up. Baseline predictors of incident HPV infection were younger age, having more than 1 lifetime sexual partner, infrequent condom use, herpes simplex virus-2 positive serology, and having a sexually transmissible infection or a different HPV type at enrollment. Baseline predictors of persistent HPV infection were younger age, having more than 1 lifetime sexual partner, and having a high-risk partner. CONCLUSIONS: The novel association between herpes simplex virus-2 seropositivity and incident HPV infection warrants further investigation. Having a high-risk partner is a potentially modifiable risk factor for persistent HPV infection. The relatively high prevalence of HPV58 has implications for vaccine development. Copyright © 2009 American Sexually Transmitted Diseases Association. DOI: 10.1097/OLQ.0b013e318194eb76


ABSTRACT: Aim: To study the epidemiology of different human papillomavirus (HPV) genotypes in cervical samples of HIV-1-infected women with normal Papanicolau smears. Design: Retrospective analysis of a prospective cohort. Patients and Methods: We selected HIV-1-infected women with 2 consecutive normal Papanicolau smears at baseline and at least 1 baseline and 1 follow-up cervical sample. HPV infection was assessed by second-generation hybrid capture (HC-2) and multiplex polymerase chain reaction (mPCR). HPV genotypes were determined by mPCR. Results: From a cohort of 139 women followed up to 4 years, 93 women meeting the inclusion criteria were analyzed. The mean period between samples was 20 months (range, 6-44 months). HPV baseline prevalence was 63% [59/93; 95% confidence interval (CI), 53% to 73%] using polymerase chain reaction and 41% (38/93; 95% CI, 31 % to 51 %) using HC-2, P = 0.007 (kappa, 0.45; P = 0.001 ). The most prevalent high oncogenic risk genotypes (HR-HPV) were HPV-16 (28%), HPV-33 (18%), HPV-52 (12%), HPV-58 (11%), and HPV-39 (11%). Infection with multiple HPV genotypes was detected in >40% of women. HPV infection persisted at follow-up in 86% (51/59; 95% CI, 77% to 95%) by polymerase chain reaction and 76% (29/38; 95% CI, 62% to 90%) by HC-2. HPV infection persisted in 55% of women with samples available beyond 3 years. The actuarial probabilities of clearance and incidence of HPV infection at 36 months were 16%
and 45%, respectively. Conclusions: HPV infection is highly prevalent and persistent among HIV-1-infected women with normal Papanicolaou smears. HR-HPV genotypes other than HPV-16 (HPV-33, HPV-52) are frequently detected in HIV-infected women. mPCR provides better surveillance of HPV infection than HC-2 methods.

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DOI: 10.1097/QAI.0b013e3181938e63


ABSTRACT: Introduction: Development of cancer after transplantation has rapidly became one of the leading causes of death in kidney transplant recipients with functioning grafts. Anogenital malignant neoplasms may occur with a 14-fold increased incidence, and human papilloma virus (HPV) infection has been recently identified as the leading cause of cervical carcinoma. We report the preliminary findings of a prospective study that evaluated the incidence of HPV infection and cervical carcinoma in a population of kidney transplant recipients. Patients and Methods: The study included 35 female recipients of a deceased donor kidney with at least 6 months of follow-up. All patients underwent a cervicovaginal brushing, an HPV DNA test, and a Papanicolaou test. Results: Twenty-two patients (62.8%) were positive for HPV DNA. Thirteen of 22 HPV DNA-positive recipients (59%) demonstrated a high-risk HPV genotype. No cytologic anomalies were detected in Papanicolaou smears. Conclusions: These preliminary data demonstrated a high incidence of HPV infection in renal transplant recipients. Most of our recipients exhibited a high-risk HPV genotype, which suggests higher aggressiveness of such infection in immunosuppressed patients. The HPV test is useful to monitor patients at higher risk of anogenital malignant neoplasms by identifying the cytologic anomalies at an earlier stage. This ongoing study will investigate the rate of progression of HPV infection and the clinical patterns of HPV-positive cytologic anomalies in renal transplant recipients. © 2009 Elsevier Inc.
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1.7 Recurrent Respiratory Papillomatosis

1.7 Recurrent Respiratory Papillomatosis

Will HPV Vaccination Impact the Burden of Recurrent Respiratory Papillomatosis?

Increasing evidence confirmed HPV 6 and 11 as the etiologic factor for most recurrent respiratory papillomatosis (RRP). Retrospective and prospective studies identified HPV 11 disease was more aggressive and the time course of RRP was impacted by intersurgeon variability, extent and severity of papillomas, and use of adjunct medical therapies. Development of a multi-national database will be important to support modeling and surveillance studies.

Priority Research

1. What impact will HPV vaccination have on the incidence and prevalence of RRP and how will newly developed registries link with other databases to demonstrate time trend changes?

1.7.1 Epidemiology


Abstract: Background. With the recent licensure of a new quadrivalent vaccine, many diseases caused by human papillomavirus (HPV) can now be prevented, including recurrent respiratory papillomatosis (RRP). The purpose of this study was to describe the burden and time course of juvenile onset RRP. Methods: A retrospective chart review was conducted of children with airway papillomatosis at the Hospital for Sick Children in Toronto, Canada, between 1994 and 2004. Statistical methods included descriptive statistics of the cohort, a repeated events survival model, and nonlinear modeling equations to describe the time course of illness. Results: Nine hundred twenty-six surgical procedures in 67 patients were identified through a review of surgical records. The median age at diagnosis was 3.2 years (range, 0.1-14.8 years) and the most common presenting symptom was hoarseness (75%). Adjuvant pharmacologic therapy (interferon or cidofovir) was used in 13 cases (19%). HPV types 6 or 11 were identified most commonly as the etiologic agent. Nonlinear modeling equations (exponential and quadratic) fit the observed data well, and were superior to linear models. Repeated events survival analysis identified significant prognostic variables: surgeon, adjuvant therapy, and anatomic score. A decision rule is presented that allows the time to next surgery to be predicted based on the previous surgery and the anatomic score. Conclusions: Most patients have a decelerating rate of debulking surgeries over time, well described by our nonlinear modeling equations. Factors affecting the time course of RRP include: intersurgeon variability, the extent and severity of papillomas at the time of laryngoscopy, and the use of adjuvant medical therapies. DOI: 10.1097/INF.0b013e318159833e

**ABSTRACT:** Background. We collected rare cases of recurrent respiratory papillomatosis (RRP) undergoing malignant transformation. We sought to identify human papillomavirus (HPV) subtypes in areas of papilloma, dysplasia, and carcinoma and investigate the pattern of protein overexpression. Methods. Three patients whose disease underwent malignant transformation from RRP to carcinoma were subjected to this study. Morphologically distinct areas in the pathology specimen of each patient were diagnosed as papilloma, dysplasia, and carcinoma. Each lesion was separately obtained by laser capture microdissection and was PCR amplified for the presence of HPV. A DNA chip was used to determine the type of HPV in each area. Immunohistochemistry for p53, Ki-67, and pRb was performed. Results. HPV type 6 was present in all specimens tested positive. Expression of p53 and Ki-67 increased with increasing severity of dysplastic change. Conclusion. Although HPV type 11 is most frequently associated with malignant change of RRP, HPV type 6 may also contribute to play an equally important role in RRP carcinogenesis. © 2008 Wiley Periodicals, Inc. DOI: 10.1002/hed.20998


**ABSTRACT:** Background. Studies on HPV infection in pregnant women and HPV transmission to the child have yielded inconsistent results. Methods: To estimate mother-to-child HPV transmission we carried out a prospective cohort study that included 66 HPV-positive and 77 HPV-negative pregnant women and their offspring attending a maternity hospital in Barcelona. To estimate HPV prevalence and genotype distribution in pregnancy we also carried out a related screening survey of cervical HPV-DNA detection among 828 pregnant women. Cervical cells from the mother were collected at pregnancy (mean of 31 weeks) and at the 6-week post-partum visit. Exfoliated cells from the mouth and external genitalia of the infants were collected around birth, at the 6-week post-partum visit, and around 3, 6, 12, and 24 months of age. All samples were tested for HPV using PCR. Associations between potential determinants of HPV infection in pregnant women and of HPV positivity in infants were also explored by logistic regression modelling. Results: Overall cervical HPV-DNA detection in pregnant women recruited in the HPV screening survey was 6.5% (54/828). Sexual behavior-related variables, previous histories of genital warts or sexually transmitted infections, and presence of cytological abnormalities were statistically significantly and positively associated with HPV DNA detection in pregnant women recruited in the cohort. At 418 infant visits and a mean follow-up time of 14 months, 19.7% of infants born to HPV-positive mothers and 16.9% of those born to HPV-negative mothers tested HPV positive at some point during infants’ follow-up. The most frequently detected genotype both in infants and mothers was HPV-16, after excluding untyped HPV infections. We found a strong and statistically significant association between mother’s and child’s HPV status.
at the 6-week post-partum visit. Thus, children of mothers’ who were HPV-positive at the post-partum visit were about 5 times more likely to test HPV-positive than children of corresponding HPV-negative mothers (p = 0.02). Conclusion: This study confirms that the risk of vertical transmission of HPV genotypes is relatively low. HPV persistence in infants is a rare event. These data also indicate that vertical transmission may not be the sole source of HPV infections in infants and provides partial evidence for horizontal mother-to-child HPV transmission. © 2009 Castellsagué et al; licensee BioMed Central Ltd.

DOI: 10.1186/1471-2334-9-74

Perinatal transmission of human papillomavirus DNA. Virology Journal, 6, art. no. 83.
ABSTRACT: The purpose was to study the perinatal transmission of human papillomavirus DNA (HPV-DNA) in 63 mother-newborn pairs, besides looking at the epidemiological factors involved in the viral DNA transmission. The following sampling methods were used: (1) in the pregnant woman, when was recruited, in cervix and clinical lesions of the vagina, vulva and perineal region; (2) in the newborn, (a) buccal, axillary and inguinal regions; (b) nasopharyngeal aspirate, and (c) cord blood; (3) in the children, buccal was repeated in the 4th week and 6th and 12th month of life. HPV-DNA was identified using two methodologies: multiplex PCR (PGMY09 and MY11 primers) and nested-PCR (genotypes 6/11, 16, 18, 31, 33, 42, 52 and 58). Perinatal transmission was considered when concordance was found in type-specific HPV between mother/newborn or mother/child. HPV-DNA genital was detected in 49 pregnant women submitted to delivery. Eleven newborns (22.4%, n = 11/49) were HPV-DNA positive. In 8 cases (16.3%, n = 8/49) there was type specific HPV concordance between mother/newborn samples. At the end of the first month of life three children (6.1%, n = 3/49) became HPV-DNA positive, while two remained positive from birth. In 3 cases (100%, n = 3/3) there was type specific HPV concordance between mother/newborn samples. In the 6th month, a child (2%, n = 1/49) had become HPV-DNA positive between the 1st and 6th month of life, and there was type specific HPV concordance of mother/newborn samples. All the HPV-DNA positive children (22.4%, n = 11/49) at birth and at the end first month of life (6.1%, n = 3/49) became HPV-DNA negative at the age of 6 months. The HPV-DNA positive child (2%, n = 1/49) from 1st to the 6th month of life became HPV-DNA negative between the 6th and 12th month of life and one child had anogenital warts. In the twelfth month all (100%, n = 49/49) the children studied were HPV-DNA negative. A positive and significant correlation was observed between perinatal transmission of HPV-DNA and the immunodepression of maternal variables (HIV, p = 0.007). Finally, the study suggests that perinatal transmission of HPV-DNA occurred in 24.5% (n = 12/49) of the cases studied. © 2009 Rombaldi et al; licensee BioMed Central Ltd.
DOI: 10.1186/1743-422X-6-83

ABSTRACT: Objectives: 1) to develop a National Database of cases of Juvenile onset Recurrent Respiratory Papillomavirus (JoRRP) in Canada; 2) to calculate trends in incidence and prevalence of JoRRP from January 1994 to December 2007 at the national and regional level; and 3) to mathematically model the natural history of JoRRP. Study design: retrospective, multi-center study. Methods: Patient demographics, clinical presentation, Human Papillomavirus (HPV) status, method and timing of treatment, and indicators of disease severity were captured with a standardized case report form. Operative records were retrospectively scored using the Derkay-Coltrera staging system for each operative intervention. Trends in incidence and prevalence of JoRRP from 1994 to 2007 were calculated at a national and regional level using national population census data. A multi-variable mixed effects linear model was used to explore the effect of surgery-specific variables on the inter-surgical interval. Non-linear least-squares regression was used to model the natural history of JoRRP. Results: Development of a National Database of children with JoRRP identified 243 cases that underwent 3021 surgical procedures. The national incidence of JoRRP from 1994 to 2007 was 0.24 per 100,000 children aged 14 years and younger. The prevalence was 1.11 per 100,000 children. The natural history of JoRRP followed a non-linear time course with 64% of cases having a decreasing annual rate of surgery over time. Conclusions: A Canadian National Database of children with JoRRP was successfully developed. Modeling of the natural history of JoRRP may have important clinical and research implications.

DOI 10.1002/lary.20901


ABSTRACT: Objectives: To identify human papillomavirus (HPV) types associated with juvenile onset recurrent laryngeal papillomatosis (RLP) in southern Africa, to determine if there is a correlation between HPV type and disease aggressiveness and to determine the diagnostic and prognostic value of rapid molecular techniques for detection and typing of HPV using laryngeal biopsies. Methods: Laryngeal biopsies from patients undergoing surgery for RLP were screened for HPV using conventional and real-time PCR techniques. Amplicons were sequenced to determine the HPV type involved. Clinical features were correlated with HPV type. Results: HPV was identified in papillomata from 18 out of 19 patients. Only HPV-6 and HPV-11 were identified, with no co-infections. There was 100% concordance between conventional and real-time PCR techniques. Patients with HPV-11 disease required more procedures and tended to have higher Derkay scores than those with HPV-6 disease. The HPV types identified in our patients were genetically similar to HPV types from geographically distinct regions. Conclusions: RLP in our patient population appears to be exclusively due to HPV-6 or HPV-11. HPV-11 disease appears to be more aggressive than HPV-6 disease. Identification of the HPV types provides motivation for inclusion of vaccines against these types in vaccination programs to protect women against infection and subsequently reduce the incidence of RLP © 2009.

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1.8 GENITAL WARTS

WHAT IS THE BURDEN OF HPV DISEASE CAUSED BY GENITAL WARTS?

Studies have confirmed the burden of disease from anogenital warts (AGW) and provided case data to evaluate potential benefits from vaccination strategies. Spain reported overall prevalence of 203/100,000 cases of AGW in men and 162/100,000 in women, corresponding to an estimated 56,000 cases each year. Mean number of visits for treatment were 3.8 with newly diagnosed AGW. Imiquimod was the most common procedure (47%) followed by cryotherapy (44%). More than half of AGW in Australia required only one treatment, with 78% treated with cryotherapy. In Manitoba, age standardized incidence rates were 149/100,000 for men and 170/100,000 for women in 1992; prevalence in 2004 was 165.2/100,000 in men and 128.4/100,000 in women. Costs for treatment were identified as 47 million Euros (third party payer) in Spain, while in Canada the average cost per episode ranged from $176 (men) to $207 (women).

Priority Research

How do we measure the impact of HPV vaccination on a wider range of HPV related diseases and can this information be used to justify expansion of vaccination to both genders?


ABSTRACT: Background. Genital warts (GW) are common and increasing in young people. Ninety percent of GW are due to Human Papillomavirus (HPV) types 6 and 11. The objective of this study was to assess the epidemiology and management costs associated with GW in Spain. Methods: A 1-year (2005) retrospective observational study was performed among a sample of gynaecologists, dermatologists and urologists in six autonomous regions in Spain. Men and women with newly diagnosed, recurrent or resistant GW were included. We estimated the incidence (new and recurrent cases) and prevalence (also including resistant cases) of GW. Healthcare resource use were collected and combined with unit costs to assess the mean cost of GW management per patient. These figures were extrapolated to the 14- to 64-year-old Spanish population to estimate the total cost of GW management from the Third Party Payer (TPP) and societal perspectives. Results: The overall annual incidence of GW was estimated at 160.4 cases per 100,000. Overall prevalence was calculated as 182.1 cases per 100,000, corresponding to 56,446 GW cases annually (14- to 64-year-old population). The mean management cost was €833 and €1056 per patient from the TPP and societal perspective, respectively. The overall annual cost was estimated at €47 million and €59.6 million, from the TPP and societal perspective, respectively. Conclusion: This study provides a first overview of the burden of GW in Spain. A quadrivalent HPV vaccine that prevents HPV 6, 11, 16, 18 related diseases will have the potential to significantly decrease the socio-economic burden associated with GW in Spain. © The Author 2008. Published by Oxford University Press on behalf of the European Public Health Association.

DOI: 10.1093/eurpub/ckn127


**ABSTRACT:** Background. The placebo arm of human papillomavirus (HPV) vaccine trials helps define the natural history of genital warts (GW). Methods. Women enrolled in the placebo arm (n = 8800) of 2 randomized trials of a quadrivalent vaccine were examined for the presence of GW for up to 9 visits over 4 years. A comprehensive examination of the perianal area, vulva, and vagina prompted biopsy. Biopsy samples were analyzed by a blinded panel of up to 4 histopathologists and tested for 14 HPV genotypes (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) by use of a polymerase chain reaction-based assay. Risk factors for the development of GW were assessed. Results. Women were followed up for an average of 3.6 years (range, 0-4.9 years). Overall, 298 (3.4%) of 8800 participants developed GW related to HPV-6 or HPV-11 (incidence rate, 0.87 cases per 100 person-years-at-risk). In total, 520 distinct lesions were diagnosed as GW. HPV DNA was detected in 472 (90.8%) lesions, with HPV-6 and HPV-11 detected in 447 (86.0%) of these lesions (94.7% of 472 HPV DNA-positive lesions). We found high-risk HPV types in 161 (31.0%) of 520 lesions. Risk factors for HPV-6-and HPV-11-related GW included infection at baseline, acquisition of new sex partners, a higher number of sex partners, and DNA positivity at baseline for a high-risk HPV type. Conclusions. We confirm the major role played by HPV-6 and HPV-11 in GW, as well as associated risk factors. A vaccine that includes these types of HPV could substantially reduce the overall burden of HPV disease. Trial registration. ClinicalTrials.gov identifiers: NCT00092521 and NCT00092534. © 2009 by the Infectious Diseases Society of America. DOI: 10.1086/597071


**ABSTRACT:** Background. A vaccine has recently been licensed in many countries that protects against the human papillomavirus types 6,11,16, and 18. Types 6 and 11 account for approximately 90% of anogenital warts (AGWs). We describe the 20-year trends in the incidence and prevalence of AGWs in Manitoba, Canada. Methods: We used linked population-based hospital and physician databases for Manitoba for 1984 to 2004. Cases were identified using tariff (billing) and ICD codes. A case was considered to be incident if it was preceded by a 12-month interval free period of AGWs care. Otherwise, it was deemed to be prevalent. An episode was considered over once a 12-month interval had elapsed without an AGW claim. Results: Approximately 25,000 Manitobans were diagnosed with AGWs between 1985 and 2004. The annual age-standardized incidence rates peaked in 1992 (men, 149.9/100,000; women 170.8/100,000). In recent years, the rates have been increasing again, particularly for men. The male:female incidence rate ratio increased from 0.76 in 1985 to 1.25 in 2004. The highest incidence rate tended to be in those aged 20 to 24 years. Trends in prevalence were similar. Prevalence in 2004 was 165.2/100,000 for men.
and 128.4/100,000 for women. Conclusions: These population-based findings suggest that AGWs are a substantial burden to Manitobans and that their pattern has changed over time, with incidence and prevalence becoming higher in men than women. Monitoring the future trends in AGWs will provide an early marker of the effectiveness and duration of protection of human papillomavirus vaccination at a population level. © 2009 American Sexually Transmitted Diseases.

DOI: 10.1097/OLQ.0b013e318198de8c


ABSTRACT: Background. External genital warts are a common sexually transmitted viral disease. We describe the patterns of treatment for initial presentations of external genital warts (EGWs) in Australian sexual health centers. Methods: This was a retrospective audit of 489 case notes from consecutive individuals who presented with a new diagnosis of EGWs to 1 of 5 major sexual health clinics in Australia. Eligibility criteria were consecutive patients aged 18 to 45 years inclusively, presenting with first ever episode of EGWs from January 1, 2004. Exclusion criteria were patients who were immunocompromised, including HIV infection, or enrollment in a treatment study for EGWs. Results: The median age at presentation of women was 23.2 years and of men 26.8 years. One quarter (n = 127) of patients had another sexually transmitted infection diagnosed at presentation. Nearly half of the patients (n = 224) presented only once for treatment. Most often, patients were treated with a monotherapy (n = 382/489; 78%), usually cryotherapy (257; 53%). Staff applied treatment in 361 (74%) cases. There was wide variation across sites, possibly reflecting local policies and budgets. We found no difference in wart resolution (n = 292; 60%) by initial treatment chosen. Conclusions: The diagnosis and treatment of genital warts constitute a sizable proportion of clinical visits to the audited sexual health services and require a large input of staff time to manage, including the application of topical treatments. Our results help complete the picture of the burden of EGWs on Australian sexual health centers before the introduction of the HPV vaccine. © 2009 American Sexually Transmitted Diseases.

DOI: 10.1097/OLQ.0b013e3181971e4e


ABSTRACT: Objectives: To determine the average cost of a case of genital warts, for both males and females, with a view to informing the current debate as to which Human papillomavirus vaccine would have maximum cost-effectiveness in the Irish population. Methods: Contact time between patients and healthcare professionals was prospectively measured at five genitourinary medicine clinics in the south-west of Ireland, over a period of 3 weeks. By identifying all those with genital warts, it was possible to calculate the proportion of total time taken by patients with this condition, and from this to calculate a cost per incident case, by gender. Results: A total of 25.5% of attendances were for genital
warts, and these patients used 26.2% of total clinic time (CI 25.4 to 27.0%). The average cost calculated for genital warts was €335 per incident case, and by gender €300 per male case and €366 per female case. Conclusions: There are considerable costs associated with the treatment of genital warts, with female cases representing a higher cost than males. By vaccinating with the quadrivalent HPV vaccine, there are significant savings to be made.

DOI: 10.1136/sti.2008.033837


Epidemiology and Costs Associated with Genital Warts in Canada. Sexually Transmitted Infections, 85(2), 111-115.

ABSTRACT: Background. Genital warts (condyloma acuminatum) remain one of the most commonly reported sexually transmitted infections (STI) worldwide. Most genital warts are caused by non-oncogenic human papilloma virus. Recurrence is common and many patients receive several rounds of treatment. There are limited data in the literature on the burden of illness and costs associated with genital warts at a population level. Methods: Episodes of anogenital warts (AGW) were identified from the physician billing database, hospitalisation records and STI clinics from 1998 to 2006. To be included from the physician billing and STI databases, the person had to have a claim that had a diagnosis of condyloma acuminatum (078.11), viral warts (078.1), viral warts unspecified (078.10) or other unspecified warts (078.19), as well as one of the relevant fee codes associated with the treatment of AGW. To be included from the hospital database, the person could be of any age and have a diagnosis of AGW (A63.0), condyloma acuminatum (078.11), viral warts (078.1 or B07), viral warts unspecified (078.10) or other unspecified warts (078.19) in any of the diagnosis fields, as well as one of the relevant procedure codes associated with the treatment of AGW. Results: A total of 39 493 people was diagnosed with AGW and during this period they had a total of 43 586 episodes. The average cost per episode of AGW was $C190 ($C176 for men; $C207 for women). The majority of treatment was with ablative therapy alone (98%). Conclusions: AGW are associated with a significant burden of illness and costs to the healthcare system.

DOI:10.1136/sti.2008.030999
1.9 WHAT OTHER CONDITIONS ARE ASSOCIATED WITH HPV?

SUMMARY

Case studies demonstrated increased susceptibility to HPV oral lesions and cancers in patients with warts, hypogammaglobulinemia, infections, and myelokathexis syndrome (WHIM) and Heck's disease.

1.9.1 Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM)


ABSTRACT: WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome is an autosomal dominant disease related to a mutation in the chemokine receptor CXCR4 resulting in altered immune function. An increased susceptibility in these patients to human papillomavirus (HPV) manifests as cutaneous warts and, in women, cervical dysplasia and squamous carcinoma. HPV-related squamous carcinoma in other sites has not been documented. We report the occurrence of HPV-related squamous cell carcinoma of the oral cavity in 2 siblings with WHIM syndrome, whose pedigree has previously been described. © 2010 Mosby, Inc.
DOI: 10.1016/j.tripleo.2009.08.011

1.9.2 Heck’s Disease


ABSTRACT: Heck’s disease or focal epithelial hyperplasia is a benign contagious disease caused by human papillomavirus types 13 or 32. It occurs with low frequency in the Iranian population. This condition is characterized by the occurrence of multiple, small papules or nodules in the oral cavity, especially on the labial and buccal mucosa and tongue. In some populations, up to 39% of children are affected. Conservative surgical excision of lesions may be performed for diagnostic or aesthetic purposes. The risk of recurrence after this therapy is minimal, and there seems to be no malignant transformation potential. In the present work, we presented the clinical case of a 12-year-old Iranian girl with oral lesions that clinically and histologically correspond to Heck’s disease.
1.10 HPV TRANSMISSION

1.10.1 Oral Sexual Behaviors, Virginity, and New Relationships

SUMMARY
The odds of men developing oral HPV infection significantly increased with increased lifetime number of oral or vaginal sex partners (P=.002; P=.001). In a study of college aged men the odds of developing oral HPV infections only increased with an increase in the number of recent open-mouthed kissing partners (P=.023). HPV infections have been found in young women without any history of sexual activity or sexual abuse (3.6% for low risk HPV, 13.6% for high risk HPV). HPV infections among newly formed couple relationships suggested a high probability of transmission among those engaging in vaginal sex (64% rate of infection) and with current partners infected with HPV. A recent study demonstrated a close association between HPV genotypes present on anogenital hairs and risk of genital warts (OR 13.0 for perianal, 16.0 for pubic, 20.0 for scrotal).

Studies about HPV infections among men and couples in new relationships confirmed lifetime number of sex partners as a significant risk factor for HPV acquisition.

ABSTRACT: Oral human papillomavirus (HPV) infection is a cause of oropharyngeal cancer. We investigated whether sexual behaviors that elevated the odds of oropharyngeal cancer developing in a case-control study similarly elevated the odds of oral HPV infection developing among control patients. HPV infection was detected in 4.8% of 332 control patients from an outpatient clinic and in 2.9% of 210 college-aged men (age range, 18-23 years). Among control patients, the odds of infection developing independently increased with increases in the lifetime number of oral (P = .007, for trend) or vaginal sex partners (P = .003, for trend). Among college-aged men, the odds of oral HPV infection developing increased with increases in the number of recent oral sex partners (P = .046, for trend) or open-mouthed kissing partners (P = .023, for trend) but not vaginal sex partners. Oral sex and open-mouthed kissing are associated with the development of oral HPV infection. © 2009 by the Infectious Diseases Society of America.
DOI: 10.1086/597755

ABSTRACT: Objective: The aim of our study was to determine the prevalence and the natural course of anogenital human papilloma virus (HPV) infections in girls prior to coitarche attending an outpatient gynecological unit. Study Design: Specimens were taken from the anogenital region of 114 unselected 4-15 year old girls who were referred consecutively for various gynecological problems. Results: Four girls were excluded because of sexual abuse. Low-risk HPV-deoxyribonucleic acid (DNA) was detected in 4 girls (3.6%) and high-risk HPV DNA in 15
1.10 HPV Transmission

children (13.6%). Two girls testing positive for HPV DNA had clinical apparent warts. After 1 year, 2 children had persistent high-risk HPV DNA, and in 1 case we found a switch from high-risk to low-risk HPV DNA. Conclusion: Subclinical genital low- and high-risk HPV infections are common in girls without any history of sexual abuse or sexual activity. We found persistence of genital HPV infection in children, which could be a reservoir for HPV-associated diseases later in life. © 2009 Mosby, Inc.


ABSTRACT: Background: No studies have examined human papillomavirus (HPV) infections among couples early in their sexual relationships when transmission is most likely. Our objective was to describe the distribution of HPV infections among recently formed couples, using the partnership as the unit of analysis. Methods: Women aged 18-24 years attending a university or junior college in Montreal enrolled in a longitudinal study with their new male partners. Self-collected vaginal swabs and clinician-collected swabs from the penis and scrotum were tested for 36 HPV genotypes. Participants self-reported sexual behavior in computerized questionnaires. We analyzed patterns of genital HPV infection in 263 couples using data obtained at enrollment. Results: Couples had engaged in vaginal sex for a median of 3.9 months. HPV was detected in 64% (169/263) of couples. In 41% (109/263), both partners harbored the same HPV type—nearly 4 times more than expected if HPV status of partners were uncorrelated. There were 583 type-specific HPV infections among 169 couples for whom at least one partner was infected. Of these, 42% were of the same type for both partners (95% confidence interval = 36%-47%). This rose from 25% among those engaging in vaginal sex for less than 2 months to 68% among those at 5 to 6 months. Conclusions: Although HPV is common, detection of the same type in persons initiating a sex relationship would be rare given type-specific prevalence rates. The high degree of concordance we found suggests a high probability of transmission. © 2009 by Lippincott Williams & Wilkins.

DOI: 10.1097/EDE.0b013e3181c1e70b


ABSTRACT: Background: We evaluated the influence of the partner’s human papillomavirus (HPV) status and sexual practices on prevalent HPV infection among new couples to study HPV transmission. Methods: Women attending university or college in Montreal, Canada, and their male partners (N = 263 couples) were enrolled in 2005-2008. HPV typing was done in self-collected vaginal swabs and clinician-collected penis and scrotum swabs. The outcome measures were overall and type-specific HPV prevalence. Results: HPV was detected in 56% of women and men. Prevalence was higher among persons with infected partners (85%) than in those whose partners were negative (19%). Type-specific detection was substantially higher among women (OR = 55.2, 95% CI: 38.0-80.1) and men (OR = 58.7, 95% CI: 39.8-86.3) if their partner harbored the type under consideration. Prevalence among women and men with 10 or more lifetime partners was 15.4 (95% CI: 5.9-40.2) and 9.5 (95% CI: 4.4-19.8) times higher
than among those with 1 partner. Frequent condom use was protective in men, particularly if his partner was HPV-infected (OR = 0.64, 95% CI: 0.50-0.82). This effect was attenuated among women with an infected partner (OR = 0.88, 95% CI: 0.69-1.11). Conclusions: The current partner’s status was the most important risk factor for prevalent HPV infection. Condoms exerted a stronger protective effect among men than among women. Copyright © 2009 American Sexually Transmitted Diseases Association DOI: 10.1097/OLQ.0b013e3181b35693


ABSTRACT: Background. Our understanding of factors associated with acquisition and clearance of human papillomavirus (HPV) in men has been limited. This study sought to determine factors associated with those aspects of HPV infection in a cohort of US men. Methods. A total of 285 men aged 18-44 years were monitored every 6 months for ~18 months. Risk-factor information was obtained at each visit by use of a self-administered questionnaire. A continuous-time 2-state Markov model was applied. Results. Lifetime number of sex partners reported at enrollment was the most significant risk factor for acquisition of all types of HPV. Men reporting >16 lifetime sex partners were at significantly elevated risk of any HPV infection (adjusted hazard ratio [AHR], 2.8 [95% confidence interval (CI), 1.1-7.1]), oncogenic HPV infection (AHR, 9.6 [95% CI, 2.4-37.8]), and nononcogenic HPV infection (AHR, 3.6 [95% CI, 1.3-9.9]), compared with those reporting 0-4 partners. Circumcised men were 3 and 6 times more likely to clear infection with any and oncogenic HPV types, respectively. In addition, having had >16 lifetime sex partners was associated with greater likelihood of clearance of oncogenic HPV infection (AHR, 4.9 [95% CI, 1.2-19.8]). Conclusion. The key factor associated with acquisition of HPV was lifetime number of sex partners, whereas circumcision was the most significant determinant for clearance of any HPV infection and oncogenic HPV infection. © 2009 by the Infectious Diseases Society of America.
DOI: 10.1086/596050

Anogenital hairs are an important reservoir of alpha-papillomaviruses in patients with genital warts. Journal of Infectious Diseases, 199(9), pp. 1270-1274

ABSTRACT: Human papillomaviruses (HPVs) were detected in 69 (43.7%) of 158 and in 7 (4.5%) of 155 anogenital hairs obtained from 53 patients with genital warts (GWs) and from 53 age-matched healthy control subjects, respectively. At least 1 hair sample was positive for 69.8% of patients and for 13.2% of control subjects. For patients, HPV was detected in 64.2%, 39.6%, and 26.9% of hairs plucked from the pubic, scrotal, and perianal regions, respectively. For 91.9% of patients, the same HPV genotype was identified in GWs and hairs from at least 1 sampling site. Having GWs was found to be strongly associated with the presence in anogenital hairs of the HPV genotype causing the GWs (range of odds ratios, 13.0-20.0). © 2009 by the Infectious Diseases Society of America.
DOI: 10.1086/597619


**ABSTRACT:** Human papillomavirus (HPV) causes cervical cancer and is strongly associated with other anogenital cancers. Multiple-type HPV infection has been associated with lengthier infection and precancerous lesions. Little is known about multiple-type HPV prevalence and associated factors in men. We examined the prevalence of and risk factors for multiple-type HPV in primarily asymptomatic men. Detection of 37 HPV types in male anogenital epithelium and semen was completed in 463 men in two U.S. cities. The proportions of men with multiple HPV of any type and with multiple oncogenic or nononcogenic types were calculated. Factors associated with multiple HPV were evaluated using multinomial logistic regression. Overall, 22.9% of men had multiple-HPV, 8.6% of men had multiple oncogenic types, and 13.4% had multiple nononcogenic types. Greater proportions of samples at the shaft, glans/corona, and scrotum had multiple HPV types (18.7%, 12.8%, and 73%, respectively) than did other anogenital sites (all <2.8%). Factors independently associated with multiple-type HPV were Hispanic ethnicity [adjusted odds ratio (AOR), 2.45; 95% confidence interval (95% CI), 1.05-5.67], concurrent detection of genital warts (AOR, 10.40; 95% CI, 1.12-96.6), smoking ≥10 cigarettes/d (AOR, 3.00; 95% CI, 1.07-8.43), greater lifetime number of female sexual partners (AOR, 13.73 for ≥21 versus 1-5; 95% CI, 5.34-35.3), and condom use less than half the time (AOR, 2.03; 95% CI, 1.07-3.84). Detection of multiple HPV types in this study of primarily asymptomatic men was common, particularly at external genital sites. Lifetime number of female sex partners, condom use, and smoking were modifiable factors associated with multiple HPV. Copyright © 2009 American Association for Cancer Research. DOI: 10.1158/1055-9965.EPI-08-0447


**ABSTRACT:** Background: A vaccine to prevent human papillomavirus (HPV) 6, HPV 11, HPV 16, or HPV 18 and associated diseases is licensed for females, and it may be licensed for men in the future. There are limited data on HPV 6/11, 16, and/or 18 seroprevalence in men. Methods: A total of 490 men aged 18 to 40 years were enrolled in a study of HPV in men in Tucson, AZ, and Tampa, FL. Enrolled men completed a self-administered questionnaire, and HPV serology was performed using HPV 6/11, 16, and 18 VLP assays. Results: Overall, seroprevalence to HPV 16 was 12.1%, HPV 6/11 was 9.7%, and to HPV 18 was 5.4%. Seroprevalence to HPV 6/11, 16, and/or 18 was 21% and was highest among 35 to 40 year olds (48%); prevalence in this age group was significantly higher compared to the 18 to 24 year olds (adjusted odds ratio [aOR] 6.8, 95% confidence interval [CI] 3.7, 12.8). Independent predictors of seropositivity to HPV 6/11, 16, and/or 18 were older age, greater number of female sex partners in the past 3 months, and current smoking. Conclusions: HPV vaccine-type seroprevalence was highest in 35 to 40 year old men. These data on the epidemiology of HPV seroprevalence in men are
useful for discussions regarding recommendations for HPV vaccine if licensed for use in men. Copyright © 2009 American Sexually Transmitted Diseases Association.
DOI: 10.1097/OLQ.0b013e3181bc094b

Adsorption of Human Papillomavirus 16 to live human sperm. PLoS ONE, 4(6), art. no. e5847.

ABSTRACT: Human Papillomaviruses (HPVs) are a diverse group of viruses that infect the skin and mucosal tissues of humans. A high-risk subgroup of HPVs is associated with virtually all cases of cervical cancer [1-3]. High-risk HPVs are transmitted sexually; however, the exact mechanisms by which sexual contact promotes virus infection remain uncertain. To study this question we asked whether capsids of HPV type 16 (a high-risk HPV) specifically interact with sperm cells. We tested if purified HPV16 virions directly adsorb to live human sperm cells in native semen and in conditions that resemble the female genital tract. We found that HPV16 capsids bind efficiently to two distinct sites at the equatorial region of the sperm head surface. Moreover, we observed that the interaction of virus with sperm can be reduced by two HPV infection inhibitors, heparin and carrageenan. Our findings suggest that 1) sperm cells may serve as motile carriers that promote virus dispersal and mucosal penetration, and 2) blocking interactions between HPV16 and sperm cells may be an important strategy for the development of antiviral therapies. © 2009 Pérez-Andino et al.
DOI: 10.1371/journal.pone.0005847

1.10.2 Male Circumcision

DOES CIRCUMCISION IMPACT HPV INFECTION ACQUISITION AND CLEARANCE?

New research has shed light on the impact of circumcision on HPV infections. One study found no relationship between circumcision and HPV infection acquisition; however another found longer HPV infection duration in uncircumcised men. One study found HPV 16 was more common among uncircumcised men with prevalence varying by anatomical site. Risk factors for HPV infection included presence of another sexually transmitted infection and lifetime number of sexual partners.

Reduced clearance of penile human Papillomavirus infection in uncircumcised men. Journal of Infectious Diseases, 201(9), 1340-1343.

ABSTRACT: The relationship between circumcision and the acquisition and clearance of human papillomavirus (HPV) infection was examined in a cohort of 357 men followed up at 2-month intervals for an average of 431 days. There were no differences in HPV acquisition by circumcision status. Clearance of HPV infection, including infection with oncogenic types, was slower in the glans/coronal sulcus of the penis of uncircumcised men than circumcised men. The median duration of HPV infection of the glans/coronal sulcus was significantly longer in uncircumcised men (154 days) than circumcised men (91 days) (Pp.04). Circumcision may protect against HPV-associated disease by enhancing the resolution of infection.
DOI: 10.1086/651607
1.10 HPV Transmission


ABSTRACT: Human papillomavirus (HPV) prevalence was estimated from 2,705 sexually active, uncircumcised, human immunodeficiency virus seronegative men aged 17-28 years in Kisumu, Kenya. HPV prevalence was 51.1% (95% confidence interval: 49.2-53.0%) in penile cells from the glans/coronal sulcus and/or shaft. HPV prevalence varied by anatomical site, with 46.5% positivity in the glans/coronal sulcus compared with 19.1% in the shaft (p < 0.0001). High-risk HPV was detected in 31.2% of glans and 12.3% of shaft samples (p < 0.0001). HPV16 was the most common type and 29.2% of men were infected with more than one HPV type. Risk factors for HPV infection included presence of C. trachomatis, N. gonorrhoea, self-reported sexually transmitted infections, and less frequent bathing. Lifetime number of sexual partners and herpes simplex virus type-2 seropositivity were also marginally associated with HPV infection. © 2009 UICC.

DOI: 10.1002/ijc.24770
Section 2
Primary Interventions
2.1 BEHAVIOR

SUMMARY

Young adult self-reported sexual debut in seven European countries identified the median age boys and girls initiate sexual activity was between 16 and 18 years of age. Sexual activity before the age of 15 varied by country.


ABSTRACT: Objective: To generate country-specific data on age of sexual debut in young adults in 7 European countries with regard to the optimal age for prophylactic human papillomavirus (HPV) vaccination. Methods: Survey of self-reported sexual debut and behavior in a sample of young adults aged 18-24 years in 7 European countries (Czech Republic, Ireland, Italy, Netherlands, Poland, Russia, France). Subjects (minimum of 500 males and 500 females per country) were recruited at public places using an in-street collecting approach in all countries except France, where the survey was conducted at home. Data were collected using a short, anonymous, self-administered questionnaire designed to gather information about any kind of sexual activity the subject might have engaged in with a partner, with standardized content to enable comparison between countries. Results: Up to 14% of young men and 22% of young women aged 18-24 years had yet to experience sexual activity at the time of the survey. Median age of sexual debut calculated by survival analysis ranged between 16 and 17 years in boys and between 17 and 18 years in girls. The proportion of boys sexually active before the age of 15 years ranged from 5.0% (Poland) to 15.8% (Italy). The proportion of girls sexually active before the age of 15 years was lower compared with boys in all countries, ranging from 2.6% (Poland) to 11.9% (the Netherlands). The first sexual partner for girls was typically at least 1 year older, irrespective of the age of sexual debut. Almost one-third of young women did not use a condom at sexual debut. Conclusions: This survey provides an update on sexual debut and behavior in young adults in some European countries. Estimated age at sexual debut ranged between 16 and 18 years and appeared to be later in girls than in boys. The proportion of girls sexually active before the age of 15 years was low (≤ 11.9%). Almost one-third of young women did not use a condom. This survey provides useful information to support current or planned HPV vaccination programs in Europe. © 2009. DOI: 10.1016/j.ygyno.2009.06.003

2.2 CIRCUMCISION

SUMMARY

Male circumcision, as a preventative health measure to reduce HPV acquisition and transmission, requires further study. Study results ranged from no protective benefits to reduced risk and reduced incidence of HPV, HIV, and HSV2 infection in circumcised and newly circumcised men.
2.1 Behaviour | 2.2 Circumcision


**ABSTRACT:** Circumcision has been reported to protect against infection with human papillomavirus (HPV) in men, but results have been inconsistent. We followed males in a birth cohort born in Dunedin, New Zealand, in 1972 and 1973 from age 3 to 32 years. Seropositivity at age 32 years for the oncogenic types HPV-16 and 18, and the nononcogenic types 6 and 11, was studied in relation to maternal reports of circumcision status at age 3 for 450 men. Seropositivity to any of these types was associated with lifetime number of sexual partners (P = 0.03), and lower moral-religious emphasis of the family of origin (P < 0.001). Circumcision was not found to be protective, with the adjusted odds ratio (95% confidence interval) for HPV6/11/16/18 seropositivity among the circumcised compared with the uncircumcised being 1.4 (0.89-2.2). Copyright © 2009 American Association for Cancer Research.

DOI: 10.1158/1055-9965.EPI-08-0353


**ABSTRACT:** There is growing interest in understanding human papillomavirus (HPV) infection and related disease among men. To date there have been numerous studies reporting HPV DNA prevalence among men from several different countries, however, few have incorporated multivariable analyses to determine factors independently associated with male HPV detection. The purpose of this study was to assess the factors independently associated with HPV detection in men ages 18 - 70 years residing in Brazil (n =343), Mexico (n =312), and the United States (US) (n =333). In samples combined from the coronal sulcus, glans penis, shaft, and scrotum, we evaluated factors associated with any, oncogenic, and nononcogenic HPV infections. In multivariable analyses, detection of any HPV infection was significantly associated with reported race of Asian/Pacific Islander, lifetime and recent number of sexual partners, and having sex in the past 3 months. Oncogenic HPV detection was independently associated with lifetime and recent number of sexual partners, and having sex in the past 3 months. Nononcogenic HPV infection was independently associated with lifetime number of sexual partners. Circumcision, assessed by clinical examination, was associated with reduced risk of HPV detection across all categories of HPV evaluated. HPV detection in men in the current study was strongly related to sexual behavior and circumcision status. Interventions such as circumcision may provide a low-cost method to reduce HPV infection. © 2008 Wiley-Liss, Inc.

DOI: 10.1002/ijc.24097

Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: Results of a randomized controlled trial conducted in orange farm, South Africa. *Journal of Infectious Diseases, 199*(1), pp. 14-19.

**ABSTRACT:** Background. A causal association links high-risk human papillomavirus (HR-HPV) and cervical cancer, which is a major public health problem. The objective of the present study was to investigate the association between male circumcision (MC) and the prevalence of HR-HPV among young men. Methods. We used data from a MC trial conducted in Orange Farm, South Africa, among men aged 18-24 years. Urethral swab samples were collected during a period of 262 consecutive days from participants in the intervention (circumcised) and control (uncircumcised) groups who were reporting for a scheduled follow-up visit. Swab samples were analyzed using polymerase chain reaction. HR-HPV prevalence rate ratios (PRRs) were assessed using univariate and multivariate log Poisson regression. Results. In an intention-to-treat analysis, the prevalences of HR-HPV among the intervention and control groups were 14.8% (94/637) and 22.3% (140/627), respectively, with a PRR of 0.66 (0.51-0.86) (P = .002). Controlling for propensity score and confounders (ethnic group, age, education, sexual behavior [including condom use], marital status, and human immunodeficiency virus status) had no effect on the results. Conclusions. This is the first randomized controlled trial to show a reduction in the prevalence of urethral HR-HPV infection after MC. This finding explains why women with circumcised partners are at a lower risk of cervical cancer than other women. Trial registration. ClinicalTrials.gov identifier: NCT00122525. © 2008 by the Infectious Diseases Society of America.

DOI: 10.1086/595566


Associations between male anogenital human papillomavirus infection and circumcision by anatomic site sampled and lifetime number of female sex partners. *Journal of Infectious Diseases, 199*(1), pp. 7-13.

**ABSTRACT:** Background. Male circumcision may lower men’s risk of human papillomavirus (HPV) infection and reduce transmission to sex partners. Reported associations between circumcision and HPV infection in men have been inconsistent. Methods. Four hundred sixty-three men in 2 US cities were tested at 6 anogenital sites and in semen for 37 types of HPV. Men were eligible if they reported sex with a woman within the past year, no history of genital warts or penile or anal cancer, and no current diagnosis of a sexually transmitted infection. Participants completed a self administered questionnaire. Circumcision status was assessed by the study clinician. Logistic regression was used to examine associations between circumcision and HPV detection at each site and in semen, with adjustment for potential confounders. Results. Seventy-four men (16.0%) were uncircumcised. Adjusted odds ratios (AORs) for any HPV genotype and circumcision were 0.53 (95% confidence interval [CI], 0.28-0.99) for any anatomic site/specimen, 0.17 (95% CI, 0.05-0.56) for the urethra, 0.44 (95% CI, 0.23-0.82) for the glans/corona, and 0.53 (95% CI, 0.28-0.99) for the penile shaft. AORs were <1.0 but not statistically significant for the scrotum, semen, anal canal, and perianal area. Conclusions. Circumcision may be protective against HPV infection
of the urethra, glans/corona, and penile shaft. © 2008 by the Infectious Diseases Society of America.

DOI: 10.1086/595567


ABSTRACT: Background: Male circumcision significantly reduced the incidence of human immunodeficiency virus (HIV) infection among men in three clinical trials. We assessed the efficacy of male circumcision for the prevention of herpes simplex virus type 2 (HSV-2) and human papillomavirus (HPV) infections and syphilis in HIV-negative adolescent boys and men. Methods: We enrolled 5534 HIV-negative, uncircumcised male subjects between the ages of 15 and 49 years in two trials of male circumcision for the prevention of HIV and other sexually transmitted infections. Of these subjects, 3393 (61.3%) were HSV-2-seronegative at enrollment. Of the seronegative subjects, 1684 had been randomly assigned to undergo immediate circumcision (intervention group) and 1709 to undergo circumcision after 24 months (control group). At baseline and at 6, 12, and 24 months, we tested subjects for HSV-2 and HIV infection and syphilis, along with performing physical examinations and conducting interviews. In addition, we evaluated a subgroup of subjects for HPV infection at baseline and at 24 months. Results: At 24 months, the cumulative probability of HSV-2 seroconversion was 7.8% in the intervention group and 10.3% in the control group (adjusted hazard ratio in the intervention group, 0.72; 95% confidence interval [CI], 0.56 to 0.92; P = 0.008). The prevalence of high-risk HPV genotypes was 18.0% in the intervention group and 27.9% in the control group (adjusted risk ratio, 0.65; 95% CI, 0.46 to 0.90; P = 0.009). However, no significant difference between the two study groups was observed in the incidence of syphilis (adjusted hazard ratio, 1.10; 95% CI, 0.75 to 1.65; P = 0.44). Conclusions: In addition to decreasing the incidence of HIV infection, male circumcision significantly reduced the incidence of HSV-2 infection and the prevalence of HPV infection, findings that underscore the potential public health benefits of the procedure. (ClinicalTrials.gov numbers, NCT00425984 and NCT00124878.) Copyright © 2009 Massachusetts Medical Society. DOI: 10.1056/NEJMoa0802556
Section 3.
Immunization
3.1 GENERAL

SUMMARY

HPV vaccine efficacy and immunogenicity has been demonstrated for five years for Gardasil and 6.4 years for Cervarix. Long-term efficacy of HPV vaccination is an important unknown factor in determining the need for booster immunization specifically since immunization is recommended for cohorts prior to sexual debut (in Canada ages 10-14) and waning protection may not be apparent for decades. Vaccine immunogenicity studies have provided surrogate markers for protection against oncogenic HPV acquisition. Long-term evaluation, incorporation of population based vaccination measurements, and HPV infection studies are needed to determine duration of efficacy. Studies assessing compliance with the three dose regime outside controlled studies will be an additional challenge for predicting protection and to determine long-term efficacy.

Priority Research

Long-term population based evaluation studies are required to determine current immunization efficacy, 2 dose versus 3 dose efficacy, and opportunities for improved uptake and compliance with full dose vaccination.


ABSTRACT: This observer-blind study compared the prophylactic human papillomavirus (HPV) vaccines, Cervarix™ (GlaxoSmithKline) and Gardasil® (Merck), by assessing immunogenicity and safety through one month after completion of the three-dose vaccination course. Women (n = 1106) were stratified by age (18-26, 27-35, 36-45 years) and randomized (1:1) to receive Cervarix™ (Months 0, 1, 6) or Gardasil® (Months 0, 2, 6). At Month 7 after first vaccination, all women in the according-to-protocol cohort who were seronegative/DNA negative before vaccination for the HPV type analyzed had seroconverted for HPV-16 and HPV-18 serum neutralizing antibodies, as measured by pseudovirion-based neutralization assay (PBNA), except for two women aged 27-35 years in the Gardasil® group who did not seroconvert for HPV-18 (98%). Geometric mean titers of serum neutralizing antibodies ranged from 2.3-4.8-fold higher for HPV-16 and 6.8-9.1-fold higher for HPV-18 after vaccination with Cervarix™ compared with Gardasil®, across all age strata. In the total vaccinated cohort (all women who received at least one vaccine dose, regardless of their serological and DNA status prior to vaccination), Cervarix™ induced significantly higher serum neutralizing antibody titers in all age strata (p < 0.0001). Positivity rates for anti-HPV-16 and -18 neutralizing antibodies in cervicovaginal secretions and circulating HPV-16 and -18 specific memory B-cell frequencies were also higher after vaccination with Cervarix™ compared with Gardasil®. Both vaccines were generally well tolerated. The incidence of unsolicited adverse events was comparable between vaccinated groups. The incidence of solicited symptoms was generally higher after Cervarix™, injection site reactions being most common. However, compliance rates with the three-dose schedules were similarly high (≥ 84%) for both vaccines. Although the importance
of differences in magnitude of immune response between these vaccines is unknown, they may represent determinants of duration of protection against HPV-16/18. Long-term studies evaluating duration of efficacy after vaccination are needed for both vaccines.

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ABSTRACT: A pooled analysis of the safety of the human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine Cervarix™ (GlaxoSmithKline) was performed in a cohort of almost 30,000 girls and women aged ≥10 years, 16,142 who received at least one dose of the HPV-16/18 vaccine and 13,811 who received one of three controls [Al(OH)3 or hepatitis A vaccine (720 or 360 EU)]. Data are available for a total of 45,988 vaccine doses. Solicited local and general symptoms were recorded for seven days after each dose. Serious adverse events (SAEs), pregnancies, medically significant conditions (MSCs) and new onset of chronic diseases (NOCDs), including new onset of autoimmune diseases (NOADs), were proactively monitored. Data were analyzed by vaccine group according to age (10-14, 15-25 and >25 years) and reporting period (months 0-7, months 7-12 and >month 12). Rates of solicited local and general symptoms were higher in the HPV-16/18 vaccine group than in the control groups. However, compliance with the three-dose schedule was high and did not differ between groups (93.4% for HPV-16/18 vaccine group versus 92.5% for pooled controls). No clinically relevant differences were seen between the HPV-16/18 vaccine and pooled control groups in rates of SAEs (2.8% versus 3.1%), MSCs (19.4% versus 21.4%), NOCDs (1.7% in both groups) or NOADs (0.4% versus 0.3%). Similarly, no differences in pregnancy outcomes or rates of withdrawals due to AEs or SAEs were observed between groups. In conclusion, analysis of this large database shows the HPV-16/18 AS04-adjuvanted cervical cancer vaccine to have a favorable safety profile in women of all ages.

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ABSTRACT: Background. Prophylactic human papillomavirus (HPV) vaccines have to provide sustained protection. We assessed efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine up to 6.4 years. Methods: Women aged 15-25 years, with normal cervical cytology, who were HPV-16/18 seronegative and oncogenic HPV DNA-negative (14 types) at screening participated in a double-blind, randomised, placebo-controlled initial study (n=1113; 560 vaccine group vs 553 placebo group) and follow-up study (n=776; 393 vs 383). 27 sites in three countries participated in the follow-up study. Cervical samples were tested every 6 months for HPV DNA. Management of abnormal cytologies was prespecified, and HPV-16/18 antibody titres were assessed. The primary
objective was to assess long-term vaccine efficacy in the prevention of incident cervical infection with HPV 16 or HPV 18, or both. We report the analyses up to 6·4 years of this follow-up study and combined with the initial study. For the primary endpoint, the efficacy analysis was done in the according-to-protocol (ATP) cohort; the analysis of cervical intraepithelial neoplasia grade 2 and above (CIN2+) was done in the total vaccinated cohort (TVC). The study is registered with ClinicalTrials.gov, number NCT00120848. Findings: For the combined analysis of the initial and follow-up studies, the ATP efficacy cohort included 465 women in the vaccine group and 454 in the placebo group; the TVC included 560 women in the vaccine group and 553 in the placebo group. Vaccine efficacy against incident infection with HPV 16/18 was 95·3% (95% CI 87·4-98·7) and against 12-month persistent infection was 100% (81·8-100). Vaccine efficacy against CIN2+ was 100% (51·3-100) for lesions associated with HPV-16/18 and 71·9% (20·6-91·9) for lesions independent of HPV DNA. Antibody concentrations by ELISA remained 12-fold or more higher than after natural infection (both antigens). Safety outcomes were similar between groups: during the follow-up study, 30 (8%) participants reported a serious adverse event in the vaccine group versus 37 (10%) in the placebo group. None was judged related or possibly related to vaccination, and no deaths occurred. Interpretation: Our findings show excellent long-term efficacy, high and sustained immunogenicity, and favourable safety of the HPV-16/18 AS04-adjuvanted vaccine up to 6·4 years. Funding: GlaxoSmithKline Biologicals (Belgium). © 2009 Elsevier Ltd. DOI: 10.1016/S0140-6736(09)61567-1


ABSTRACT: Context: In June 2006, the Food and Drug Administration licensed the quadrivalent human papillomavirus (types 6, 11, 16, and 18) recombinant vaccine (qHPV) in the United States for use in females aged 9 to 26 years; the Advisory Committee on Immunization Practices then recommended qHPV for routine vaccination of girls aged 11 to 12 years. Objective: To summarize reports to the Vaccine Adverse Event Reporting System (VAERS) following receipt of qHPV. Design, Setting, and Participants: Review and describe adverse events following immunization (AEFIs) reported to VAERS, a national, voluntary, passive surveillance system, from June 1, 2006, through December 31, 2008. Additional analyses were performed for some AEFIs in prelicensure trials, those of unusual severity, or those that had received public attention. Statistical data mining, including proportional reporting ratios (PRRs) and empirical Bayesian geometric mean methods, were used to detect disproportionality in reporting. Main Outcome Measures: Numbers of reported AEFIs, reporting rates (reports per 100 000 doses of distributed vaccine or per person-years at risk), and comparisons with expected background rates. Results: VAERS received 12 424 reports of AEFIs following qHPV distribution, a rate of 53.9 reports per 100 000 doses distributed. A total of 772 reports (6.2% of all reports) described serious AEFIs, including 32 reports of death. The reporting rates per 100 000 qHPV doses distributed were 8.2 for syncope; 75 for local site reactions; 6.8 for dizziness; 5.0 for nausea; 4.1 for headache; 3.1 for hypersensitivity reactions;
3.1 GENERAL

2.6 for urticaria; 0.2 for venous thromboembolic events, autoimmune disorders, and Guillain-Barré syndrome; 0.1 for anaphylaxis and death; 0.04 for transverse myelitis and pancreatitis; and 0.009 for motor neuron disease. Disproportional reporting of syncope and venous thromboembolic events was noted with data mining methods. Conclusions: Most of the AEFI rates were not greater than the background rates compared with other vaccines, but there was disproportional reporting of syncope and venous thromboembolic events. The significance of these findings must be tempered with the limitations (possible underreporting) of a passive reporting system. ©2009 American Medical Association.
DOI: 10.1001/jama.2009.1201


ABSTRACT: Purpose: The human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine (Cervarix™) has been shown to be well-tolerated and immunogenic in females aged 10 to 55 years, and up to 100% effective for the prevention of HPV-16/18 infection and associated precancerous cervical lesions in females aged 15 to 25 years. This study is the first to evaluate the immunogenicity and safety of the vaccine in males. Methods: Healthy males aged 10 to 18 years were randomized (2:1 ratio) to receive HPV-16/18 AS04-adjuvanted vaccine (n = 181) or hepatitis B virus (HBV) control vaccine (n = 89) at 0, 1, and 6 months, and were followed for 7 months. Results: All initially seronegative subjects in the HPV-16/18 group seroconverted for HPV-16 and 18 (ELISA) at month 2. At month 7, all subjects were seropositive, and the HPV-16 and -18 antibody levels were, respectively, four- and twofold higher than at month 2. The anti-HPV-16 and -18 antibody responses for males aged 10 to 18 years and 10 to 14 years, respectively, were higher than those reported for females aged 15 to 25 years and 10 to 14 years, respectively, in a previous study. The reactogenicity profiles of the HPV-16/18 AS04 and HBV vaccines were similar, except that pain and swelling at the injection site were more common in the HPV-16/18 group. Conclusions: The HPV-16/18 AS04-adjuvanted vaccine is immunogenic and well tolerated in boys aged 10 to 18 years. Further data on the potential public health benefits of vaccination of boys are required before any recommendations can be made. © 2009 Society for Adolescent Medicine.


ABSTRACT: Background. Although the peak incidence of human papillomavirus (HPV) infection occurs in most populations within 5-10 years of first sexual experience, all women remain
at risk for acquisition of HPV infections. We tested the safety, immunogenicity, and efficacy of the quadrivalent HPV (types 6, 11, 16, 18) L1 virus-like-particle vaccine in women aged 24-45 years. Methods: Women aged 24-45 years with no history of genital warts or cervical disease were enrolled from community health centres, academic health centres, and primary health-care providers into an ongoing multicentre, parallel, randomised, placebo-controlled, double-blind study. Participants were allocated by computer-generated schedule to receive quadrivalent HPV vaccine (n=1911) or placebo (n=1908) at day 1, and months 2 and 6. All study site investigators and personnel, study participants, monitors, and central laboratory personnel were blinded to treatment allocation. Coprimary efficacy endpoints were 6 months' or more duration of infection and cervical and external genital disease due to HPV 6, 11, 16, 18; and due to HPV 16 and 18 alone. Primary efficacy analyses were done in a per-protocol population, but intention-to-treat analyses were also undertaken. This study is registered with ClinicalTrials.gov, number NCT00090220. Findings: 1910 women received at least one dose of vaccine and 1907 at least one dose of placebo. In the per-protocol population, efficacy against the first coprimary endpoint (disease or infection related to HPV 6, 11, 16, and 18) was 90.5% (95% CI 73.7-97.5, four of 1615 cases in the vaccine group vs 41/1607 in the placebo group) and 83.1% (50.6-95.8, four of 1601 cases vs 23/1579 cases) against the second coprimary endpoint (disease or infection related to HPV 16 and 18 alone). In the intention-to-treat population, efficacy against the first coprimary endpoint was 30.9% (95% CI 11.1-46.5, 108/1886 cases vs 154/1883 cases) and against the second coprimary endpoint was 22.6% (-2.9 to 41.9, 90/1886 cases vs 115/1883 cases), since infection and disease were present at baseline. We recorded no vaccine-related serious adverse events. Interpretation: The quadrivalent HPV vaccine is efficacious in women aged 24-45 years not infected with the relevant HPV types at enrolment. Funding: Merck (USA). © 2009 Elsevier Ltd. DOI: 10.1016/S0140-6736(09)60691-7


ABSTRACT: Objectives: Strong and sustained HPV-16 and -18 antibody responses have been observed in previously unexposed women aged 15-25 years vaccinated with the AS04-adjuvanted HPV-16/18 L1 virus-like particle vaccine. While awaiting the extended results of ongoing trials, our objective was to predict the long-term persistence of anti-HPV-16/18 antibodies in vaccinees by applying three statistical models using immunogenicity data from vaccinees with serum samples collected up to 6.4 years after first vaccination. Two different data lock-points (up to 5.5 years and up to 6.4 years) were used to assess the robustness of the models. Methods: Three statistical models were applied to estimate the long-term persistence of anti-HPV-16/18 antibodies in 393 women vaccinated with the AS04-adjuvanted HPV-16/18 vaccine. Individual antibody levels for each study participant at each timepoint up to 6.4 years were input to previously published power-law and modified power-law models. The power-law model estimates antibody decay over time. The modified power-law model takes into account both antibody persistence over time and immune
A third model, the piece-wise model, fits the data based on three different non-overlapping intervals (between months 7 and 12, months 12 and 21, and over 21 months), corresponding to the observed decay of vaccine-induced antibodies. Results: HPV-16 and -18 antibodies peaked at Month 7 and gradually plateaued at months 18-24 and remained stable through 6.4 years. Mean antibody levels at the last timepoint were several fold higher than those associated with natural infection. All three models predict that HPV-16 and -18 mean antibody levels will remain well above those associated with natural infection for at least 20 years, when using data from 5.5 as well as 6.4 years’ follow-up. Predictions are similar for the modified power-law model and improve with longer follow-up for both the power-law and the piece-wise models. Conclusions: Vaccination with the AS04-adjuvanted HPV-16/18 vaccine is predicted to provide long-term persistence for both HPV-16 and -18 antibodies, independent of the statistical model applied. Model predictions are based on conservative mathematical assumptions. Since the input of longer term data of up to 6.4 years showed an improved profile compared with that for data up to 5.5 years, the predictions of antibody persistence based on population means are conservative when predicting that antibody levels will remain well above levels induced by natural infection for 20 years. © 2009 Elsevier Inc. DOI: 10.1016/j.ygyno.2009.01.011


ABSTRACT: Quadrivalent human papillomavirus (HPV) vaccine has been shown to provide protection from HPV 6/11/16/18-related cervical, vaginal, and vulvar disease through 3 years. We provide an update on the efficacy of the quadrivalent HPV vaccine against high-grade cervical, vaginal, and vulvar lesions based on end-of-study data from three clinical trials. Additionally, we stratify vaccine efficacy by several baseline characteristics, including age, smoking status, and Papanicolaou (Pap) test results. A total of 18,174 females ages 16 to 26 years were randomized and allocated into one of three clinical trials (protocols 007, 013, and 015). Vaccine or placebo was given at baseline, month 2, and month 6. Pap testing was conducted at regular intervals. Cervical and anogenital swabs were collected for HPV DNA testing. Examination for the presence of vulvar and vaginal lesions was also done. Endpoints included high-grade cervical, vulvar, or vaginal lesions (CIN 2/3, VIN 2/3, or ValN 2/3). Mean follow-up time was 42 months post dose 1. Vaccine efficacy against HPV 6/11/16/18-related high-grade cervical lesions in the per-protocol and intention-to-treat populations was 98.2% [95% confidence interval (95% CI), 93.3-99.8] and 51.5% (95% CI, 40.6-60.6), respectively. Vaccine efficacy against HPV 6/11/16/18-related high-grade vulvar and vaginal lesions in the per-protocol and intention-to-treat populations was 100.0% (95% CI, 82.6-100.0) and 79.0% (95% CI, 56.4-91.0), respectively. Efficacy in the intention-to-treat population tended to be
lower in older women, women with more partners, and women with abnormal Pap test results. The efficacy of quadrivalent HPV vaccine against high-grade cervical and external anogenital neoplasia remains high through 42 months post vaccination. ©2009 American Association for Cancer Research. DOI: 10.1158/1940-6207.CAPR-09-0031


ABSTRACT: Background. The human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine was immunogenic, generally well tolerated, and effective against HPV-16 or HPV-18 infections, and associated precancerous lesions in an event-triggered interim analysis of the phase III randomised, double-blind, controlled PAPillomaTRIal against Cancer In young Adults (PATRICIA). We now assess the vaccine efficacy in the final event-driven analysis. Methods: Women (15-25 years) were vaccinated at months 0, 1, and 6. Analyses were done in the according-to-protocol cohort for efficacy (ATP-E; vaccine, n=8093; control, n=8069), total vaccinated cohort (TVC, included all women receiving at least one vaccine dose, regardless of their baseline HPV status; represents the general population, including those who are sexually active; vaccine, n=9319; control, n=9325), and TVC-naive (no evidence of oncogenic HPV infection at baseline; represents women before sexual debut; vaccine, n=5822; control, n=5819). The primary endpoint was to assess vaccine efficacy against cervical intraepithelial neoplasia 2+ (CIN2+) that was associated with HPV-16 or HPV-18 in women who were seronegative at baseline, and DNA negative at baseline and month 6 for the corresponding type (ATP-E). This trial is registered with ClinicalTrials.gov, number NCT00122681. Findings: Mean follow-up was 34·9 months (SD 6·4) after the third dose. Vaccine efficacy against CIN2+ associated with HPV-16/18 was 92·9% (96·1% CI 79·9-98·3) in the primary analysis and 98·1% (88·4-100) in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncogenic types (ATP-E cohort). Vaccine efficacy against CIN2+ irrespective of HPV DNA in lesions was 30·4% (16·4-42·1) in the TVC and 70·2% (54·7-80·9) in the TVC-naive. Corresponding values against CIN3+ were 33·4% (9·1-51·5) in the TVC and 87·0% (54·9-97·7) in the TVC-naive. Vaccine efficacy against CIN2+ associated with 12 non-vaccine oncogenic types was 54·0% (34·0-68·4; ATP-E). Individual cross-protection against CIN2+ associated with HPV-31, HPV-33, and HPV-45 was seen in the TVC. Interpretation: The HPV-16/18 AS04-adjuvanted vaccine showed high efficacy against CIN2+ associated with HPV-16/18 and non-vaccine oncogenic HPV types and substantial overall effect in cohorts that are relevant to universal mass vaccination and catch-up programmes. Funding: GlaxoSmithKline Biologicals. © 2009 Elsevier Ltd. DOI: 10.1016/S0140-6736(09)61248-4
3.2 Vaccine Impact on Cervical Screening Programs


**ABSTRACT:** The Advisory Committee for Immunization Practices has recommended routine human papillomavirus (HPV) vaccination of 11 to 12-year-old girls and catch-up for females 13 to 26 years of age. The 3 doses are administered at 0, 2 months (minimum 4 weeks), and 6 months (minimum 12 weeks after the second dose). Low socioeconomic status, a primary language other than English, being an ethnic minority, not having health insurance, and not having consistent transportation were associated with poor hepatitis B virus vaccine completion in adolescents. In contrast, completion rates increase when providers take advantage of opportunities for vaccination (e.g., sick visits) and have reminder systems. The purpose of this study was to describe the completion rates and timeliness of HPV vaccine receipt in university-associated practices. We also evaluated whether patient demographics and reasons for the clinic visit were associated with completion and if the reason for the visit was associated with timeliness. The overall completion rate for the HPV vaccination series in this study was only 58.2%, and there was a significant drop-off in uptake between the second dose and the third dose. Notably, more than half of the patients who did not complete the series had a clinic visit after the time when they were scheduled for their missing vaccination, indicating that there were high numbers of missed opportunities for vaccine series completion.

DOI: 10.1177/0009922809337534

3.2 VACCINE IMPACT ON CERVICAL SCREENING PROGRAMS

**SUMMARY**

Clinical trial data have shown moderate impacts of HPV vaccination on some non-vaccine oncogenic HPV types (specifically HPV types 31, 33, 45, 52, 58) suggesting cross protection for women (177% reduction overall; as much as 40% for types 31 and 45). The long-term benefit of cross protection requires further evaluation. HPV 16/18 are markedly reduced in CIN 1 and CIN 2 among women vaccinated, under the age of 25. Major reductions in genital wart incidence among vaccinated women occurred in Australia (25.1% decrease per quarter in 2008). Modeling studies predicted reductions in cervical dysplasia and cervical cancer disease burdens with higher vaccine uptake rates, with some studies recommending catch up programs to improve vaccination impact in jurisdictions with lower uptake rates.


The impact of quadrivalent human papillomavirus (HPV; Types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine hpv types in sexually active women aged 16-26 years. *Journal of Infectious Diseases, 199*(7), pp. 936-944.
ABSTRACT: Background. We evaluated the impact of a quadrivalent human papillomavirus (HPV) vaccine on infection and cervical disease related to 10 nonvaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) associated with 20% of cervical cancers. The population evaluated included HPV-naive women and women with preexisting HPV infection and/or HPV-related disease at enrollment. Methods. Phase 3 efficacy studies enrolled 17,622 women aged 16-26 years. Subjects underwent cervicovaginal sampling and Pap testing on day 1 and then at 6-12-month intervals for up to 4 years. HPV typing was performed on samples from enrollment and follow-up visits, including samples obtained for diagnosis or treatment of HPV-related disease. All subjects who received ≥1 dose and returned for follow-up were included. Results. Vaccination reduced the rate of HPV-31/33/45/52/58 infection by 17.7% (95% confidence interval [CI], 5.1% to 28.7%) and of cervical intraepithelial neoplasia (CIN) 1-3 or adenocarcinoma in situ (AIS) by 18.8% (95% CI, 7.4% to 28.9%). Vaccination also reduced the rate of HPV-31/58/59-related CIN1-3/AIS by 26.0% (95% CI, 6.7% to 41.4%), 28.1% (95% CI, 5.3% to 45.6%), and 37.6% (95% CI, 6.0% to 59.1%), respectively. Although a modest reduction in HPV-31/58/59-related CIN2 or worse was observed, the estimated reduction was not statistically significant. Conclusions. These cross-protection results complement the vaccine’s prophylactic efficacy against disease associated with HPV-6, -11, -16, and -18. Long-term monitoring of vaccinated populations are needed to fully ascertain the population-based impact and public health significance of these findings. Trial registration. ClinicalTrials.gov identifiers: NCT00092521, NCT00092534, and NCT00092482. © 2009 by the Infectious Diseases Society of America. DOI: 10.1086/597309


ABSTRACT: Background. Human papillomavirus (HPV)-6/11/16/18 vaccine reduces the risk of HPV-6/11/16/18-related cervical intraepithelial neoplasia (CIN) 1-3 or adenocarcinoma in situ (AIS). Here, its impact on CIN1-3/AIS associated with nonvaccine oncogenic HPV types was evaluated. Methods. We enrolled 17,622 women aged 16-26 years. All underwent cervicovaginal sampling and Pap testing at regular intervals for up to 4 years. HPV genotyping was performed for biopsy samples, and histological diagnoses were determined by a pathology panel. Analyses were conducted among subjects who were negative for 14 HPV types on day 1. Prespecified analyses included infection of 6 months’ duration and CIN1-3/AIS due to the 2 and 5 most common HPV types in cervical cancer after HPV types 16 and 18, as well as all tested nonvaccine types. Results. Vaccination reduced the incidence of HPV-31/45 infection by 40.3% (95% confidence interval [CI], 13.9% to 59.0%) and of
3.2 Vaccine Impact on Cervical Screening Programs

CIN1-3/AIS by 43.6% (95% CI, 12.9% to 64.1%), respectively. The reduction in HPV-31/33/45/52/58 infection and CIN1-3/AIS was 25.0% (95% CI, 5.0% to 40.9%) and 29.2% (95% CI, 8.3% to 45.5%), respectively. Efficacy for CIN2-3/AIS associated with the 10 nonvaccine HPV types was 32.5% (95% CI, 6.0% to 51.9%). Reductions were most notable for HPV-31. Conclusions. HPV-6/11/16/18 vaccine reduced the risk of CIN2-3/AIS associated with nonvaccine types responsible for 20% of cervical cancers. The clinical benefit of cross-protection is not expected to be fully additive to the efficacy already observed against HPV-6/11/16/18-related disease, because women may have >1 CIN lesion, each associated with a different HPV type. Trial registration. ClinicalTrials.gov identifiers: NCT00092521, NCT00092534, and NCT00092482. © 2009 by the Infectious Diseases Society of America. DOI: 10.1086/597307


ABSTRACT: Purpose: To evaluate the safety and immunogenicity of a therapeutic human papillomavirus (HPV)16 DNA vaccine administered to women with HPV16+cervical intraepithelial neoplasia (CIN)2/3. Experimental Design: This phase I trial incorporated the standard ‘3+3’ dose-escalation design with an additional 6 patients allocated to the maximally tolerated dose. Healthy adult women with colposcopically directed, biopsy-proven HPV16+ CIN2/3 received 3 i.m. vaccinations (0.5, 1, or 3 mg) of a plasmid expressing a Sig-E7(detox)-heat shock protein 70 fusion protein on days 0, 28, and 56, and underwent standard therapeutic resection of the cervical squamocolumnar junction at day 105 (week 15). The safety and immunogenicity of the vaccine and histologic outcome based on resection at week 15 were assessed. Results: Fifteen patients were evaluable (3 each at 0.5 and 1mg, 9 at 3 mg). The vaccine was well tolerated: most adverse events were mild, transient injection-site discomfort; no dose-limiting toxicities were observed. Although HPVE7-specific T-cell responses to E7 detected by enzyme-linked immunospot assays (IFN-γ) were of low frequency and magnitude, detectable increases in response subsequent to vaccination were identified in subjects in the second and third cohorts. Complete histologic regression occurred in 3 of 9 (33%; 7-70% confidence interval) individuals in the highest-dose cohort. Although the difference is not significant, it is slightly higher than would be expected in an unvaccinated cohort (25%). Conclusions: This HPV16 DNA vaccine was safe and well tolerated. Whereas it seems possible to elicit HPV-specific T-cell responses in patients with established dysplastic lesions, other factors are likely to play a role in lesion regression. © 2009 American Association for Cancer Research. DOI: 10.1158/1078-0432.CCR-08-1725
SECTION 3 - IMMUNIZATION


ABSTRACT: Objective: In the quadrivalent (types 6/11/16/18) HPV vaccine (GARDASIL®/SILGARD®) clinical program, 73% of women aged 16-26 were naïve to all vaccine HPV types. In these women, prophylactic administration of the vaccine was highly effective in preventing HPV 6/11/16/18-related cervical disease. Of the remaining women, 15% had evidence of past infection with one or more vaccine HPV types (seropositive and DNA negative) at the time of enrollment. Here we present an analysis in this group of women to determine the efficacy of the HPV 6/11/16/18 vaccine against new cervical and external anogenital disease related to the same vaccine HPV type which had previously been cleared. Vaccine tolerability in this previously infected population was also assessed.

Results: Subjects were followed for an average of 40 months. Seven subjects in the placebo group developed cervical disease, and eight subjects developed external genital disease related to a vaccine HPV type they had previously encountered. No subject receiving HPV 6/11/16/18 vaccine developed disease to a vaccine HPV type to which they were seropositive and DNA negative at enrollment.

Methods: 18,174 women were enrolled into three clinical studies. The data presented comprise a subset of these subjects (n = 2,617) who were HPV seropositive and DNA negative at enrollment (for ≥1 vaccine type). In each study, subjects were randomized in a 1:1 ratio to receive HPV 6/11/16/18 vaccine or placebo at day 1, month 2 and month 6 (without knowledge of baseline HPV status). Procedures performed for efficacy data evaluation included detailed genital examination, Pap testing and collection of cervicovaginal and external genital specimens. Analyses of efficacy were carried out in a population stratified by HPV serology and HPV DNA status at enrollment. Conclusions: These results suggest that natural HPV infection-elicited antibodies may not provide complete protection over time, however the immune response to the HPV 6/11/16/18 vaccine appears to prevent reinfection or reactivation of disease with vaccine HPV types. Vaccine-related adverse experiences were higher among subjects receiving vaccine, mostly due to increased injection site adverse experiences. © 2009 Landes Bioscience.


ABSTRACT: Objectives: Human papillomavirus (HPV) is a sexually transmitted infection of particular interest because of its high prevalence rate and strong causal association with cervical cancer. Two prophylactic vaccines have been developed and different countries have made or will soon make recommendations for the vaccination of girls. Even if there
is a consensus to recommend a vaccination before the beginning of sexual activity, there are, however, large discrepancies between countries concerning the perceived usefulness of a catch-up procedure and of boosters. The main objective of this article is to simulate the impact on different vaccination policies upon the mid- and long-term HPV 16/18 age-specific infection rates. Methods: We developed an epidemiological model based on the susceptible-infective-recovered approach using Swiss data. The mid- and long-term impact of different vaccination scenarios was then compared. Results: The generalization of a catch-up procedure is always beneficial, whatever its extent. Moreover, pending on the length of the protection offered by the vaccine, boosters will also be very useful. Conclusions: To be really effective, a vaccination campaign against HPV infection should at least include a catch-up to early reach a drop in HPV 16/18 prevalence, and maybe boosters. Otherwise, the protection insured for women in their 20s could be lower than expected, resulting in higher risks to later develop cervical cancer. © 2009 Birkhäuser Verlag, Basel/Switzerland.

DOI: 10.1007/s00038-009-0081-3


ABSTRACT: Objective: To assess the expected impact in France of a quadrivalent HPV 6/11/16/18 vaccine on the occurrence of genital HPV-induced lesions in women. Methods: A Markov model based on a quadrivalent vaccination of 14-year-old girls as recommended in France was performed to assess the number of subjects needed to vaccinate to prevent an HPV-related event during their lifetime and the expected annual number of cases which could be prevented by vaccination. This model was based on prevalence data reported in four large French studies (EDiTH I-IV) reporting an HPV 6/11/16/18 prevalence of 82% (95% CI: 78.5-85.1) in cervical cancer (CC), 64% (95% CI: 59.7-68.1) in CIN2/3, 34% (95% CI: 28.9-38.1) in low-grade squamous intraepithelial lesions (LSIL) and 83% (95% CI 77.6-87.8) in female external acuminata condylomata (EAC) cases. Results: Using a theoretical vaccine efficacy of 100%, 130 young women need to be vaccinated to prevent a case of CC, 17 for a case of CIN2/3 and 13 for a case of EAC. Immunization of 80% of 14-year-old girls could prevent 2495 CC (72%), 17,985 CIN2/3 (54%), 8004 CIN1 (27%), and 22,531 EAC female cases (65%) in France annually. Conclusion: A good adhesion to the preferentially recommended HPV quadrivalent vaccination would thus substantially reduce the burden of female genital lesions in France. © 2009 Elsevier Masson SAS.

DOI: 10.1016/j.jgyn.2009.04.008

**SECTION 3 - IMMUNIZATION**

**ABSTRACT:** Background. Vulvar intraepithelial neoplasia is a chronic disorder caused by high-risk types of human papillomavirus (HPV), most commonly HPV type 16 (HPV-16). Spontaneous regression occurs in less than 1.5% of patients, and the rate of recurrence after treatment is high. METHODS: We investigated the immunogenicity and efficacy of a synthetic long-peptide vaccine in women with HPV-16-positive, high-grade vulvar intraepithelial neoplasia. Twenty women with HPV-16-positive, grade 3 vulvar intraepithelial neoplasia were vaccinated three or four times with a mix of long peptides from the HPV-16 viral oncoproteins E6 and E7 in incomplete Freund’s adjuvant. The end points were clinical and HPV-16-specific T-cell responses. RESULTS: The most common adverse events were local swelling in 100% of the patients and fever in 64% of the patients; none of these events exceeded grade 2 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute. At 3 months after the last vaccination, 12 of 20 patients (60%; 95% confidence interval [CI], 36 to 81) had clinical responses and reported relief of symptoms. Five women had complete regression of the lesions, and HPV-16 was no longer detectable in four of them. At 12 months of follow-up, 15 of 19 patients had clinical responses (79%; 95% CI, 54 to 94), with a complete response in 9 of 19 patients (47%; 95% CI, 24 to 71). The complete-response rate was maintained at 24 months of follow-up. All patients had vaccine-induced T-cell responses, and post hoc analyses suggested that patients with a complete response at 3 months had a significantly stronger interferon-γ-associated proliferative CD4+ T-cell response and a broad response of CD8+ interferon-γ T cells than did patients without a complete response. CONCLUSIONS: Clinical responses in women with HPV-16-positive, grade 3 vulvar intraepithelial neoplasia can be achieved by vaccination with a synthetic long-peptide vaccine against the HPV-16 oncoproteins E6 and E7. Complete responses appear to be correlated with induction of HPV-16-specific immunity. Copyright © 2009 Massachusetts Medical Society. DOI: 10.1056/NEJMoa0810097


**ABSTRACT:** Objective: This study aimed to determine if the Australian human papillomavirus (HPV) vaccination programme has had a population impact on presentations of genital warts. Methods: Retrospective study comparing the proportion of new clients with genital warts attending Melbourne Sexual Health Centre (MSHC) from January 2004 to December 2008. Australia provided free quadrivalent HPV vaccine to 12-18-year-old girls in a school-based programme from April 2007, and to women 26 years and younger through general practices from July 2007. Results: 36 055 new clients attended MSHC between 2004 and 2008 and genital warts were diagnosed in 3826 (10.6%; 95% CI 10.3 to 10.9). The proportion of women under 28 years with warts diagnosed decreased by 25.1% (95% CI 30.5% to 19.3%) per quarter in 2008. Comparing this to a negligible increase of 1.8% (95% CI 0.2% to 3.4%) per quarter from the start of 2004 to the end of 2007 also in women under 28 years generates strong evidence of a difference in these two trends (p<0.001). There was
no evidence of a difference in trend for the quarterly proportions before and after the end of 2007 for any other subgroup, and on only one occasion was there strong evidence of a trend different to zero, for heterosexual men in 2008 in whom the average quarterly change was a decrease of 5% (95% CI 0.5% to 9.4%; p=0.031). Conclusions: The data suggest that a rapid and marked reduction in the incidence of genital warts among vaccinated women may be achievable through an HPV vaccination programme targeting women, and supports some benefit being conferred to heterosexual men.

DOI: 10.1136/sti.2009.037788


**ABSTRACT:** Objective. Evaluate the efficacy of catch-up HPV vaccination in sexually active young women and the potential impact of HPV vaccines on the practice of organized screening. Sample. (1) Women enrolled in the Future II study and (2) from a separate population-based study in Iceland. Methods. (1) Analysis of cytological and histological results and colposcopic examinations among 710 women, aged 18-23, with less than five sexual partners, irrespectively of baseline HPV status at enrolment. (2) The impact on screening practice as determined by evaluating the distribution of 12 oncogenic HPV types in 582 cervical intraepithelial lesions (CIN 2-3) and cancer cases. Main outcome measures. (1) Distribution of evaluated parameters according to age at enrolment. (2) Age distribution of four HPV groups, within age classes and HPV groups: mean time to development of lesions, mean time to development of CIN 2-3+, cumulative frequency for CIN 2-3+ lesions after the last normal smear. Results. (1) After an average 52 months of post-enrolment follow-up, significant reductions in all evaluated parameters were observed in women aged 18-19 at enrolment. (2) Among women <25 years, the proportion of cases with only HPV 16/18 was significantly lower and the proportion containing HPV16/18 plus ≥1 out of 10 non-vaccine HPV types (31/33/45/52/58/35/39/51/56/59) was higher than at age 25-49. The proportion of cases containing only the non-vaccine types was the same within all age groups. Cases with HPV 16/18 and some non-vaccine types decreased significantly with age and accumulated more slowly after the last negative smear. Conclusions. Catch-up vaccination of younger women should be considered in the context of sexual practices and the effects of prevalent disease on observed vaccine efficacy. Current data do not support a change in the lower age limit or screening intervals for women. © 2009 Informa UK Ltd. (Informa Healthcare, Taylor & Francis AS).

DOI: 10.1080/00016340802566770


**ABSTRACT:** Human papillomavirus vaccine prevents infection by two major oncogenic types of the virus. Continued screening is needed in vaccinated women to prevent cancers caused by high-risk types not included in the vaccine. An exaggerated sense of protection from the
vaccine could lead to a decline in the rate of screening among vaccinated women, which in principle could lead to an increase in the incidence of cervical cancer. We present a simple mathematical model of vaccination, screening, and disease incidence, including an analysis of the effect of data uncertainties. For a population with opportunistic screening and 30% vaccine coverage, screening rates in vaccinated women would have to decline by at least 80% (median value of probabilistic uncertainty analysis) before the incidence of cervical cancer would increase in the era since the introduction of the vaccine. By comparison, the decline needed is at least 49% in a population with organised screening and 70% vaccine coverage. In populations that have highly effective cervical screening programmes, incidence of cervical cancer starts to increase after smaller, but still substantial, decreases in screening. Introduction of vaccine is unlikely to lead to an increased incidence of cervical cancer as a result of diminished screening. © 2010 Elsevier Ltd.


ABSTRACT: Background: Human papillomavirus (HPV) vaccination has been approved in more than 90 countries and is being implemented in many of these. In the UK, vaccination for girls aged 12-13 with catch-up for girls up to age 18 was introduced in 2008, using the bivalent GSK vaccine (Cervarix). Methods: We modelled the proportion of abnormal smears, cervical intraepithelial neoplasia grade 3 (CIN3) and invasive cancer, which will be prevented in women aged 20-29 in the UK as a result of HPV vaccination. Results: It will take many years for the full benefit of vaccination to be achieved. The earliest effects will be seen in women aged 20-29. With 80% coverage in women aged 12-13, we project an eventual 63% reduction in invasive cancer, a 51% reduction in CIN3 and a 27% reduction in cytological abnormalities before age 30. The full effect in this age group will not be seen until 2025, although half of the benefit will be seen by 2019 in England, where screening starts at age 25. However in Scotland and Wales, where screening starts at age 20, 50% of the benefit for CIN3 and abnormal smears (but not cancer) will be seen earlier. Conclusion: Substantial reductions in disease can be anticipated by vaccination, but most of the benefit will not be apparent for at least another decade. High vaccine coverage is the key factor for achieving these benefits. Copyright of British Journal of Cancer.

DOI: 10.1038/sj.bjc.6605528


ABSTRACT: Aim: Cervical cancer incidence and mortality have decreased for the last 20 years in Austria; however, they remain relatively high in comparison to other European countries. Screening quality has been suboptimal. In this paper we aim to predict the population-wide long-term effects on cervical cancer morbidity and mortality after introducing an HPV vaccination for 12-year-old girls (and boys) in addition to current screening.
3.3 Vaccination Choice | 3.4 Vaccination Strategies - Improving Uptake

in comparison with screening only. Methods: Health effects are predicted by a dynamic transmission model that was previously applied in the UK and the Norwegian contexts and validated for Austria. Outcomes analyzed are restricted to cervical cancer mortality and morbidity, which are predicted until 2060 assuming a coverage rate between 65% and 85%, a duration of protection between 10 years and lifelong, and a vaccine efficacy between 80% and 100% in the base case and best case, respectively. Additionally, implications for cancer epidemiology until 2088 are estimated. Results: Compared to screening only, screening plus vaccination of 12-year-old girls (and boys) would result in a median reduction of 10% (15%) fewer new cancer cases and 13% (20%) fewer cervical cancer deaths under best case assumptions over 52 years in the overall female population. In 2060, female population-based incidence and mortality would decrease by 27% and 43%, respectively, when vaccinating girls only and by 37% and 45% when additionally vaccinating boys. After 2060, a continuous further decrease in incidence and mortality can be expected with a maximum of minus 43% and 53%, respectively, in 2088 when vaccinating girls only. Conclusion: Although a constant decrease in cervical cancer incidence and mortality is to be expected after introducing a population-wide HPV vaccination program in Austria, the reduction predicted by this model is lower than expected from clinical trials. This is due to several factors, such as low coverage rate and the long time horizon required for generating the maximum benefit of the vaccination in the overall population. In the context of limited resources, for further reducing cervical cancer in Austria, HPV vaccination programs need to be weighed against other public health alternatives such as improving screening quality. © 2009 Springer-Verlag. DOI: 10.1007/s10389-009-0276-3

3.3 Vaccination Choice

SUMMARY

Both HPV 16 and 18 vaccines (Gardasil and Cervarix) appear to offer equivalent protection for these two oncogenic types. Research and development of multivalent vaccines and non-virus like particle vaccines have been identified as future alternatives to current vaccine choices.


ABSTRACT: PURPOSE OF REVIEW: Prophylactic human papillomavirus (HPV) L1 virus like particle (VLP) vaccines have been shown, in large randomized controlled clinical trials, to be very immunogenic, well tolerated and highly efficacious against ano-genital disease caused by the vaccine HPV types. However, these vaccines, at the present, protect against only two of the 15 oncogenic genital HPV types, they are expensive, delivered by intramuscular injection and require a cold chain. RECENT FINDINGS: The challenges are to develop cheap, thermostable vaccines that can be delivered by noninjectable methods that provide long-term (decades) protection at mucosal surfaces to most, if not all, oncogenic HPV types that is as good as the current VLP vaccines. Polyvalent VLP vaccines covering several oncogenic types are in clinical trials. The most promising of the non-VLP second generation vaccines
include L1 capsomers and L2 protein and peptides, suitably adjuvanted. Recent data on the mechanism of viral entry and the dynamics of the interaction of the viral capsid proteins L1 and L2 with the cell surface provide a rationale for the protection offered by these new approaches. SUMMARY: These second generation vaccines are immunogenic and can provide broad protection but are either at early stage in clinical trial or not in trials. The current VLP prophylactic vaccines are likely to be the only option for the coming decade. © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

DOI: 10.1097/QCO.0b013e328334c0e1

3.4 VACCINATION STRATEGIES – IMPROVING UPTAKE

SUMMARY

HPV vaccine uptake in Australia’s school based and catch up programs identified a less than expected uptake by females between the ages of 12 and 26. Factors impeding maximal coverage included short notice for vaccine program implementation, negative media, and lack of general practitioner HPV vaccine encouragement to eligible females.


Challenges, lessons learned and results following the implementation of a human papilloma virus school vaccination program in South Australia. Australian and New Zealand Journal of Public Health, 33(4), pp. 365-370.

ABSTRACT: Objective: To describe the process and challenges in the roll out of a large cervical cancer vaccination program to protect against human papilloma virus (HPV) infection. Methods: This article describes the process of planning and implementing a HPV vaccination program using the existing state-wide framework that supports vaccine delivery to all 219 high schools in South Australia. The decision was made to offer three doses of HPV vaccine to 50,191 female students in Years 8-12 during the 2007 school year. Results: By November 2007, despite many challenges, the school vaccination program had delivered 107,541 doses of HPV vaccine. Coverage of dose 1 was highest in Years 8 (83%) and 10 (70%), but was reduced for doses 2 and 3 in all year levels, with dose 3 coverage ranging from 55% (Year 11) to 77% (Year 8). Conclusions: The introduction of a large school-based vaccination program at short notice posed new challenges for the co-ordination and implementation. Not all schools supported the introduction of HPV vaccine, resulting in reduced access for some students. Negative media messages provided a strong platform for individuals who opposed vaccination. These factors may have contributed to the less-than-expected uptake of HPV vaccine. Implications: Historically, there has been high uptake of other vaccines given to adolescents. However, the introduction of HPV vaccine may have adversely affected the uptake of Hepatitis B vaccine, given concurrently in the school program. Further studies are needed to determine if this is likely to have a negative effect on the public perception of the value of vaccine programs in general. © 2009 The Authors.

DOI: 10.1111/j.1753-6405.2009.00409.x

**ABSTRACT:** Background. The quadrivalent human papilloma virus (HPV) vaccine provides protection against HPV types 6 and 11, and 16 and 18. The Australian Government’s offer of free vaccination to women aged 18-26 years of age through general practitioners ends 30 June 2009. Objective: To determine the percentage of women attending Family Planning New South Wales (FPNSW) clinics aged 26 years or less who were aware of the free HPV vaccination program and had received a full course of the vaccine or had at least one injection. Method: A questionnaire to assess knowledge, attitudes, awareness and utilisation of the free vaccination catch up program for women aged 26 years or less through GPs was given to women attending the Ashfield, Newcastle and Penrith FPNSW clinics during May and June 2008 by the clinic receptionist for completion before seeing the clinician. Results: Two hundred and ninety-four women aged 15-26 years (mean age 21.7 ± 2.8) completed the questionnaire out of a total of 512 women in that age group who visited a FPNSW clinic; response rate 57.4%. Eighty-three percent had heard about the vaccine and 56% had presented to a GP for at least one injection. The majority of women (213, 72.4%) had visited a GP in the previous 6 months. In total, GPs had suggested having the vaccine to 110 (37.4%) women during a recent visit; 59 (53.6%) of these women had visited a GP specifically to have the HPV vaccine. Of the 179 who responded to the question about awareness of the availability of a free course of HPV vaccine, 76 (42.5%) were unaware that they could obtain free vaccination through a GP. Conclusion: General practitioners should use opportunistic visits by young women to provide information about the catch up HPV vaccination program and encourage them to participate in the program. As the offer of free vaccination through GPs ends 30 June 2009 it is important that GPs encourage as many eligible women as possible to participate. The reduction in incidence of cervical cancer in Australia depends on maximal coverage of eligible women.

### 3.5 COST

**SUMMARY**

Modeling studies have provided important health policy information when complete information about future impacts of various HPV vaccination strategies has been absent. Using current vaccine efficacy data, vaccine costs, and cervical cancer screening rates, cost effectiveness studies have not demonstrated value for women over the age of 30 who continue to be screened at least every two years or for males. However, vaccinating 12 year old females demonstrated significant decreases in cervical cancer incidence rates and related health care costs.

**Priority Research**

Research to analyze available HPV clinical end points from health service databases, incorporating the data into modeling studies to validate the strategy methodology and predicted outcomes, and understand real health effectiveness outcomes.

Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in women older than 30 years in the United States. *Annals of Internal Medicine, 151*(8), pp. 538-545.

**ABSTRACT:** Background. Women older than 30 years are the main beneficiaries of improved cervical cancer screening with human papillomavirus (HPV) DNA testing. The role of vaccination against HPV types 16 and 18, which is recommended routinely for preadolescent girls, is unclear in this age group. Objective: To assess the health and economic outcomes of HPV vaccination in older U.S. women. Design: Cost-effectiveness analysis with an empirically calibrated model. Data Sources: Published literature. Target Population: U.S. women aged 35 to 45 years. Time Horizon: Lifetime. Perspective: Societal. Intervention: HPV vaccination added to screening strategies that differ by test (cytology or HPV DNA testing), frequency, and start age versus screening alone. Outcome Measures: Incremental cost-effectiveness ratios (2006 U.S. dollars per quality-adjusted life-year [QALY] gained). Results of Base-Case Analysis: In the context of annual or biennial screening, HPV vaccination of women aged 35 to 45 years ranged from $116 950 to $272 350 per QALY for cytology with HPV DNA testing for triage of equivocal results and from $193 690 to $381 590 per QALY for combined cytology and HPV DNA testing, depending on age and screening frequency. Results of Sensitivity Analysis: The probability of HPV vaccination being cost-effective for women aged 35 to 45 years was 0% with annual or biennial screening and less than 5% with triennial screening, at thresholds considered good value for money. Limitation: The natural history of the disease and the efficacy of the vaccine in older women are uncertain. Conclusion: Given currently available information, the effectiveness of HPV vaccination for women older than 30 years who are screened seems to be small. Compared with current screening that uses sensitive HPV DNA testing, HPV vaccination is associated with less attractive cost-effectiveness ratios in this population than those for other, well-accepted interventions in the United States. Primary Funding Source: National Cancer Institute, Centers for Disease Control and Prevention, and the American Cancer Society. © 2009 American College of Physicians.


**ABSTRACT:** Background: Despite the fact that approximately 70% of Canadian women undergo cervical cancer screening at least once every 3 years, approximately 1,300 women were diagnosed with cervical cancer and approximately 380 died from it in 2008. This study estimates the effectiveness and cost-effectiveness of vaccinating 12-year old Canadian females with an AS04-adjuvanted cervical cancer vaccine. The indirect effect of vaccination, via herd immunity, is also estimated. Methods: A 12-health-state 1-year-cycle Markov model was developed to estimate lifetime HPV related events for a cohort of 12-year old females. Annual transition probabilities between health-states were derived from published literature and Canadian population statistics. The model was calibrated using Canadian cancer statistics. From a healthcare perspective, the cost-effectiveness of introducing a vaccine with efficacy against
HPV-16/18 and evidence of cross-protection against other oncogenic HPV types was evaluated in a population undergoing current screening practices. The base-case analysis included 70% screening coverage, 75% vaccination coverage, $135/dose for vaccine, and 3% discount rate on future costs and health effects. Conservative herd immunity effects were taken into account by estimated HPV incidence using a mathematical model parameterized by reported age-stratified sexual mixing data. Sensitivity analyses were performed to address parameter uncertainties.

Results: Vaccinating 12-year old females (n = 100,000) was estimated to prevent between 390-633 undiscounted cervical cancer cases (reduction of 47%-77%) and 168-275 undiscounted deaths (48%-78%) over their lifetime, depending on whether or not herd immunity and cross-protection against other oncogenic HPV types were included. Vaccination was estimated to cost $18,672-$31,687 per QALY gained, the lower range representing inclusion of cross-protective efficacy and herd immunity. The cost per QALY gained was most sensitive to duration of vaccine protection, discount rate, and the correlation between probability of screening and probability of vaccination. Conclusion: In the context of current screening patterns, vaccination of 12-year old Canadian females with an ASO4-ajuvanted cervical cancer vaccine is estimated to significantly reduce cervical cancer and mortality, and is a cost-effective option. However, the economic attractiveness of vaccination is impacted by the vaccine’s duration of protection and the discount rate used in the analysis. © 2009 Anonychuk et al; licensee BioMed Central Ltd.


**ABSTRACT:** Objective: To assess the cost effectiveness of including preadolescent boys in a routine human papillomavirus (HPV) vaccination programme for preadolescent girls. Design: Cost effectiveness analysis from the societal perspective. Setting: United States. Population: Girls and boys aged 12 years. Interventions: HPV vaccination of girls alone and of girls and boys in the context of screening for cervical cancer. Main outcome measure: Incremental cost effectiveness ratios, expressed as cost per quality adjusted life year (QALY) gained. Results: With 75% vaccination coverage and an assumption of complete, lifelong vaccine efficacy, routine HPV vaccination of 12 year old girls was consistently less than $50 000 per QALY gained compared with screening alone. Including preadolescent boys in a routine vaccination programme for preadolescent girls resulted in higher costs and benefits and generally had cost effectiveness ratios that exceeded $100 000 per QALY across a range of HPV related outcomes, scenarios for cervical cancer screening, and assumptions of vaccine efficacy and duration. Vaccinating both girls and boys fell below a willingness to pay threshold of $100 000 per QALY only under scenarios of high, lifelong vaccine efficacy against all HPV related diseases (including other non-cervical cancers and genital warts), or scenarios of lower efficacy with lower coverage or lower vaccine costs. Conclusions: Given currently available information, including boys in an HPV vaccination programme generally exceeds conventional thresholds of good value for money, even under favourable conditions of vaccine protection and health benefits. Uncertainty still exists in many areas that can either strengthen or attenuate our findings. As new information emerges, assumptions and analyses will need to be iteratively revised to continue to inform policies for HPV vaccination. DOI: 10.1136/bmj.b3884


**ABSTRACT:** We evaluated the cost-effectiveness of HPV 16 18 vaccination for girls aged 12 years in The Netherlands in addition to cervical cancer screening. For this purpose, we developed a simulation model that describes the relation between each of the high-risk human papillomavirus (hrHPV) types and cervical disease, allowing the occurrence of multiple type-specific infections. Model parameters were derived from Dutch cohort studies, including a large population-based screening trial, and from the national cervical cancer registry. The model satisfactorily reproduced Dutch data on HPV infection and the presence of cervical lesions. For our base-case scenario in which 85% of the girls aged 12 years were vaccinated against types 16 18 (95% efficacy, lifelong protection), the model predicted a decrease of 60% in the number of cervical cancer cases and cervical cancer deaths indicating that substantial health benefits can be achieved. Health savings were robust against changes in the vaccine efficacy (varied from 85% to 98%) but savings showed a substantial reduction when the efficacy started waning 10 years after vaccination. The discounted costs per quality-adjusted life-year (QALY) were €19,500/QALY (range €11,000 to €25,000/QALY) and lied near the cost-effectiveness threshold of €20,000 QUA used in The Netherlands. The simulations further showed that vaccination cannot replace screening because vaccination without screening was less effective than screening in preventing cancer in women over 40 years of age. In conclusion, our model results support the implementation of HPV 16 18 vaccination in young women in addition to cervical cancer screening, © 2008 Wiley-Liss, Inc.
DOI: 10.1002/ijc.24000


**ABSTRACT:** Objectives: The cost-effectiveness of adding a human papillomavirus (HPV) vaccination program in 12-year-old females to the recommended cervical cancer screening in Belgium is examined. Moreover, the health and economic consequences of a potential decline in screening uptake after initiation of a HPV vaccination program are investigated. Methods: A static Markov model is developed to estimate the direct effect of vaccination on precancerous lesions and cervical cancers. Results: Vaccination is estimated to avoid 20 percent of the cervical cancers occurring in a 12-year-old girls’ cohort and to cost €32,665 per quality-adjusted life-year (QALY) gained (95 percent credibility interval [CrI]: €17,447 to €68,078), assuming a booster injection after 10 years, a limited duration of protection and discounting costs and effects at 3 percent and 1.5 percent, respectively. Assuming lifelong protection, HPV vaccination is estimated to cost €14,382 (95 percent CrI: €9,238 to €25,644) per QALY gained, while avoiding 50 percent of the cervical cancer cases. In the base-case, a 10 percent reduction in screening compliance after vaccination obliterates the effect of vaccination on cervical cancer cases avoided, whereas further declines in the level
of screening compliance even turned out to be detrimental for the cohort’s health, inducing a mean loss in QALYs and life-year gained compared with the situation prevaccination.

Conclusions: An HPV vaccination program should only be considered if the level of screening after vaccination can be maintained. Copyright © 2009 Cambridge University Press.

DOI: 10.1017/S0266462309090217


ABSTRACT: Aim: Clinical trials have demonstrated the efficacy of the tetravalent human papillomavirus (HPV) vaccination in the prevention of cervical cancer and genital warts associated with HPV types 6, 11, 16 and 18. We used an empirically calibrated Markov cohort model of the natural history of HPV to assess the cost-effectiveness of the vaccine administered to 12-year-old girls alongside existing cervical screening programmes in Germany.

Subjects and methods: The model estimated cervical cancer (CC), cervical intraepithelial neoplasia (CIN) and genital wart lifetime risks and total lifetime health care costs, life years gained and quality-adjusted life years (QALY) gained. The analysis was conducted from the perspective of the German health care payer. Results: In the base case (considering a lifetime duration of protection and 100% efficacy) it was estimated that 2,835 cervical cancer cases and 679 deaths could be prevented among a cohort of 400,000, at an incremental cost per QALY gained of 10,530 €. A total of 120 girls needed to be vaccinated to prevent 1 case of CC. Cost-effectiveness is sensitive to a duration of protection of less than 20 years and to the discount rate for costs and benefits. Conclusion: A policy of vaccinating adolescent girls has been recommended by the German Standing Committee on Vaccinations. This study has demonstrated that such a policy is cost-effective based on thresholds of cost-effectiveness that apply in Germany. © 2008 Springer-Verlag.

DOI: 10.1007/s10389-008-0228-3


ABSTRACT: Background. In the Netherlands, low cervical cancer incidence and mortality rates might limit the cost-effectiveness of vaccination against the human papillomavirus (HPV). We examined the effect on cervical cancer incidence and mortality of adding HPV vaccination to the current Dutch cervical cancer screening situation and calculated the cost-effectiveness. Methods: Costs and effects were estimated under favorable assumptions (ie, that HPV vaccination provides lifelong protection against 70% of all cervical cancers, has no side effects, and is administered to all women regardless of their risk of cervical cancer) by using the microsimulation screening analysis (MISCAN) model. The impact of changes in the price of vaccination, number of booster vaccinations, vaccination attendance rate, vaccination efficacy, cervical cancer incidence level, and quality-of-life assumptions was investigated in sensitivity analyses. Results: Using the current price of €118 per vaccine dose and with discounting of costs and effects at an annual rate of 3%, adding HPV vaccination to the current Dutch screening situation had a cost-effectiveness ratio of €53500 per quality-year.
adjusted life-year (QALY) gained. The threshold price per vaccine dose at which the cost-effectiveness of vaccination would correspond to an acceptability threshold of €20000 per QALY gained was €40. With the addition of one or more (up to four) booster vaccinations during a lifetime, this threshold price decreased to €33 for one booster (to €16 for four boosters). With a doubling of the cervical cancer incidence level, the cost-effectiveness ratio was €24400 per QALY gained and the maximum price per dose at threshold of €20000 was €97. All threshold prices were lower under less favorable effectiveness assumptions.

Conclusions: In the Netherlands, HPV vaccination is not cost-effective even under favorable assumptions. To become cost-effective, the vaccine price would have to be decreased considerably, depending on the effectiveness of the vaccine.

DOI: 10.1093/jnci/djp183


**ABSTRACT:** Background. The introduction of a quadrivalent human papillomavirus (HPV; types 6, 11, 16, 18) vaccine is expected to significantly reduce the burden of cervical cancer, cervical intraepithelial neoplasia (CIN), genital warts and other HPV-related diseases. Objective: To determine the cost effectiveness of providing a quadrivalent (6,11,16,18) HPV vaccine programme in adolescent females aged 12 years in addition to the existing cervical cancer screening programme in Belgium. Methods: A Markov state-transition model was developed for the Belgian context in order to evaluate the long-term impact of vaccinating a cohort of girls aged 12 years alongside the existing screening programme. Women were followed until the age of 85 years. A vaccine that would prevent 100% of diseases associated with HPV-6, -11, -16 and -18, with lifetime duration of efficacy, 80% coverage, in conjunction with current screening, was compared with screening alone. For this analysis, 35% of cases of CIN-1, 55% of CIN-2/3, 75% of cervical cancer and 90% of genital warts were considered to be attributable to HPV-6, -11, -16 and -18. The model estimated lifetime risks and total lifetime healthcare costs, survival and QALYs for cervical cancer, CIN and genital warts. Outcomes validation was applied. Model outcomes also included incremental costs per life-year gained and incremental costs per QALY gained. The analysis was conducted from the perspective of the Belgian healthcare payer, and costs were in year 2006 values. Results: The model estimated a reduction in the lifetime risk of cervical cancer from 0.94% to 0.34%, therefore preventing 362 cases of cervical cancer and 131 related deaths in a cohort of 60 000 girls aged 12 years in Belgium. The base-case scenario suggests quadrivalent HPV vaccination in addition to current cervical screening in Belgium to be cost effective at €10 546 per QALY. This is within the accepted range of cost-effective interventions in Europe. This cost effectiveness is maintained for different parameter assumptions in the sensitivity analysis, with the exception of very high discount rates for costs and medical benefits, but, even in the worst case, ratios were still less than €50 000 per QALY. Even when a separate scenario modelled the requirement for a booster vaccination to sustain a lifetime duration of protection, the results remained cost effective at €17 388 per QALY. Conclusions: Vaccination with a quadrivalent HPV vaccine appears to be a cost-effective public health intervention in conjunction with the existing screening programme in Belgium. The additional costs of
introducing vaccination to the established screening programme would be offset by the potential savings from not having to treat the diseases caused by HPV-6, -11, -16 or -18. © 2009 Adis Data Information BV.

DOI: 10.2165/00019053-200927030-00006


**ABSTRACT:** The recent approval of human papillomavirus (HPV) vaccine means that decision makers need information beyond that available from randomized clinical trials to recommend funding for this vaccination programme. Modelling and economic studies have addressed some of those information needs. We conducted a qualitative systematic review to summarize the existing data. Review articles were obtained from an extensive literature search on studies using mathematical modelling (either a Markov or transmission dynamic model) to determine the effectiveness or cost effectiveness of an HPV vaccine compared with the current cytology-based Pap smear screening programme. A total of 21 studies (but 22 models) were included in the review after being assessed for methodological quality. All of the included studies had used a mathematical model to determine the effectiveness of an HPV vaccine, whilst 13 had also conducted a cost-effectiveness analysis. Although the studies used different model structures, baseline parameters and assumptions, all studies showed that vaccination would decrease rates of HPV infection, precancerous lesions and cervical cancer. Studies had a consistent message with respect to cost effectiveness: a female-only vaccination programme is cost effective compared with the current cytology-based Pap smear screening programme, while the cost effectiveness of a male and female vaccination programme is generally not cost effective compared with female-only vaccination. © 2009 Adis Data Information BV.

DOI: 10.2165/00019053-200927020-00004

Economic evaluation of human papillomavirus vaccination in developed countries. *Public Health Genomics, 12*(5-6), pp. 343-351.

**ABSTRACT:** Background. With promising efficacy results from randomized control trials of human papillomavirus (HPV) vaccines and the availability of new screening paradigms, policymakers are being asked to make recommendations and decisions regarding the optimal strategies to reduce HPV infection and disease. Such decisions are increasingly being made with significant input from mathematical and economic models. The demand for modeling has resulted in the publication of numerous mathematical models looking at the cost-effectiveness of HPV vaccination. Objective: To review published models that have been used to evaluate the cost-effectiveness of HPV vaccination in developed countries and highlight points of consensus and disagreement in methods and findings. Methods: This review consists of cost-effectiveness studies published in the peer-reviewed literature before August 2008. Results: Despite variations in methods, modeling studies are producing consistent conclusions: (1) vaccinating young girls
against HPV is likely to be cost-effective; (2) vaccinating boys will most likely not be cost-effective in countries that can reach high coverage rates in girls, and (3) results are most sensitive to the duration of vaccine protection. However, results from analyses examining the effectiveness and cost-effectiveness of vaccinating boys when coverage rates are low (≤80%) and catch-up strategies have reached conflicting conclusions. Copyright © 2009 S. Karger AG.

DOI: 10.1159/000214924


Cost of treatment and QALYs lost due to genital warts: Data for the economic evaluation of HPV vaccines in the United Kingdom. *Sexually Transmitted Diseases, 36*(8), pp. 515-521.

**ABSTRACT:** BACKGROUND: Data on the burden of genital warts in terms of treatment costs and detriment to quality of life (QoL) are required to assess cost-effectiveness of quadrivalent human papillomavirus vaccination. We investigated the cost of treatment and period of time for which QoL is affected to obtain estimates of quality-adjusted life year (QALY) loss associated with an episode of genital warts. METHODS: Adults diagnosed with genital warts attending the York sexually transmitted disease clinic during two 3-month periods in 2006 and 2007 were enrolled (n = 189). Data on cost of treatment and duration of episode of care were collected from a retrospective case note review. QALY loss was calculated by applying estimates of the duration of time for which QoL was affected to the previously reported detriment to QoL associated with genital warts. RESULTS: The average cost per episode of care was $286 (£139, 95% CI: $246-$327). Estimated loss of QALYs ranged from 0.0045 (95% CI: 0.0014-0.0078) to 0.023 (95% CI: 0.0072-0.039).

CONCLUSIONS: Genital warts present a significant burden both to individuals and to the health service. Data on the burden of genital warts should be incorporated into economic evaluations of human papillomavirus vaccination strategies. © Copyright 2009 American Sexually Transmitted Diseases Association.

DOI: 10.1097/OLQ.0b013e3181a74c2c


**ABSTRACT:** Sexually transmitted human papillomavirus (HPV) infection is very common in men and women. Oncogenic HPV is strongly associated with cancers and high-grade dysplasias of the anogenital tract, including the anus, penis, and also a proportion of oropharyngeal cancers. In reducing male disease burden, some consider screening and treatment for high-grade anal dysplasia (AIN) to prevent anal cancer in high-risk populations. Such strategies have wide implications for the workforce, and require more evidence for the optimal management of AIN. Male sexual behavior, with consequent HPV infection and disease contribute to considerable disease burden in females. Hence, inclusion of males in prophylactic HPV vaccination programs should prevent HPV-related disease in males as well as substantially reducing disease burden in females. Clinical trial data in males 16–26 years for the quadrivalent vaccine show it is well tolerated, induces a strong type-specific
immunological response comparable to that of females, and reduced vaccine HPV-type-related genital infection, as well as disease. Cost–benefit analyses and mathematical modeling show that the most cost-effective strategy involves routine administration of this vaccine to 12-year-old females, with catch-up vaccination of 12- to 24-year-olds, with the most effective strategy in disease reduction including men and/or boys in the program. Such a vaccination strategy including 12-year-old boys is projected by 2050 to reduce HPV 16 infection by 88–94% in females and 68–82% in males, plus the aforementioned male HPV-related cancers by 22–27%. Therefore, inclusion of males in an HPV vaccination program is likely to have significant health and economic benefits over and above those observed from current female-only programs. However, comprehensive cost–benefit analyses are needed to determine the efficacy of these programs in the overall population. Such analyses will be crucial for the design, acceptance, and implementation of these vaccination programs into clinical practice globally. © 2010 Published by Elsevier Inc. DOI: 10.1016/j.ygyno.2010.01.027

3.6 KNOWLEDGE, ATTITUDES, BELIEFS

3.6.1 Public

SUMMARY

Studies conducted in school and University settings demonstrated weak HPV knowledge association with cervical cancer. Insurance coverage and cost of vaccination (OR 5.31) and perceived social norms from family and friends (OR 2.21) impacted vaccination intention. When school aged girls participated in vaccine decision-making with their parents, immunization rates improved (48%-77%).


ABSTRACT: Background. Certain types of human papillomavirus (HPV) can cause cervical and other cancers. A vaccine that protects against HPV types responsible for 70% of cervical cancers is available to females ages 9-26. Objective: To examine correlates of stage of vaccine adoption among women ages 18-22. Methods: In 2007, female students (n = 4774) at a New England University in the U.S. were invited to complete an on-line survey that assessed knowledge of HPV, perceived susceptibility, severity, vaccine benefits/barriers, social and subjective norms, and stage of vaccine adoption. Results: 1897 women (40%) responded; complete data were available for 1401. About half (53%) were planning to be vaccinated, 12% had received the vaccine, 15% were undecided, and 7% had decided against vaccination. HPV knowledge was low (mean 58%). In multivariate analyses, social norms was the strongest correlate of
stage; each standard deviation increase in social norms score was associated with more than four times the odds of intending to be vaccinated within the next 30 days, compared with those who had decided against vaccination (OR = 4.15; 95% CI 2.17-6.36). Conclusions: Acceptance of the vaccine was high, although misconceptions about viral transmission, availability of treatment, and the role of Pap tests were common. Perceived norms were strongly associated with intentions. Interventions on college campuses should stress vaccination as a normative behavior, provide information about viral transmission, and stress the role of continued Pap screening. © 2008 Elsevier Inc.


Human papillomavirus vaccine uptake, predictors of vaccination, and self-reported barriers to vaccination. Journal of Women’s Health, 18(10), pp. 1679-1686.

ABSTRACT: Objective: To describe human papillomavirus (HPV) vaccine uptake, predictors of vaccination, and barriers to vaccination in young women. Methods: Participants were 13-26-year-old girls and women recruited from an urban, hospital-based clinic. Between June and December 2007, 6 months after they had completed a baseline survey, they were recontacted to assess receipt of at least one HPV vaccine dose and barriers to receiving the vaccine. We assessed whether demographic factors, gynecological history, and attitudes measured at baseline were associated with vaccination at follow-up using logistic regression. Results: Of the 262 women who completed the baseline study, 189 (72%) participated in this follow-up study. At follow-up, 68 of 189 (36%) had received ≥1 HPV vaccine dose. Factors measured at baseline that predicted vaccination 6 months later included insurance coverage for HPV vaccination (odds ratio [OR] 5.31, 95% confidence interval [CI] 1.61-17.49) and the belief that one's parents, partners, and clinicians endorsed HPV vaccination (OR 2.21, 95% CI 1.29-3.79); those with a history of an abnormal Pap test were less likely to have received the vaccine (OR 0.30, CI 0.10-0.92). Of the 121 who were unvaccinated, 54 (45%) had not returned to the clinic since the baseline study, 51 (42%) had returned but were not offered vaccine, and 15 (12%) had declined vaccination. Conclusions: Interventions to increase HPV vaccination rates in women in the catch-up age group for vaccination should ensure that vaccine costs are covered, promote HPV vaccination as normative, and establish clinic-based systems to prevent missed opportunities for vaccination. © 2009, Mary Ann Liebert, Inc.

DOI: 10.1089/jwh.2008.1329


Knowledge, attitudes, and informational behaviors of college students in regard to the human Papillomavirus. Journal of American College Health, 58(2), pp. 141-149.

ABSTRACT: Objective: To assess students’ human papillomavirus (HPV) knowledge, attitudes, and behaviors. Participants/ Methods: Students (N = 1,282) at a large, public university in the Northeast United States completed a questionnaire during February 2008 assessing HPV knowledge, prevalence, transmission, cervical cancer risk and stigma; sexual behavior, vaccination status, as well as past and preferred sources of information about HPV and sexual
health. Results: A majority of respondents know of HPV. However, understanding was insufficient in several important areas. Overwhelmingly, respondents heard about HPV via television commercials yet preferred to obtain sexual health information from physicians. Hearing about HPV on a TV commercial was associated with increased knowledge. More knowledge of HPV was associated with less stigma. Men exhibit a higher level of stigma and less knowledge than women. Conclusions: Publicly funded health campaigns aimed at increasing knowledge about HPV are overdue and necessary. This is especially true for efforts targeting young adults about this extremely common sexually transmitted infection (STI). © 2009 Heldref Publications.

DOI: 10.1080/07448480903221368


Knowledge and Early Adoption of the HPV Vaccine Among Girls and Young Women: Results of a National Survey. Journal of Adolescent Health, 45(5), pp. 453-462.

ABSTRACT: Purpose: In 2006, universal human papillomavirus (HPV) vaccination of females ages 9 to 26 years became a formal recommendation, yet little is known about knowledge and adoption of this vaccine. Methods: A cross-sectional survey of females aged 13 to 26 years was drawn from a nationally representative panel, and developed and maintained by Knowledge Networks, Inc. (Menlo Park, CA). Outcome measures included: (a) knowledge about HPV and the HPV vaccine, (b) barriers to vaccine adoption, and (c) prevalence and correlates of early vaccine receipt. Results: Overall, 1,011 of 2,143 subjects (47%) completed the survey. Thirty percent of 13- to 17-year-olds and 9% of 18- to 26-year-olds reported receipt of at least one HPV injection. Knowledge about HPV varied; however, 5% or fewer subjects believed that the HPV vaccine precluded the need for regular cervical cancer screening or safe-sex practices. Adjusting for healthcare utilization and sources of information, vaccine receipt was more likely among 13- to 17-year-olds who reported a recent healthcare visit (adjusted odds ratio [AOR] 7.31, confidence interval [CI] 2.00-26.8) and reported discussing the HPV vaccine (AOR 4.50, CI 1.02-19.90) with a healthcare provider; and more likely among 18- to 26-year-olds who reported discussing the HPV vaccine (AOR 3.08, CI 1.21-7.80) with family or a healthcare provider (AOR 11.92, CI 2.62-54.27). Conclusions: Few girls and young women believe that the HPV vaccine is protective beyond the true impact of the vaccine. Despite moderate uptake, many females at risk of acquiring HPV have not yet received the vaccine. These findings suggest the important role of both healthcare providers and parents in HPV vaccine adoption. © 2009 Society for Adolescent Medicine.

DOI: 10.1016/j.jadohealth.2009.04.021


ABSTRACT: The aim of the study was to investigate knowledge of and attitudes to sexually transmitted infection (STI) and STI prevention with special focus on human papillomavirus (HPV) and the new vaccine against HPV, among 16-year-old high school
students in a Swedish context. A study-specific questionnaire was distributed to 572 first year high school students from five different high schools in a medium-sized town in Sweden. The students lacked knowledge of HPV and its association with cervical cancer. Similarly, their knowledge of the new vaccine was limited. Their attitude to condom use when having sex with a new partner was positive, but decreased if oral contraceptives were used and if they were vaccinated against an STI. The main source of information was the school, followed by youth clinics and the media. The results highlight the clinical importance for school nurses and personnel at youth clinics to inform adolescents about HPV and its association with cancer.

DOI: 10.1258/ijsa.2008.008200


**ABSTRACT:** Objective: To investigate knowledge of human papillomavirus (HPV) and attitudes to HPV vaccination and condom use among Swedish first year upper secondary school students. Methods: Classroom questionnaire filled in by 608 students from a strategic sample of seven upper secondary schools in Sweden. Results: Only 13.5 (n=82) of the students had heard about HPV and 6 (n=35) were aware of HPV vaccination. As many as 84 (n=508) would like to be vaccinated against HPV. The high cost of vaccination was the greatest obstacle (total group 37, n=227); among girls the second major hindrance was the fear of needles (19, n=65). Before considering an HPV vaccination 73 (n=443) wanted more information and 36 (n=220) would like to receive such information from the school nurse. The students considered it less likely that they would use a condom when having intercourse with a new partner if they were vaccinated than if they were not (p<0.001). Conclusion: Despite intensive marketing directed at potential vaccine consumers, knowledge of HPV and of HPV vaccines was very low among first year upper secondary school students. Their attitude towards vaccination was positive but most of them wanted more information before considering vaccination. © 2009 European Society of Contraception and Reproductive Health.

DOI: 10.3109/13625180903229605


**ABSTRACT:** Men play an important role in transmission of human papillomavirus (HPV). Both in men and in women HPV causes great morbidity, such as cervical cancer, penile and anal cancer, and genital warts. The awareness of HPV and its consequences is essential to a successful vaccination program against HPV. In this study, we assessed awareness of HPV in Danish men. A random sample of men aged 18-45 years from the general male population was invited to participate in the study. The participants filled in a self-administered questionnaire with questions concerning awareness of HPV, lifestyle, and sexual habits. In the period from November 2006 to June 2007, more than 23 000 men were included in the study (participation rate approximately 71%). Overall, 10% of the participants reported
to have heard of HPV. Comparison with an earlier study in Danish women showed lower awareness in men than in women (25%). Higher educational level and history of self-reported genital warts were the strongest predictors of having heard of HPV. Furthermore, condom use and excellent self-rated health were significantly correlated with awareness of HPV. In contrast, no correlations were found with age, lifetime number of sexual partners, and smoking and drinking patterns. In conclusion, we found that awareness of HPV among Danish men was scarce. The low level of awareness of HPV, particularly in men, can be a barrier in preventing HPV-related diseases. Education is warranted to increase such awareness to ensure success of HPV vaccination. © 2009 Lippincott Williams & Wilkins, Inc.


**ABSTRACT:** Background. There is little information on girls’ experiences of human papillomavirus (HPV) vaccination in the prevention of cervical cancer. We investigated the views of adolescent girls who had been offered the vaccine as part of a feasibility study conducted in Manchester. Methods: All 12 to 13-year-old girls in two primary care trusts were offered three doses of Cervarix (manufactured by GlaxoSmithKline). A letter was sent to 1084 parents who had consented to research follow-up. It requested parents to pass a questionnaire regarding HPV vaccination to their daughters to complete and post back in a prepaid envelope. Results: A total of 553 girls completed the questionnaire. Altogether, 77% (422) had shared with their parents in the vaccine decision. In all, 42% (n13) of girls, whose parents refused vaccination, stated that they wanted the vaccine, whereas 10% (50) of those who were vaccinated did not want the vaccine. Although 54% (277) said the vaccine was very important to them, 39% (153) of vaccinated girls thought they might not recommend it to others. The vaccine was perceived to be painful and there were exaggerated rumours of serious adverse events and needle scares. A total of 79% (420) of girls agreed with a statement that vaccination reminded them of the risks of sexual contact, but 14% (73) agreed they might take more sexual risks because they had been vaccinated. Conclusion: Girls of this age form their own views on HPV vaccination but parental support for vaccination remains important, especially for completing the three doses. By discussing the vaccine, parents can encourage their daughters to determine the importance and implications of HPV vaccination. © 2009 Cancer Research UK.

DOI: 10.1038/sj.bjc.6605362


**ABSTRACT:** Objectives: To report awareness of human papillomavirus (HPV) and HPV vaccine among women aged 18-49 years and, for recommended women aged 18-26 years, estimate initiation of HPV vaccination and describe factors associated with vaccination initiation among a national sample. Methods: Data were analyzed from the National...
Immunization Survey-Adult, a nationally representative telephone survey conducted May-August 2007. Questions were asked about awareness of HPV and HPV vaccine and vaccine receipt. Results: A total of 1102 women aged 18-49 years were interviewed, 168 were aged 18-26 years. Overall, awareness of HPV (84.3%) and of HPV vaccine (78.9%) were high. Among women 18-26 years of age, vaccination initiation (≥ 1 dose) was 10%. Factors associated with vaccination included not being married, living ≥ 200% of the federal poverty index, having health insurance, and vaccination with hepatitis B vaccine. HPV vaccination initiation among women aged 27-49 years was 1%. Conclusions: Awareness of HPV and HPV vaccine were high. Two to 5 months after national HPV vaccination recommendations were published, one in ten women 18-26 years old had initiated the HPV vaccine series. Women at a higher socio-economic level were more likely to receive the vaccination. Vaccination initiation and completion will likely increase over the next years. Monitoring uptake is important to identify sub-groups that may not be receiving the vaccination.

DOI: 10.1016/j.ypmed.2008.11.010


ABSTRACT: Objective: To assess knowledge of and attitudes towards human papillomavirus (HPV), Pap testing, and the HPV vaccine. Methods: In a multicenter U.S. cohort study, women with the human immunodeficiency virus (HIV) and at-risk comparison women completed 44-item standardized self-report questionnaires exploring their knowledge of cervical cancer prevention, HPV, and HPV vaccination. Results were correlated with demographic variables, measures of education and attention, and medical factors. Data were clustered using principal component analysis. Significant associations were assessed in multivariable models. Results: Among 1588 women, HIV seropositive women better understood facts about cervical cancer prevention and HPV than seronegative women, but both had substantial knowledge deficits. Almost all women considered Pap testing important, although 53% of HIV seropositive and 48% of seronegative women considered cervical cancer not preventable (P = 0.21). Only 44% of HIV seropositive women knew Paps assess the cervix, versus 42% of HIV seronegative women (P = 0.57). Both groups understood that HPV causes genital warts and cervical cancer (67% of HIV seropositive vs. 55% of seronegative women, P = 0.002). About half of both groups considered HPV vaccination extremely important for cervical cancer prevention. HIV seronegative women were more likely to report learning of HPV vaccination through advertising than from clinicians (81% vs. 64%, P < 0.0001). Conclusion: High risk women need effective education about cervical cancer prevention, HPV, and HPV vaccination. © 2010 Elsevier Inc.

DOI: 10.1016/j.ygyno.2009.12.030


ABSTRACT: This study aimed to ascertain the attitudes of men who have sex with men
3.6 Knowledge, Attitudes, Beliefs

(MSM) to the human papillomavirus (HPV) vaccine and to determine the age at which MSM would be willing to ask for the HPV vaccine in relation to their age of sexual debut. Of 205 MSM attending the Melbourne Sexual Health Centre between December 2007 and January 2008, 200 (98%; median age 27 years) completed the study questionnaire. Only 30% were aware that there was a vaccine available for protection against infection with certain HPV types. When informed of the increased risk of anal cancer among MSM, 47% of MSM indicated that they would be willing to pay $A450 for the vaccine course. A total of 93% indicated that they would be willing to disclose that they were MSM to a health professional in order to obtain the vaccine for free, but not until a median age of 20 years: 2 years after the median age of sexual debut (18 years) and after a median of 15 sexual partners. If the HPV vaccine is targeted to MSM, the challenge will be for MSM to be vaccinated before they acquire HPV infection.

DOI: 10.1136/sti.2008.032581


**ABSTRACT:** Background: State and national policymakers are actively debating the merits of legally mandating the human papillomavirus (HPV) vaccine. Methods: This was a cross-sectional pilot study designed to identify factors associated with HPV vaccination in 170 high school girls and the decision making by girls about vaccination. Results: Overall, 48.4% participated in the vaccination decision making and 37.8% were vaccinated, but there were significant vaccine-related knowledge gaps. Girls often lacked basic knowledge necessary to make vaccine decisions. Vaccination was significantly associated with older age, vaccine information sources, and higher vaccine-related knowledge, but not with estimates of risk of HPV-related diseases, religion, or frequency of health care visits. Conclusions: This paper describes the first study to have identified factors associated with HPV vaccination among California high school girls and to have documented that a high percentage are participating in the vaccination decision making. These findings have implications for adolescent health education and nursing practice and provide new information relevant to the current public policy debates about mandatory vaccination. © 2010 National Association of Pediatric Nurse Practitioners.

DOI: 10.1016/j.pedhc.2008.11.004


**ABSTRACT:** Objective: Cervical HPV is the most common sexually transmitted disease among college-age women. This study aimed to assess knowledge and attitudes towards HPV infection, HPV vaccination and cervical cancer among female university students, to provide insight into development of HPV educational information. Study design: A cross-sectional survey using a convenience sample. A total of 1083 ethnically diverse female
students attending a public university were approached and 650 were interviewed. Results: Knowledge regarding HPV, HPV vaccination, cervical screening and cervical cancer risk factors was remarkably poor. Across the sample, the mean total knowledge score (14-item) was only 3.25 (S.D. ±2.41; 95% CI 3.07-3.44). Only 10.3% had heard of the newly released HPV vaccine. Approximately 48% of participants indicated an intention to receive an HPV vaccine. Intention to receive an HPV vaccine was significantly associated with knowledge of HPV and genital warts (OR 1.53; 95% CI 1.25-1.88), and knowledge of cervical screening and cervical cancer risk factors (OR 1.21; 95% CI 1.11-1.33). Of those who refused HPV vaccination, 50.9% doubted the safety and efficacy of the new vaccine, and 41.5% perceived themselves as not at risk of HPV infection. Conclusion: The findings suggest that providing education about the etiology of cervical cancer and the HPV link is an essential component to enhance HPV vaccine uptake. © 2009 Elsevier Ireland Ltd.


ABSTRACT: The quadrivalent human papillomavirus virus vaccine was recently licensed for use in males in the United States. This study reviews available published literature on acceptability among parents, health care providers, and young males. Among 23 published articles, half were conducted in the United States. The majority (87%) used quantitative survey methodology, and 13% used more explorative qualitative techniques. Convenience samples were used in most cases (74%) and 26% relied on nationally representative samples. Acceptability of a human papillomavirus virus (HPV) vaccine that protects against cervical cancer and genital warts was high in studies conducted among male college students (74%-78%) but lower in a community sample of males (33%). Among mothers of sons, support of HPV vaccination varied widely from 12% to 100%, depending on the mother’s ethnicity and type of vaccine, but was generally high for a vaccine that would protect against both genital warts and cervical cancer. Health providers’ intention to recommend HPV vaccine to male patients varied by patient age but was high (82%-92%) for older adolescent patients. A preference to vaccinate females over males was reported in a majority of studies among parents and health care providers. Messages about cervical cancer prevention for female partners did not resonate among adult males or parents. Future acceptability studies might incorporate more recent data on HPV-related disease, HPV vaccines, and cost-effectiveness data to provide more current information on vaccine acceptability.
DOI: 10.1016/j.jadohealth.2009.11.199


ABSTRACT: Background. The recent proliferation of studies describing factors associated with HPV vaccine acceptability could inform health care providers in improving vaccine coverage and support future research. This review examined measures of HPV and HPV-vaccine
knowledge, attitudes, beliefs, and acceptability, described psychometric characteristics, and provided recommendations about their use. Methods: A systematic search of Medline, CINAHL, PsycInfo, and ERIC through May 2008 for English language reports of quantitative data from parents, young adults or adolescents yielded 79 studies. Results: The majority of studies were cross-sectional surveys (87%), self-administered (67%), conducted before prophylactic vaccines were publicly available (67%) and utilized convenience samples (65%). Most measured knowledge (80%), general attitudes about HPV vaccination (40%), and willingness to vaccinate one’s daughter (26%). Two-thirds did not report reliability or validity measures. The majority did not specify a theoretical framework. Conclusions: Use of theoretical framework, consistent labeling of constructs, more rigorous validation of measures, and testing of measures in more diverse samples are needed to yield measurement instruments that will produce findings to guide practitioners in developing successful community and clinical interventions.

DOI: 10.1016/j.vaccine.2010.03.063

3.6.2 Racial/Cultural Differences

SUMMARY

Women’s knowledge, attitudes, and beliefs regarding HPV and HPV-related diseases have been associated with ethnic and cultural disparities. Most studies identified a low level of knowledge about HPV and a high intention to vaccinate male and female children. One study in the United States identified girls in lowest-income families more likely to be vaccinated. Older age, socio-economic status, ethnicity, and religion were associated with HPV vaccination awareness and acceptability. Recommendations have focused on developing culturally appropriate communication strategies including community involvement, appropriate delivery methods, and advocacy for high-risk groups.

Priority Research

Research methodology should incorporate community involvement, ownership, and long-term sustainability to create culturally appropriate messaging, strategies, and long-term evaluation of the impact on primary and secondary HPV prevention activities in Canada.


ABSTRACT: Objective: To explore Chinese women’s perceptions of human papillomavirus (HPV) vaccination and their intention to be vaccinated. Design: A cross-sectional community-based survey study. Setting: Thirteen community women’s health centres of The Family Planning Association of Hong Kong. Sample: A total of 1450 ethnic Chinese women aged 18 or above who attended the health centres. Methods: Participants completed a written
consent and an anonymous questionnaire onsite. Main outcome measures: Knowledge and beliefs about HPV and HPV vaccination against cervical cancer and participants’ own intention to be vaccinated. Results: About 38% of the participants (n = 527) had heard of HPV and 50% (n = 697) had heard of vaccination against cervical cancer. HPV infection was perceived to be stigmatising and detrimental to intimate, family and social relationships. Despite misconceptions and a grossly inadequate knowledge about HPV and HPV vaccination, 88% of the participants (n = 1219) indicated that they would likely be vaccinated. Majoritv of the participants believed that sexually experienced women should be vaccinated, while 27% opposed vaccinating sexually naive women. Younger age women who perceived a disruptive impact of HPV infection on intimate relationship and their partners’ approval were significantly associated with a positive intention to be HPV vaccinated. Conclusions: The easy acceptability of HPV vaccination among the mostly sexually experienced Chinese participants and their knowledge deficit on the subject may implicate potential misuse of the vaccines and a false sense of security against cervical cancer. There is a dire need for culturally sensitive and tailored education for the public, women of different ages and their partners about HPV and HPV vaccination. Emphasis must be placed on the prophylactic nature of the current vaccines, the uncertain effects when given to sexually experienced women, the importance of adolescent vaccination and the need for continued cervical screening whether vaccinated or not. © 2009 The Authors.
DOI: 10.1111/j.1471-0528.2008.01988.x


ABSTRACT: Objective: Recent scientific advances have lead to the development of a prophylactic, quadrivalent HPV vaccine conferring. We surveyed Latino and non-Latino women directly to examine what motivates them to vaccinate themselves, their daughters, and their sons. Methods: A written survey was administered to 86 Latinas and 141 non-Latinas, ages 18-55, and attending a general medicine, gynecology, or pediatric unit at an academic center. The instrument included questions on demographics, knowledge and attitudes toward the HPV vaccine, attitudes toward HPV vaccination for the respondents’ daughters and/or sons, and the effect of vaccine acceptability on women’s attitudes towards their sexual behavior and cervical cancer screening practices. Results: Acceptance for the HPV vaccine was high, with 73% of non-vaccinated, eligible women stating that they would vaccinate themselves. Cervical cancer prevention was the primary motivation for seeking vaccination. Most respondents reported that vaccination should still be accompanied by cervical cancer screening. Seventy-percent of eligible respondent agreed to vaccinate their daughters (97% of Latino and 68.2% of non-Latino mothers, p = 0.0078). Eighty-six percent of eligible participants agreed to vaccinate their sons (92.3% of Latino and 76.9% of non-Latino mothers, p = 0.0490). Cervical cancer prevention and anal/penile cancer prevention were the primary motivation reported for accepting the vaccine in their daughters and sons, respectively. Fewer than 20% of eligible respondents cited protection of women against developing cervical cancer as the motivation to vaccinate their son(s). Conclusions: Among
vaccine-eligible women, HPV vaccination acceptance for themselves, their daughters, and potentially their sons is high and primarily motivated by cancer prevention for the individual vaccinated. © 2008 Elsevier Inc.
DOI: 10.1016/j.ygyno.2008.12.010


**ABSTRACT:** Context: Because cervical cancer mortality in the United States is twice as high among black women as white women and higher in rural areas, providing human papillomavirus (HPV) vaccine to rural black adolescents is a high priority. Purpose: To identify racial differences in knowledge and attitudes about HPV, cervical cancer, and the HPV vaccine that may influence uptake of the vaccine. Methods: We interviewed women (91 black and 47 white) living in a rural area of the Southern United States in 2006. Analyses controlled for socioeconomic status, age, and recruitment location. Findings: More white respondents had heard of HPV than had black respondents (57% vs 24%, *P* <.001), and whites had higher HPV knowledge (42% vs 29% correct responses, *P* <.05). Blacks were less likely than whites to think that cervical cancer would be a serious threat to their daughters’ health (75% vs 96%, *P* <.001). More blacks than whites thought the ideal age to receive the vaccine was 17 years or older (63% vs 40%, *P* <.05). Blacks reported lower intentions to vaccinate their daughters than whites (*M* = 4.14 vs 4.55, *P* <.05 in unadjusted analyses, but not statistically significant in adjusted analyses). Conclusions: Black and white respondents had different awareness, knowledge, and beliefs related to the HPV vaccine. Communication-based interventions to maximize uptake of the HPV vaccine in the rural, Southern United States may need different messages for black parents of adolescent girls. © 2009 National Rural Health Association.
DOI: 10.1111/j.1748-0361.2009.00204.x


**ABSTRACT:** Study Objective: We sought to evaluate knowledge of human papilloma virus (HPV) and attitudes toward the HPV vaccine among emergency department (ED) patients. Design: Cross-sectional survey. Setting: Three Boston EDs. Participants: We enrolled consecutive patients during two 24-hour periods at each site. Interventions: None. Main Outcome Measures: Knowledge of HPV and attitudes toward the HPV vaccine. Results: We enrolled 387 patients (81% of eligible). Overall, 242 (63%) participants had heard of HPV and 203 (52%) supported state-mandated vaccination. In the multivariate model, characteristics associated with lower awareness of HPV were: (1) older age (compared to age 18-26-years: OR 0.45 [95% CI, 0.20-0.99] for age 27-44 years, OR 0.26 [95% CI, 0.12-0.56] for age 45-64 years, and OR 0.10 [95% CI, 0.04-0.28] for age 65 year or older), (2) black race (compared to white: OR 0.31 [95% CI, 0.15-0.64]); and (3) lower annual household income (OR 0.39 [95% CI, 0.19-0.81] for $40,000 or less). Of those people who had heard of HPV, 82% knew
of its relationship to cervical cancer, but only 61% thought it was a sexually transmitted disease (STD). Support for state-mandated vaccination was higher among participants who knew that HPV was an STD (OR 2.9 [95% CI 1.7-5.0]), but was not higher among those who had heard of HPV (OR 0.64 [95% CI 0.34-1.2]) or who knew that HPV causes cervical cancer (OR 0.85 [95% CI 0.45-1.6]). Conclusions: Support for state-mandated HPV vaccination appears to be driven more by the knowledge that HPV is an STD than by its role in cervical cancer. Awareness that HPV is transmitted through sexual activity does not decrease support for vaccination and may actually enhance it. © 2009 North American Society for Pediatric and Adolescent Gynecology.


**ABSTRACT:** Background. Studies of human papillomavirus (HPV) awareness and HPV vaccine acceptability have included few non-white participants, making it difficult to explore ethnic differences. This study assessed HPV awareness and HPV vaccine acceptability in a sample of women representing the major UK ethnic minority groups. Methods: A cross-sectional study design was used to assess awareness of HPV and acceptability of HPV vaccination. Participants were recruited using quota sampling to ensure adequate representation of ethnic minority women: Indian, Pakistani, Bangladeshi, Caribbean, African and Chinese women (n=750). A comparison sample of white British women (n=200) was also recruited. Results: Awareness of HPV was lower among ethnic minority women than among white women (6-18% vs 39% in white women), and this was not explained by generational status or language spoken at home. In a subsample who were mothers (n=601), ethnicity and religion were strongly associated with acceptability of HPV vaccination. Acceptability was highest among white mothers (63%) and lowest among South Asians (11-25%). Those from non-Christian religions were also less accepting of the vaccine (17-34%). The most common barriers to giving HPV vaccination were a need for more information, sex-related concerns and concern about side effects. South Asian women were the most likely to cite sex-related concerns, and were also least likely to believe the vaccine would offer their daughters protection. Conclusion: These findings suggest some cultural barriers that could be addressed in tailored information aimed at ethnic minority groups. They also highlight the importance of recording ethnicity as part of HPV vaccine uptake data.

DOI: 10.1136/jech.2008.085886


**ABSTRACT:** The aim of this study was to evaluate knowledge about human papillomavirus (HPV) in individuals with genital warts compared with women from the general population without genital warts. Human papillomavirus (HPV) knowledge among women reporting treatment for genital warts compared with HPV knowledge in women reporting no treatment was assessed using data from the population-based 2005 Health Information
National Trends Survey (HINTS). Three percent (N=97) of women answered yes and 97% (N=3,450) no to Have you ever been treated for venereal warts or condyloma? Women who reported treatment for genital warts, were more likely to have heard of HPV (odds ratio (OR): 2.4, 95% confidence interval (CI): 1.4-4.2 vs. no or don’t know), to have been told they had HPV (OR: 24.5, 95% CI: 11.4-52.8), and to have accurate information about HPV, such as HPV causes cancer (OR: 2.7, 95% CI: 1.8-4.3). A large proportion (41%) of women who reported treatment for genital warts, however, had not heard of HPV. These women tended to be older, poorer, less educated, non-Hispanic Black, less likely to have had a recent Pap test, and divorced, widowed, or separated. Women with genital warts are learning about HPV, but socioeconomically disadvantaged groups may need to be targeted.

DOI: 10.1080/10810730902873067

163. **Bingham, A., Drake, J.K., LaMontagne, D.S. (2009).**


**ABSTRACT:** Objectives: (1) To synthesize sociocultural results from diverse populations related to vaccine decision-making, understanding of cervical cancer and its etiology, experience with previous vaccinations, human papillomavirus (HPV) vaccine concerns, and information needed to foster acceptance; (2) to contextualize findings in light of recent studies; and (3) to discuss implications for communication strategies to facilitate vaccine acceptance. Design: Descriptive qualitative synthesis of sociocultural studies in 4 countries using iterative theme-based analyses. Setting: Four developing countries: India, Peru, Uganda, and Vietnam. Participants: Criterion-based sample of 252 focus group discussions and 470 in-depth interviews with children, parents, teachers/administrators, health workers/managers, and community/religious leaders. A knowledge, attitudes, and practices survey was administered to 879 children and 875 parents in Vietnam. Results: We found that vaccine decision-making was primarily done by parents, with children having some role. Understanding of cervical cancer and HPV was limited; however, the gravity of cancer and some symptoms of cervical cancer were recognized. Vaccination and government-sponsored immunization programs were generally supported by respondents. Sentiments toward cervical cancer vaccines were positive, but concerns about quality of delivery, safety, adverse effects, and the effect on fertility were raised. Communities requested comprehensive awareness-raising and health education to address these concerns. Conclusion: Sociocultural studies help elucidate the complexities of introducing a new vaccine from the perspective of children, parents, and communities. Strategies for introducing the HPV vaccine should address community concerns through effective communication, appropriate delivery, and targeted advocacy to make the program locally relevant. ©2009 American Medical Association.

DOI: 10.1001/archpediatrics.2009.50


Singaporean women’s knowledge of human papillomavirus (HPV) and attitudes toward HPV vaccination. *Women and Health, 49*(4), pp. 334-351.
ABSTRACT: With a vaccination program currently planned to protect Singaporean women from human papillomavirus, a need arises for assessing Singaporean women’s knowledge of human papillomavirus and attitudes toward human papillomavirus vaccination to identify barriers to a successful program and to help inform health education campaigns. A representative sample of 2,145 women aged between 18 and 49 years were randomly selected from households throughout Singapore and interviewed with a similar questionnaire to that used in a recent study of Australian women. Although Singaporean women’s knowledge of human papillomavirus was poor, with only 20% having heard of it, attitudes toward human papillomavirus vaccination were generally positive. The most trusted sources of information about human papillomavirus and vaccination were gynecologists and general practitioners. Based on our findings, an urgent need exists in Singapore for accurate and accessible information about human papillomavirus and the benefits of vaccination. DOI: 10.1080/03630240903158420


ABSTRACT: Background. A human Papillomavirus (HPV) vaccine was approved by the Food and Drug Administration for use among women/girls in 2006. Since that time, limited research has examined HPV vaccine uptake among adolescent girls and no studies have examined the role of geographic disparities in HPV vaccination. Purpose: The purpose of this study is to examine geographic disparity in the prevalence of human Papillomavirus (HPV) vaccination and to examine individual, county, and state-level correlates of vaccination. Methods: Three-level random intercept multilevel logistic regression models were fitted to data from girls aged 13-17 years living in six U.S. states using data from the 2008 Behavioral Risk Factor Surveillance System (BRFSS) and the 2000 U.S. census. Results: Data from 1709 girls nested within 274 counties and six states were included. Girls were predominantly white (70.6%) and insured (74.5%). Overall, 34.4% of girls were vaccinated. Significant geographic disparity across states (variance=0.134, SE=0.065) and counties (variance=0.146, SE=0.063) was present, which was partially explained by state and county poverty levels. Independent of individual-level factors, poverty had differing effects at the state and county level: girls in states with higher levels of poverty were less likely whereas girls in counties with higher poverty levels were more likely to be vaccinated. Household income demonstrated a similar pattern to that of county-level poverty: compared to girls in the highest income families, girls in the lowest-income families were more likely to be vaccinated. Conclusions: The results of this study suggest geographic disparity in HPV vaccination. Although higher state-level poverty is associated with a lower likelihood of vaccination, higher county-level poverty and lower income at the family level is associated with a higher likelihood of vaccination. Research is needed to better understand these disparities and to inform interventions to increase vaccination among all eligible girls. DOI: 10.1016/j.amepre.2010.01.018

166. Downs, L. S., Scarinci, I., Einstein, M., Collins, Y., Flowers, L. (2010). Overcoming the Barriers to HPV Vaccination in High-Risk Populations in the US. *Gynecologic*
ABSTRACT: Objectives. To review populations of women in the United States at high risk for cervical cancer, assess known reasons for existing outcome disparities, and discuss potential strategies to reduce barriers to HPV vaccination and current strategies for cervical cancer prevention. Methods. An expert forum conducted September 12–13, 2008, by the Society of Gynecologic Oncologists including 56 experts in cervical cancer and titled “Future strategies of cervical cancer prevention: what do we need to do now to prepare?” Results. Although epidemiological data is useful and necessary to identify populations at high risk for cervical cancer, an understanding of the knowledge and attitudes regarding HPV and cervical cancer prevention of racial/ethnic groups and sub-groups within racial/ethnic categories is critical for the implementation of effective targeted and effective educational efforts. Inequities in cervical cancer screening, diagnosis and treatment and HPV vaccination may arise from a number of barriers including access to healthcare, cultural beliefs, and limited awareness of options. Conclusions. Initiatives to promote uptake of prophylactic HPV vaccination that target high-risk women need to be implemented before existing disparities widen. Although acceptability of HPV vaccination is promising, uptake is still low among low-income populations and specific racial/ethnic minorities. To address limited vaccine uptake it may be beneficial to establish national/state guidelines as well as culturally relevant interventions at the individual and community levels. The successful implementation of multiple integrated initiatives on HPV awareness, knowledge, and vaccination will diminish existing disparities in cervical cancer incidence and mortality.

DOI: 10.1016/j.ygyno.2010.02.011

3.6.3 Education/Intervention

SUMMARY

Research demonstrated that anxiety related to screening test result and HPV test result can be reduced with clearly communicated HPV information. Education that focused on cervical cancer as preventable and rare and highlighted the natural clearance of HPV infections was found to be reassuring and reduced anxiety about HPV and HPV test results.


ABSTRACT: We sought to describe information that makes women feel (1) uncertain and (2) reassured about their human papillomavirus (HPV) status and the potential health implications of an HPV DNA test result and (3) to examine information seeking after receiving their result. Thirty women (previously tested HPV negative) read factual information on HPV and cervical cancer and were asked which facts were uncertainty inducing and which were reassuring. Twenty-four facts reassured women of their HPV negative status, 11 facts made women feel uncertain, and 10 facts made them feel both. The most common reason for seeking information in the future was receiving a positive test result. The authors
Outline what specific facts about HPV health providers can emphasize to alleviate anxiety and encourage women to feel reassured of their low cancer risk following a negative test result.

DOI: 10.1080/07399330903066434


Anticipated shame and worry following an abnormal Pap test result: The impact of information about HPV. *Preventive Medicine, 48*(5), pp. 415-419.

**ABSTRACT:** Objectives: To evaluate the impact of HPV and cervical cancer information on women's anticipated feelings of worry and shame if they received an abnormal cervical screening result. Measures: Data were obtained from a British population-based survey of 1081 women aged 25-64 years, carried out in 2006-7. Women were given 'phased' information about HPV and asked whether it would make them feel more or less worried and ashamed if they had an abnormal Pap result. Results: At baseline, 5.5% women anticipated shame if they had an abnormal Pap test but 88.8% anticipated worry. General and prevalence information about HPV led 4.6% and 5.8% of women to say they would feel more ashamed, while 14.2% said they would feel more ashamed following sexual transmission information. About a third of women also said they would feel more worried having read the information. These responses were more common in women with little education and from non-white ethnic groups. Conclusions: HPV information could make women feel more worried about getting an abnormal Pap result, and may make some women feel more ashamed. Worryingly, this may particularly be true for women in groups with low screening uptake rates. Care needs to be taken to ensure HPV information is clear and does not raise unnecessary anxiety. © 2008 Elsevier Inc.

DOI: 10.1016/j.ypmed.2008.11.004


**ABSTRACT:** Objective. To assess women's knowledge, concerns, and willingness for adjunct high-risk human papillomavirus (HR-HPV) testing before and after an educational intervention. Materials and Methods. At the time of their annual gynecologic examination, women aged 30 years and older received an educational intervention about HR-HPV. Subjects completed preintervention and postintervention questionnaires. Demographic characteristics were summarized using frequency measures. Comparisons between the pre-education and posteducation questionnaires were performed using Fisher exact test. Results. Fifty women completed the study. After the educational intervention, 77% of women were willing to be tested for HR-HPV. Sixty-seven percent of women would be likely to return for their annual gynecologic examination even if a Pap smear was not required for 3 years. Education statistically reduced concern regarding a positive HR-HPV result with 60% pre-education and 27% posteducation very concerned (p = .002). When surveyed about what their concerns would be if tested positive for HR-HPV, women associate future cervical cancer diagnosis (38% pre-education vs 48% posteducation, p = .903) but not partner
infidelity (0%) with testing positive for HRHPV. Knowledge concerning HPV, cervical cancer, and cervical cancer screening was statistically improved after the educational intervention in all but 2 questions. Conclusion. Women 30 years and older are willing to have adjunct HR-HPV testing, with education reducing their degree of concern about testing positive. Women who test positive would be most concerned about getting cervical cancer. Women would be willing to return for yearly gynecologic examinations, even if a Pap smear was not needed for 3 years. Education improves women's knowledge of HPV, cervical cancer, and cervical cancer screening, but did not allay the concern for getting cervical cancer. © 2009, American Society for Colposcopy and Cervical Pathology.

DOI: 10.1097/LGT.0b013e31818a53f0

3.6.4 Parents

SUMMARY
Parents are an important source of information and approval for HPV vaccine decision-making. Parent's awareness of HPV and HPV vaccination varied by gender, race, education, and income (P<0.001). Parents living in communities with elevated cancer rates were more likely to have their older daughter vaccinated than daughters of vaccine age recommendation, 17.5% of 16-18 year olds versus 6.4% of 10-12 year olds. Physician recommendation was a significant factor in decision making. One Canadian study of parental intentions to vaccinate sons found positive associations between positive attitudes toward HPV vaccination (AOR 41.5) and perceived subjective norms (AOR 7.8).


ABSTRACT: Background. Differential access to basic health information may contribute to persistent cervical cancer disparities. We examined whether human papillomavirus (HPV) vaccine awareness, HPV knowledge, and use of information sources about the vaccine differ by sociodemographic characteristics associated with cervical cancer. Methods: Study participants (n = 889) were caregivers of adolescent girls ages 10 to 18 years living in southeastern North Carolina. Analyses simultaneously controlled for caregivers’ gender, race, age, education, income, and rural residence. Results: Although most caregivers were aware of HPV (83%) and the HPV vaccine (82%), awareness differed by gender, race, education, and income. The largest differences were for race, with 87% of Whites versus 68% of African Americans having heard of the vaccine (P < 0.001). Caregivers correctly answered an average of 69% of questions on HPV, with differences by race and education. Most respondents heard of the HPV vaccine through drug company advertisements (83%) or broadcast media coverage (69%). African Americans were less likely than Whites to have heard about the vaccine from advertisements but more likely from a broadcast source (P < 0.05). Health care providers (88%) and the internet (65%) were the most favored sources for future information about the vaccine. Vaccine uptake was associated with awareness, knowledge, and media use. Discussion: Whereas drug company advertisements seem to play a central role in high HPV vaccine awareness, doctors and the internet are the preferred future “go to” sources
SECTION 3 - IMMUNIZATION

for seeking out information. Communication-based interventions for caregivers from cervical cancer risk groups, especially African Americans, may need to use different communication
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DOI: 10.1158/1055-9965.EPI-08-0418

Mothers’ intention for their daughters and themselves to receive the human papillomavirus vaccine: A national study of nurses. Pediatrics, 123(6), pp. 1439-1445.

ABSTRACT: OBJECTIVES. The aims of this study were to examine mothers’ intention to vaccinate their daughters and themselves against human papillomavirus and to determine which demographic, behavioral, and attitudinal factors were associated with intention to vaccinate daughters. METHODS. We surveyed 10 521 US mothers, all nurses, between June 2006 and February 2007. Multivariable logistic regression models were used to determine which of the following factors were associated with a mother’s intention to vaccinate a 9-to 12-year-old daughter: demographic factors, gynecologic history, belief that one’s daughter should have regular Papanicolaou testing, beliefs about Papanicolaou testing outcomes (3-item scale), and beliefs about human papillomavirus vaccines (7-item scale measuring beliefs about human papillomavirus vaccine efficacy, impact of vaccination on sexual and Papanicolaou screening behaviors, severity of and susceptibility to human papillomavirus, and anticipated clinician recommendations). RESULTS. Of the 8832 mothers who completed a survey (84% response rate), 7207 had a daughter. Among mothers with a daughter, 48% intended to vaccinate a daughter if she were 9 to 12 years of age, 68% if she were 13 to 15 years of age, and 86% if she were 16 to 18 years of age. Forty-eight percent intended to receive the vaccine themselves if recommended. In multivariable regression models, variables significantly associated with intention to vaccinate a 9- to 12-year-old daughter included belief that one’s daughter should have regular Papanicolaou testing and beliefs about human papillomavirus vaccines. CONCLUSIONS. In this first national study of mothers’ attitudes about human papillomavirus vaccines, mothers’ intention to vaccinate a daughter <13 years of age was lower than intention to vaccinate an older daughter, contrasting with national recommendations to target 11- to 12-year-old girls for vaccination. Educational interventions designed to affect mothers’ willingness to vaccinate daughters should focus on human papillomavirus vaccine efficacy, behavioral impact of vaccination, perceived risk of human papillomavirus, and clinician support for vaccination. Copyright © 2009 by the American Academy of Pediatrics.
DOI: 10.1542/peds.2008-1536


ABSTRACT: Purpose: We assessed human papillomavirus (HPV) vaccination of adolescent girls living in communities with elevated cervical cancer rates. Methods: During July to October 2007, we conducted interviews with a probability sample of parents (or guardians) of 10- to 18-year-old girls in five North Carolina counties with cervical cancer rates substantially higher than the national average. Estimates are weighted. Results: We
interviewed 889 (73%) of 1220 eligible parents; 38% were black. Overall, 10.3% (95% confidence interval [CI] 7.7%-13.5%) of daughters had received at least 1 dose of HPV vaccine. Only 6.4% of 10- to 12-year-olds had initiated vaccination, versus 17.5% of 16- to 18-year-olds (odds ratio [OR] 3.1, 95% CI 1.4-6.9). Older age of daughters and doctor’s recommendation were the only factors independently associated with vaccine initiation. Main reasons reported for not initiating HPV vaccine were: needing more information (22%) or never having heard of the vaccine (14%), believing daughter is too young (16%) or not yet sexually active (13%), and not having gone to the doctor yet (13%). Only 0.5% of parents cited concern about HPV vaccine making a teenage girl more likely to have sex as a main reason for not vaccinating. Of 780 parents with unvaccinated daughters, 62% reported their daughters “probably” or “definitely” will, and 10% reported their daughters “definitely won’t” get HPV vaccine in the next year. Conclusions: Approximately 1 year after its introduction, HPV vaccine had been initiated by only 10% of adolescent girls in an area with elevated cervical cancer rates; however, most parents intended for their daughters to be vaccinated. Additional efforts are needed to ensure that parents’ intentions to vaccinate are realized.

DOI: 10.1016/j.jadohealth.2009.03.029

Understanding the Reasons Why Mothers Do or Do Not Have Their Adolescent Daughters Vaccinated Against Human Papillomavirus. *Annals of Epidemiology*, 19(8), pp. 531-538.

**ABSTRACT:** Purpose: The objective of this study was to compare the reasons why mothers do or do not have their adolescent daughters vaccinated against HPV. Methods: Mothers of vaccinated and unvaccinated 11- to 17-year-old girls seen during preventive care visits in outpatient family medicine or pediatric clinics underwent an audiotaped structured telephone interview that used open-ended questions to assess the reasons underlying maternal decisions about HPV vaccination. Qualitative methods categorized maternal responses into themes. Results: Interviews of 52 mothers (19 declining vaccination, 33 accepting) identified several distinct factors underlying their decisions about HPV vaccination. Lack of knowledge about HPV, age-related concerns, and low perceived risk of infection were commonly cited reasons for declining vaccination. Desire to prevent illness, physician recommendation, and a high perceived risk of infection were commonly identified motivating factors. Both groups of mothers had significant concerns about vaccine safety. Locus of control (e.g., mother or daughter) of health-related decisions arose as a novel factor influencing this decision that had not been previously described in the context of HPV vaccination. Conclusions: Addressing safety concerns, educating parents about the age-specific risk of HPV infection, and promoting strong physician recommendation for vaccination may be the most useful targets for future interventions to increase HPV vaccine utilization. © 2009 Elsevier Inc.

DOI: 10.1016/j.annepidem.2009.03.011


**ABSTRACT:** Though many studies have documented correlates of HPV vaccine acceptability,
our study is one of the first to examine correlates of vaccine initiation. The current study aimed to identify modifiable correlates of HPV vaccine initiation among adolescent girls in high risk communities and whether correlates varied by race and urban/rural status. In 2007, we conducted a cross-sectional survey of 889 parents of adolescent girls aged 10-18 living in areas of North Carolina, USA with high cervical cancer rates. We analyzed data using logistic regression. Health Belief Model constructs were associated with HPV vaccine initiation in multivariate analyses, including doctor’s recommendation to get HPV vaccine, perceived barriers to obtaining HPV vaccine, and perceived potential vaccine harms. While exploratory stratified analyses suggested that many of the same parent beliefs were important correlates of HPV vaccine initiation regardless of racial group or urban/rural status, a few differences did exist. These potentially modifiable beliefs offer well-defined targets for future interventions designed to increase HPV vaccine coverage. However, the beliefs’ relative importance may differ between racial groups and regions. © 2009 Elsevier Ltd. DOI: 10.1016/j.socscimed.2009.05.024


Intention of parents to have sons receive the human Papillomavirus vaccine. *Sexually Transmitted Infections*, 84(4): 318-323.

**ABSTRACT:** Background. Although already approved for use in males in some jurisdictions, there is little information about parental attitudes toward having their sons receive the human papillomavirus (HPV) vaccine. The goal of this study was to ascertain parental intentions to vaccinate their sons with an HPV vaccine and to determine factors that predict this intention. Methods: Parents of children aged 8–18 years were recruited from across Canada through random digit dialling. Participants were asked to respond to a series of questions in the context of a Grade 6 (age 11/12 years old), publicly funded school-based HPV vaccine programme, including their intention to vaccinate their sons with the HPV vaccine. Parents were also asked about a series of characteristics thought to predict intention to vaccinate as well as demographic characteristics. Backwards logistic regression was conducted to calculate adjusted odds ratios (AOR) to identify the factors that are predictive of parents’ intention to vaccinate their son(s) against HPV. Results: Of the 1381 respondents with male children, 67.8% (95% CI 65.3 to 70.3) intend to vaccinate their son(s) against HPV. Parents who had positive attitudes toward vaccines and the HPV vaccine in particular (AOR 41.5, 95% CI 9.5 to 181.7), parents who were influenced by subjective norms (AOR 7.8, 95% CI 5.8 to 10.5), parents who felt that the vaccine had limited influence on sexual behaviour (AOR 2.3, 95% CI 1.6 to 3.3) and parents who were aware of HPV (AOR 1.4, 95% CI 1.1 to 2.0) were significantly more likely to report an intention to vaccinate boys against HPV. In contrast, residence in British Columbia compared to Atlantic Canada (AOR 0.4, 95% CI 0.2 to 0.8) and higher education (AOR 0.7, 95% CI 0.5 to 0.9) were negatively associated with intention to vaccinate. Parents who reported an intention to vaccinate their daughters were also highly likely to report an intention to vaccinate their sons (k=0.9, p<0.001). Discussion: The majority of Canadian parents would intend to have their male children receive the HPV vaccine in the context of a publicly funded school-based immunisation programme. Overall attitudes toward vaccine, recommendations from health professionals and impact of the
vaccine on sexual practices are important predictors of intention to have a male child receive the HPV vaccine.

DOI:10.1136/sti.2007.029389


**ABSTRACT:** Background. Information on factors that influence parental decisions for actual human papillomavirus (HPV) vaccine receipt in publicly funded, school-based HPV vaccine programs for girls is limited. We report on the level of uptake of the first dose of the HPV vaccine, and determine parental factors associated with receipt of the HPV vaccine, in a publicly funded school-based HPV vaccine program in British Columbia, Canada. Methods and Findings: All parents of girls enrolled in grade 6 during the academic year of September 2008–June 2009 in the province of British Columbia were eligible to participate. Eligible households identified through the provincial public health information system were randomly selected and those who consented completed a validated survey exploring factors associated with HPV vaccine uptake. Bivariate and multivariate analyses were conducted to calculate adjusted odds ratios to identify the factors that were associated with parents’ decision to vaccinate their daughter(s) against HPV. 2,025 parents agreed to complete the survey, and 65.1% (95% confidence interval [CI] 63.1–67.1) of parents in the survey reported that their daughters received the first dose of the HPV vaccine. In the same school-based vaccine program, 88.4% (95% CI 87.1–89.7) consented to the hepatitis B vaccine, and 86.5% (95% CI 85.1–87.9) consented to the meningococcal C vaccine. The main reasons for having a daughter receive the HPV vaccine were the effectiveness of the vaccine (47.9%), advice from a physician (8.7%), and concerns about daughter’s health (8.4%). The main reasons for not having a daughter receive the HPV vaccine were concerns about HPV vaccine safety (29.2%), preference to wait until the daughter is older (15.6%), and not enough information to make an informed decision (12.6%). In multivariate analysis, overall attitudes to vaccines, the impact of the HPV vaccine on sexual practices, and childhood vaccine history were predictive of parents having a daughter receive the HPV vaccine in a publicly funded school-based HPV vaccine program. By contrast, having a family with two parents, having three or more children, and having more education was associated with a decreased likelihood of having a daughter receive the HPV vaccine. Conclusions: This study is, to our knowledge, one of the first population-based assessments of factors associated with HPV vaccine uptake in a publicly funded school-based program worldwide. Policy makers need to consider that even with the removal of financial and health care barriers, parents, who are key decision makers in the uptake of this vaccine, are still hesitant to have their daughters receive the HPV vaccine, and strategies to ensure optimal HPV vaccine uptake need to be employed.

DOI:10.1371/journal.pmed.1000270


Predictors of Parents’ Willingness to Vaccinate for Human Papillomavirus and Physicians’
SECTION 3 - IMMUNIZATION

Intentions to Recommend the Vaccine. Women's Health Issues, 20(1), pp. 28-34.

ABSTRACT: Background. The present study examined potential predictors of parents’ willingness to vaccinate their children for human papillomavirus (HPV) and physicians’ intentions to encourage parents to vaccinate their children, now that the U.S. Food and Drug Administration (FDA) has approved a highly effective vaccine. Methods: Parents (n = 100) and physicians (n = 100) were surveyed on-line in fall 2006, 4 months after the HPV vaccine, Gardasil, was approved by the FDA as a prophylactic vaccine for females ages 9-26 years. Results: Religiosity, perceiving their children as susceptible to HPV, and perceived negative consequences of HPV infection were significant predictors of parents’ intent to vaccinate. Physician specialty and whether or not physicians would vaccinate their own children were significant predictors of physicians’ intent to encourage parents to vaccinate their children. Conclusion: Campaigns aimed at increasing HPV vaccination should focus on educating parents about children’s susceptibility to and the potential negative consequences of HPV infection. Furthermore, because there is now a significant body of evidence indicating that pediatricians and gynecologists have high intentions to encourage parents to vaccinate their children, the focus should be placed on strengthening the intentions of physicians in other specialties who serve children and their parents. © 2010 Jacobs Institute of Women’s Health. DOI: 10.1016/j.whi.2009.08.007


ABSTRACT: In this population-based survey undertaken in Sweden in 2007, we investigated correlates of attitudes to human papillomavirus (HPV) vaccination among parents of children aged 12-15 years. We invited 16,000 parents of girls and 4,000 parents of boys, randomly selected from the Swedish population. Response rates were 70 and 69%, respectively. Multinomial logistic regression models were applied to investigate correlates of acceptability to HPV vaccination. Among studied parents, 76% were willing to vaccinate their child if the vaccine is for free and 63% were willing to vaccinate even if the vaccine comes with a cost. Having heard of HPV was associated with both willingness to vaccinate if the vaccine is free (odds ratio [OR]: 1.42; 95% confidence interval [CI]: 1.21-1.66) and willingness to vaccinate even if the vaccine is not free (OR: 1.96; 95% CI: 1.75-2.20) compared with those who never heard of HPV. Beliefs about vaccine safety and efficacy were also strong correlates of willingness to vaccinate. Parents born outside Europe and those with higher education were less willing to vaccinate if the vaccine is not free. In conclusion, the willingness to vaccinate was reasonably high and cost did not appear to be a major barrier. Information about vaccine safety and efficacy is important and parents need information about HPV and the HPV vaccine. © 2009 UICC. DOI: 10.1002/ijc.24712


ABSTRACT: The quadrivalent vaccine has been shown to be safe and efficacious against HPV infection in men. It is expected, though, that male vaccination rates will remain low.
Therefore this literature review examines the attitudes of parents, young men, and HCPs toward HPV vaccination and other sexually transmitted infections (STI). It appears that parents are interested in vaccinating their sons against HPV and other (STI). In addition, adolescent and adult males are interested in receipt of HPV vaccine and other vaccines for prevention of STI. Health care providers have a general preference for vaccinating females, but they indicate a willingness to recommend HPV vaccine for their male patients. This is important given the “permissive” recommendation for male HPV vaccination issued by the US Advisory Committee on Immunization Practices (ACIP). Cost effectiveness studies have shown that vaccinating males and females is less cost effective than vaccinating females alone. With low female vaccination rates, both cost effectiveness and health benefits increase. It is clear that males have poor knowledge of HPV infection, morbidity, transmission and prevention. Regardless of vaccination strategies adopted, efforts should be made to educate males about HPV and its health implications. In addition, there are more challenges to overcome before male vaccination can be successfully implemented.

DOI: 10.1016/j.ygyno.2010.01.028

3.6.5 Physicians and Nurses

SUMMARY

Research in the United Kingdom and the United States assessed physician professional characteristics related to likelihood to recommend HPV vaccination. Common characteristics were identified as individual belief and buy-in (OR 5.38) and availability of insurance coverage (OR 1.02). Few physicians felt comfortable recommending vaccination to girls within the target age of 11-12 years, demonstrating a lack of adherence to vaccine recommendations. Nurse support of HPV vaccination was related to individual level of knowledge and support received from colleagues.

Priority Research

Efforts to improve physician and community nurse involvement in vaccination strategies of at risk and publicly funded cohorts (alternative to school based vaccination programs) should coincide with evaluation of effectiveness of provider directed activities and monitoring of vaccination practice outcomes.


ABSTRACT: Objective: Assess health care providers’ attitudes and practices regarding adolescent immunizations, including factors that either impede or facilitate vaccination. Methods: Focus groups-In 2005, 3 focus groups were conducted in Monroe County, NY for (1) urban primary care physicians (PCPs); (2) suburban PCPs; and (3) nurses from practices represented in PCP groups. Audiotaped discussions were transcribed and analyzed using Atlas.ti. Key informant interviews-We recruited knowledgeable informants (18 physicians,
6 nurses) from across the US. The authors conducted in-depth telephone interviews with the participants, typed their interview notes, and sent them to the participant for verification. Separately for nurses, urban physicians, and suburban physicians results for each question were listed and reviewed by the authors. Themes were added to those from the focus groups. Results: Three overarching themes were identified: professional buy-in (e.g., reimbursement, professional organization recommendations, disease and vaccine characteristics, office consensus); parent/adolescent buy-in (e.g., school requirements, perception of MD recommendations, cost and insurance coverage, media reports, disease and vaccine characteristics, “vaccine fatigue”), and delivery factors (e.g., vaccine supply, ordering, timing and scheduling, consent). Conclusions: Providers identified intertwined system issues that color their attitudes about adolescent immunization. Practice implications: Buy-in and delivery factors must be addressed before high immunization rates will be achieved. © 2008 Elsevier Ireland Ltd.


ABSTRACT: Aim: To investigate the willingness of clinicians to recommend human papillomavirus (HPV) vaccination, the strength of support for a national HPV vaccine programme and to determine which factors, if any, affected these. Methods: An online, invitation-only questionnaire was developed and distributed to three medical professional groups in the West Yorkshire Region, United Kingdom. Results: Two hundred twenty-two responders were included in the final analysis, from the following specialties: general practice (62), paediatrics (103) and obstetrics and gynaecology (57). The majority of doctors were in favour of a National Health Service-funded national vaccination programme. Over 90% supported vaccination of girls as early as ages 11-13. Fewer doctors felt comfortable recommending vaccination to parents of girls under 16 than to young women. Latent class analysis demonstrated that doctors’ self-rated knowledge of the HPV vaccine was an important determinant of willingness to recommend vaccination. Younger, more recently qualified doctors were less likely to be willing to recommend vaccination. Conclusions: There is widespread support for vaccination. Information provision to doctors will be important in maximising clinician confidence in recommending vaccination, and may be most beneficial when targeted at more junior doctors. © 2009 Paediatrics and Child Health Division.

DOI: 10.1111/j.1440-1754.2009.01589.x


Human papillomavirus vaccine recommendations and agreement with mandated human papillomavirus vaccination for 11-to-12-year-old girls: A statewide survey of Texas physicians. Cancer Epidemiology Biomarkers and Prevention, 18(8), pp. 2325-2332.

ABSTRACT: Background. The purpose of this study was to examine Texas physicians’ recommendations for the quadrivalent human papillomavirus (HPV) vaccine in 11-to-12-year-
old girls, intention to recommend HPV vaccines to 11-to-12-year-old boys, and attitudes about mandated HPV vaccination for 11-to-12-year-old girls. Materials and Methods: We conducted a cross-sectional, web-based survey of Texas physicians who provide direct patient care in family medicine, pediatrics, obstetrics/gynecology, and internal medicine in September 2008. The three outcome variables were: HPV vaccine recommendations to 11-to-12-year-old girls, likelihood of recommending the vaccine to 11-to-12-year-old boys, and agreement with mandated vaccination of 11-to-12-year-old girls. Univariate and logistic regression analyses were used to determine practice-related and attitudinal factors associated with each outcome. Results: Of the 1,122 respondents, 48.5% stated they always recommended HPV vaccines to girls, 68.4% were likely to recommend the vaccine to boys, and 41.7% agreed with mandated vaccination. In multivariate logistic regression models, variables independently associated with recommendation to 11-to-12-year-old girls included: percentage of patients with Medicaid (odds ratio [OR], 1.02; 95% confidence interval [95% CI], 1.01-1.03), academic versus nonacademic practice (OR, 2.11; 95% CI, 1.05-4.23), office procedures to maximize vaccination (OR, 1.25; 95% CI, 1.01-1.56), HPV knowledge (OR, 1.25; 95% CI, 1.04-1.49), valuing HPV vaccine information from both professional organizations (OR, 1.90; 95% CI, 1.15-3.16) and professional conferences (OR, 1.68; 95% CI, 1.10-2.57), belief in mandated HPV vaccination (OR, 5.38; 95% CI, 3.28-8.83), and barriers to vaccination (OR, 1.08; 95% CI, 1.00-1.16). Discussion: Half of the physicians in this study did not follow current recommendations for universal HPV vaccination of 11-to-12-year-old girls. Factors linked to vaccine recommendations may be targeted in educational or policy interventions.

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DOI: 10.1158/1055-9965.EPI-09-0184


ABSTRACT: Title: Cervical cancer prevention by vaccination: nurses’ knowledge, attitudes and intentions. Aim: This paper is a report of a survey: (1) to document nurses’ knowledge, attitudes and information needs regarding human papillomavirus prevention and (2) to determine factors associated with their willingness to recommend human papillomavirus vaccines. Background. Persistent infection with human papillomavirus has been causally linked to cervical cancer. Two human papillomavirus vaccines have recently been approved for use in more than 65 countries. Nurses’ level of support for the prevention of human papillomavirus related diseases by vaccination has not been researched. Methods: A survey was conducted in 2007. Self-administered questionnaires were mailed to 1799 randomly selected nurses. Descriptive statistics were generated for all variables. Multivariable logistic regression models were estimated to determine variables associated with the willingness to recommend human papillomavirus vaccines. Results: A total of 946 questionnaires were analyzed and showed that: 97% of nurses perceived routinely recommended vaccines as very useful; 93% would support human papillomavirus vaccination if it is publicly funded; 85% would recommend human papillomavirus vaccines to their patients; 33%, 46% and 61% expect the vaccination to permit screening to begin later in life, reduction of
the frequency of screening, and reduction of the number of postscreening interventions, respectively. Respondents’ knowledge score was 3·8 out of 7. Several modifiable factors, including knowledge, perceived self-efficacy, and societal and colleagues support were associated with willingness to recommend vaccines. Conclusion: Most nurses’ support human papillomavirus vaccination, but their active involvement should not be taken for granted. Targeted educational efforts are needed to ensure nurses’ involvement in the prevention of human papillomavirus-related diseases. © 2009 The Authors. Journal compilation © 2009 Blackwell Publishing Ltd. DOI: 10.1111/j.1365-2648.2008.04900.x


**ABSTRACT:** Purpose: We assessed U.S. physicians’ attitudes and perceptions regarding potential human Papillomavirus (HPV) vaccination of males. Methods: We surveyed a random sample of 2,714 pediatricians and family practitioners identified in administrative claims of a U.S. health plan as HPV vaccinators of females; 595 pediatricians and 499 family practitioners participated. Results: Most physicians would recommend HPV vaccination to males aged 11–12 (63.9%), 13–18 (93.4%), and 19–26 (92.7%) years. Physicians agreed that males should be vaccinated to prevent them from getting genital and anal warts (52.9% strongly and 36.0% somewhat) and to protect females from cervical cancer (75.3% strongly and 20.8% somewhat). Physicians agreed that an HPV vaccine recommendation for males would increase opportunities to discuss sexual health with adolescent male patients (58.7% strongly, 35.3% somewhat). Most did not strongly agree (15.4% strongly, 45.4% somewhat) that parents of adolescent male patients would be interested in HPV vaccination for males, that a gender-neutral HPV vaccine recommendation would increase acceptance by adolescent females and their parents (19.6% strongly, 42.0% somewhat), or that a gender-neutral recommendation would improve current female vaccination rates (10.4% strongly, 26.0% somewhat). Conclusions: Physicians who currently vaccinate females against HPV supported the concept of vaccinating males for its benefits for both sexes. They agreed that a gender-neutral HPV vaccination recommendation would be appropriate with regard to public health and believed that it would increase opportunities for sexual health discussions, but were less sure that such a recommendation would change patient or parental attitudes toward HPV vaccination or improve current HPV vaccination efforts. © 2010 Society for Adolescent Medicine.

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Section 4
Screening
SUMMARY

HPV testing as a primary, cotest, and reflex test continued to be evaluated to identify whether improvements in screening sensitivity, specificity, positive predictive value, and cost could be achieved. Many studies confirmed that HPV testing improved disease detection rates in screening and follow-up treatment, was more cost effective, and was a more sensitive screening test for women over the age of 30. In addition, two studies demonstrated primary HPV DNA screening with cytology triage in women over the age of 30 was more specific than conventional screening and decreased colposcopy follow up and referral rates. Another study demonstrated women between the ages of 25-29 had the highest rates of intensified follow-up following HPV positive test results (21.9%). Clinical end points continued to be evaluated utilizing HPV testing to predict persistence and progression of disease (OR 18.6 for progression to CIN; PPV 10.3% and NPV 99.4%). HPV testing offered opportunities to reach high risk populations through HPV self-sampling testing, bypassing traditional barriers of access to preventive health care services.

Priority Research

1. Screening from a national perspective should consider alternative screening testing modalities for hard to reach and geographically remote women.

2. Different testing strategies for women who are unscreened, underscreened, vaccinated, and unvaccinated should be evaluated.

3. Management guidelines for HPV positive and cytology negative results need to be established and evaluated based on different screening history and age classifications.

4.1 HPV TESTING


HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. The Lancet Oncology, 10(7), pp. 672-682.

ABSTRACT: Background. Testing for human papillomavirus (HPV) DNA is reportedly more sensitive than cytology for the detection of high-grade cervical intraepithelial neoplasia (CIN). The effectiveness of HPV testing in primary cervical screening was assessed in the ARTISTIC trial, which was done over two screening rounds approximately 3 years apart (2001-03 and 2004-07) by comparing liquid-based cytology (LBC) combined with HPV testing against LBC alone. Methods: Women aged 20-64 years who were undergoing routine screening as part of the English National Health Service Cervical Screening Programme in Greater Manchester were randomly assigned (between July, 2001, and September, 2003) in a ratio of 3:1 to either combined LBC and HPV testing in which the results were revealed and acted on, or to combined LBC and HPV testing where the HPV result was concealed from the patient and investigator. The primary outcome was the detection rate of cervical
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intraepithelial neoplasia grade 3 or worse (CIN3+) in the second screening round, analysed by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Number ISRCTN25417821. Findings: There were 24 510 eligible women at entry (18 386 in the revealed group, 6124 in the concealed group). In the first round of screening 233 women (1.27%) in the revealed group had CIN3+, compared with 80 (1.31%) women in the concealed group (odds ratio [OR] 0.97, 95% CI 0.75-1.25; p>0.2). There was an unexpectedly large drop in the proportion of women with CIN3+ between the first and second rounds of screening in both groups, at 0.25% (29 of 11 676) in the revealed group and 0.47% (18 of 3866 women) in the concealed group (OR 0.53, 95% CI 0.30-0.96; p=0.042). For both rounds combined, the proportion of women with CIN3+ were 1.51% (revealed) and 1.77% (concealed) (OR 0.85, 95% CI 0.67-1.08; p=0.2). Interpretation: LBC combined with HPV testing resulted in a significantly lower detection rate of CIN3+ in the second round of screening compared with LBC screening alone, but the effect was small. Over the two screening rounds combined, co-testing did not detect a higher rate of CIN3+ or CIN2+ than LBC alone. Potential changes in screening methodology should be assessed over at least two screening rounds. Funding: National Institute of Health Research Health Technology Assessment Programme. © 2009 Elsevier Ltd. DOI: 10.1016/S1470-2045(09)70156-1


ABSTRACT: Objectives: Primary cervical screening uses cytology to detect cancer precursor lesions (cervical intraepithelial neoplasia stage 3 or beyond (CIN3+)). Human papillomavirus (HPV) testing could add sensitivity as an adjunct to cytology or as a first test, reserving cytology for HPV-positive women. This study addresses the questions: Does the combination of cytology and HPV testing achieve a reduction in incident CIN3+?; Is HPV testing cost-effective in primary cervical screening?; Is its use associated with adverse psychosocial or psychosexual effects?; and How would it perform as an initial screening test followed by cytology for HPV positivity? Design: ARTISTIC was a randomised trial of cervical cytology versus cervical cytology plus HPV testing, evaluated over two screening rounds, 3 years apart Round 1 would detect prevalent disease and round 2 a combination of incident and undetected disease from round 1. Setting: Women undergoing routine cervical screening in the NHS programme in Greater Manchester. Participants: In total 24,510 women aged 20-64 years were enrolled between July 2001 and September 2003. Interventions: HPV testing was performed on the liquid-based cytology (LBC) sample obtained at screening. Women were randomised in a ratio of 3:1 to have the HPV test result revealed and acted upon if persistently positive in cytology-negative cases or concealed. A detailed health economic evaluation and a psychosocial and psychosexual assessment were also performed. Main outcome measures: The primary outcome was CIN3+ in round 2. Secondary outcomes included an economic assessment and psychosocial effects. A large HPV genotyping study was also conducted. Results: In round 1 there were 313 CIN3+ lesions, representing a prevalence in the revealed and concealed arms of 1.27% and 1.31% respectively (p = 0.81). Round 2 (30-48 months)
involved 14,230 (58.1%) of the women screened in round 1 and only 31 CIN3+ were detected; the CIN3 rate was not significantly different between the revealed and concealed arms. A less restrictive definition of round 2 (26-54 months) increased CIN3+ to 45 and CIN3+ incidence in the arms was significantly different (p = 0.05). There was no difference in CIN3+ between the arms when rounds 1 and 2 were combined. Prevalence of high-risk HPV types was age-dependent. Overall prevalence of HPV16/18 increased with severity of dyskaryosis. Mean costs per woman in round 1 were £72 and £56 for the revealed and concealed arms (p < 0.001); an age-adjustment reduced these mean costs to £65 and £52. Incremental cost-effectiveness ratio for detecting additional CIN3+ by adding HPV testing to LBC screening in round 1 was £38,771. Age-adjusted mean cost for LBC primary screening with HPV triage was £39 compared with £48 for HPV primary screening with LBC triage. HPV testing did not appear to cause significant psychosocial distress. Conclusions: Routine HPV testing did not add significantly to the effectiveness of LBC in this study. No significant adverse psychosocial effects were detected. It would not be cost-effective to screen with cytology and HPV combined but HPV testing, as either triage or initial test triaged by cytology, would be cheaper than cytology without HPV testing. LBC would not benefit from combination with HPV; it is highly effective as primary screening but HPV testing has twin advantages of high negative predictive value and automated platforms enabling high throughput. HPV primary screening would require major contraction and reconfiguration of laboratory services. Follow-up continues in ARTISTIC while maintaining concealment for a further 3-year round of screening, which will help in screening protocol development for the post-vaccination era. © 2009 Queen's Printer and Controller of HMSO.

DOI: 10.3310/hta13510


ABSTRACT: Objective. Atypical squamous cells of undetermined significance (ASCUS) cells, occurring in organized cytological screening, may be either high-risk human papillomavirus (HPV) positive or negative. To refine the assessment of women with ASCUS, a high-risk HPV-DNA test is recommended as triage in Sweden. Methods. A total of 197 consecutive women (mean age 39 years, range 21-60) with a diagnosis of ASCUS from the primary screening were selected for triage. Their cervical smears were collected and evaluated by using conventional cytological examination in combination with a high-risk HPV-DNA test (hybrid capture 2). The women were categorized into four groups: Group A, Cytology + /HPV + ; Group B, Cytology- / HPV + ; Group C, Cytology + /HPV-; and Group D, Cytology- / HPV-. Women within Groups A-C were admitted for colposcopy and cervical biopsy. The women in Group D were considered as a low-risk group for tumor development, and were re-examined after three years in the next round of the organized screening. Results. In women in Group A (n=58) the prevalence of histological verified CIN2-3 was 41%, in Group B (n=41) 20%, and in Group C (n=9) 0%. In Group D (n=89), repeated primary screening three years later revealed CIN2-3 in two biopsies from 74 women studied (3%). The prevalence of a high-risk HPV infection decreased with age in women with ASCUS. It was 74% in women 30 years and 19% in women 50 years. Conclusions. Adding a high-risk HPV test in secondary screening increased the identification of
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women with CIN2-3 lesions by 33% in comparison with repeat cytology (p=0.01). The clinical significance of the ASCUS diagnosis varied with age of the women.

DOI: 10.1080/00016340903160952


**ABSTRACT:** Objective: To assess the use of human papillomavirus genotyping in cervical intraepithelial neoplasia posttreatment follow-up. Study Design: Prospective observational study. Ninety women underwent cytologic testing and human papillomavirus genotyping at the follow-up visit after conization. Cones were retrospectively genotyped. A second cytologic follow-up was performed. Results: Margin status and presence of cervical intraepithelial neoplasia 3+ in the cone were poor predictors of treatment outcome (sensitivity, < 50%; diagnostic odds ratio, ≤ 2.5). Presence of high-/intermediate-risk human papillomavirus types predicted 100% of residual high-grade squamous intraepithelial lesion/cervical intraepithelial 2+ at a specificity of 73%. Testing only 13 high-risk types showed equal sensitivity but higher specificity (86%; P < .01). Persistent high-risk human papillomavirus infection (13 types) detected high-grade residual disease with a sensitivity of 60% at a very high specificity (95%), resulting in a positive predictive value of 43%, which exceeded the positive predictive values of all other criteria. Conclusion: Testing for high-risk human papillomavirus identified all recurrent/residual high-grade cervical intraepithelial neoplasia. Focusing on women with persistent human papillomavirus types through genotyping substantially increased positive predictive value but at a loss in sensitivity. © 2009 Mosby, Inc.

DOI: 10.1016/j.ajog.2009.01.005


**ABSTRACT:** OBJECTIVE: To estimate the 5-year age group-specific test positives for Pap tests and human papillomavirus (HPV) testing in a large, general screening population of women 30 and older. METHODS: Using data from Kaiser Permanente Northern California, a large health maintenance organization that introduced cotesting in 2003, we evaluated the cotesting results overall and by 5-year age groups. Women (n=580,289) who opted for and underwent cotesting (n cotests=812,598) between January 2003 and April 2008 were included in the analysis. Pap tests interpreted as atypical squamous cells of undetermined significance (ASC-US) or more severe were considered to be positive. Women were tested for carcinogenic HPV using an assay approved by the U.S. Food and Drug Administration. Binomial exact 95% confidence intervals (CIs) were calculated. RESULTS: Overall, 6.27% (95% CI 6.21-6.32%) of cotests were carcinogenic HPV positive, and only 3.99% (95% CI 3.94-4.03%) cotests had normal cytology and were carcinogenic HPV positive. By comparison, 5.18% (95% CI 5.13-5.23%) of cotests had ASC-US or more severe cytology, and 2.87% (95% CI 2.84-2.91%) of cotests had ASC-US or more severe cytology and were carcinogenic HPV negative. CONCLUSION: In a general screening population, concerns
about excessive HPV test positives among women aged 30 years and older are not borne out. © 2009 by The American College of Obstetricians and Gynecologists. Published by Lippincott Williams & Wilkins.
DOI: 10.1097/AOG.0b013e3181996ffa

Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. Journal of the National Cancer Institute, 101(23), pp. 1612-1623.

ABSTRACT: Background - Human papillomavirus (HPV) DNA testing has shown higher sensitivity than cytology for detecting cervical lesions, but it is uncertain whether the higher sensitivity is dependent on the age of the woman being screened. We compared the age-specific performance of primary HPV DNA screening with that of conventional cytology screening in the setting of an organized population-based cervical cancer screening program in Finland. Methods - From January 1, 2003, to December 31, 2005, randomized invitations were sent to women aged 25-65 years for routine cervical cancer screening by primary high-risk HPV DNA testing (n = 54207) with a Hybrid Capture 2 assay followed by cytology triage for women who were HPV DNA positive or by conventional cytology screening (n = 54218). In both screening arms, cytology results of low-grade squamous intraepithelial lesion or worse triggered a referral for colposcopy. Relative rates (RRs) of detection to assess test sensitivity, specificity, and positive predictive values (PPVs) with 95% confidence intervals (CIs) were calculated for the histological endpoints of cervical intraepithelial neoplasia (CIN) grade 1 or higher (CIN 1+), CIN grade 2 or higher (CIN 2+), and CIN grade 3 or higher (CIN 3+). All statistical tests were two-sided. Results - The overall frequency of colposcopy referrals was 1.2% in both screening arms. Women younger than 35 years were referred more often in the HPV DNA screening vs the conventional screening arm (RR = 1.27, 95% CI = 1.01 to 1.60). The prevalence of histologically confirmed CIN or cancer was 0.59% in the HPV DNA screening arm vs 0.43% in the conventional screening arm. The relative rates of detection for CIN 1, CIN 2, and CIN 3+ for HPV DNA screening with cytology triage vs conventional screening were 1.44 (95% CI = 0.99 to 2.10), 1.39 (95% CI = 1.03 to 1.88), and 1.22 (95% CI = 0.78 to 1.92), respectively. The specificity of the HPV DNA test with cytology triage was equal to that of conventional screening for all age groups (99.2% vs 99.1% for CIN 2+, P = .13). Among women aged 35 years or older, the HPV DNA test with cytology triage tended to have higher specificity than conventional screening. The PPVs for HPV DNA screening with cytology triage were consistently higher than those for conventional screening. In both screening arms, the test specificities increased with increasing age of the women being screened, whereas the highest PPVs were observed among the youngest women being screened. Overall, 72% of women in the HPV DNA screening arm vs 6.6% of women in the conventional screening arm were recommended for intensified follow-up, and the percentages were highest among 25-to 29-year-olds (21.9% vs 10.0%, respectively). Conclusions - Primary HPV DNA screening with cytology triage is more sensitive than conventional screening. Among women aged 35 years or older, primary HPV DNA screening with cytology triage is also more specific than conventional screening and decreases colposcopy referrals and follow-up tests.
DOI: 10.1093/jnci/djp367


**ABSTRACT:** Purpose: The aim of study was to investigate factors predicting persistence or relapse of disease after cervical conisation for high-grade squamous intraepithelial lesions (CIN 2 or 3). Methods: The study involved 78 women with high-grade squamous intraepithelial lesions, conservatively treated with loop electroexcision procedure for cervical conisation and subsequent with CO2 laser-vaporisation of the cervical bed. Histological specimens were totally included and examined by an experienced pathologist. To evaluate the efficacy of treatment, the patients were examined with colposcopy and Pap smear 4 months after surgery and with PCR to search for and genotyping of HPV, 10 months after treatment. Results: During the post-treatment follow-up, the cytologic examination showed persistent/relapsing disease in six patients (7.6%). In only 1 case, the deep margin of the cone was considered positive for CIN (16%). Ten months after treatment, viral typing revealed the persistence of high-risk HPV in all of these patients. Conversely, the viral follow-up of the other 72 patients without persisting/relapsing disease after treatment disclosed low-risk HPV genotypes in 6 cases, high-risk HPV in 2 cases (2.7%), whereas 7 cases had positive margins for CIN (9.7%). The risk of persistence and relapse of CIN in the group with positive margins was not statistically significant (P = 0.87), whereas it was in the group with HR-HPV positive (P = 0.000048). Conclusion: HPV testing is the most sensitive mean of identifying persistence or relapse early and is therefore capable of optimising follow-up after the treatment of high-grade CIN. © 2009 Springer-Verlag. DOI: 10.1007/s00404-009-1316-5


Human papillomavirus typing and viral gene expression analysis for the triage of women with abnormal results from papanicolaou test smears to colposcopy. *Archives of Pathology and Laboratory Medicine, 133*(10), pp. 1577-1586.

**ABSTRACT:** Context. - A cascade of molecular tests for human papillomavirus (HPV), as a follow-up to Papanicolaou test screening, could eliminate unnecessary colposcopy. Tests based on detection of HPV E6 messenger RNA (mRNA) are already being used as screening tools, but there is a good biological rationale for expecting that an increase in the relative amounts of HPV E6 mRNA in cervical samples may better predict cancerous transformation. Objective. - To compare some of the available diagnostic methods and our novel method of relative quantification (RQ) of HPV gene expression for the effective triage of women with abnormal results from Papanicolaou tests to colposcopy. Design. - Sensitivities, specificities, and likelihood ratios were calculated for repeat Papanicolaou test smears, HPV DNA polymerase chain reactions, HPV genotyping, HPV-16 E6 mRNA detection, and the RQ of HPV-16 E6 mRNA calibrated to cellular RNA and DNA levels and standardized to viral load. Results. - Human papillomavirus genotype in combination with a repeat Papanicolaou test can be used to categorize most women (96%) with cervical intraepithelial neoplasia of grade 2 or higher for colposcopy while eliminating 44% of women with cervical intraepithelial neoplasia 1 or less. The presence of HPV-16 E6 mRNA (P < .001) and RQ of HPV-16 E6 mRNA (P < .001) displayed significant median differences among the various grades of cervical intraepithelial neoplasia.
Further testing of women who are positive for HPV-16 demonstrated that the RQ of E6 mRNA has diagnostic potential when combined with Papanicolaou testing in populations with higher disease prevalence. Conclusions: - The RQ of HPV E6 mRNA and HPV genotype could be useful in a cascade of diagnostic testing designed to refer women with findings of cervical abnormalities for colposcopy or treatment while reducing triage numbers.


Prevalence of high-risk human papillomavirus type 16/18 infection among women with normal cytology: Risk factor analysis and implications for screening and prophylaxis. 

**ABSTRACT:** Objective: To determine the prevalence of high-risk human papillomavirus (HR-HPV) 16/18 infection of uterine cervix among women in the reproductive age group, with cytologically normal cervical (Pap) smears; to analyse the risk factors for HR-HPV acquisition and to address their implications for cervical cancer screening and prophylaxis in a low resource setting.

Methods: Cervical samples from 769 cytologically negative women (age 18-45 years) attending a tertiary care centre in Delhi were subjected to HPV DNA testing and HR-HPV 16/18 and low-risk (LR)-HPV 6/11 sub-typing by polymerase chain reaction. Univariate risk factor analysis was carried out in HR-HPV positive (n = 86) versus HR-HPV negative women (n = 683) by chi-square test. Results: The overall HPV prevalence among cytologically normal women was 16.6%. HR-HPV 16 was detected in 10.1%, whereas HPV18 was detected in 1% of women. HR-HPV 16/18 comprised 67% of the total HPV positives. There was no decline in HR-HPV positivity with age, and women aged 40-44 years were at significantly increased risk for HR-HPV prevalence (P = 0.03). Statistically significant associations of HR-HPV infection were found with risk factors such as high parity (P = 0.04), cervicitis/hypertrophic cervix (P = 0.01), unhealthy cervix (P = 0.04), rural residence (P = 0.03), low socioeconomic status (P = 0.01) and illiteracy (P = 0.07). Conclusions: Although the sample size was small, based on the observation that HR-HPV 16 and 18 contributed significantly to the overall HPV prevalence in our setting, we speculate that testing/prophylaxis for these prevalent high-risk types could perhaps make cervical cancer screening and preventive programmes cost-effective. Larger community-based studies on HPV prevalence and persistence are required to validate these findings before definitive recommendations can be made to the policy makers. © 2008 Blackwell Publishing Ltd.

DOI: 10.1111/j.1365-2303.2008.00611.x


High-risk HPV DNA detected in less than 2% of over 25,000 cytology negative imaged liquid-based Pap test samples from women 30 and older. *Gynecologic Oncology, 115*(2), pp. 257-261.

**ABSTRACT:** Objective: The purpose of this study was to document the prevalence of high-risk HPV DNA (HPV) in the largest cohort of woman studied to date with negative ThinPrep Imaging system (TIS)-imaged Pap tests. Methods: Women with negative (TIS)-imaged ThinPrep Pap Tests (TPPT) who also were tested for HPV were identified between July 1, 2005 and December 31, 2007 from a large women’s hospital practice. HPV detection rates were compared for women with either presence or absence of a transformation zone/endocervical cell sample (EC/TZS). Results: 26,558 negative TPPT also underwent HPV testing. HPV
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detection was higher in women younger than 30 and sharply declined in women 30-39 (P < 0.001). Declining HPV detection rates continued in the 40-49 age group (age 30-39 vs. 40-49; 2.8% vs. 1.7%, P < 0.001) and then levelled off. No statistically significant difference for HPV prevalence was identified comparing women with and without a TZ/ECS. Conclusion: This is the largest study to date documenting very low HPV detection rates in women screened cytology negative with computer-imaged liquid-based Pap methods now representing a major portion of the U.S. cervical cytology market. Findings of very low rates of HPV detection in 490 (1.9%) of 25,259 cytology negative women 30 and older extend and confirm previously reported findings in smaller study populations. Because HPV testing provides an objective measure of relative residual risk for cervical neoplasia after screening, these data are relevant to discussions on how best to combine cytology and HPV testing in screening low risk populations. © 2009 Elsevier Inc.

DOI: 10.1016/j.ygyno.2009.07.010


ABSTRACT: Background. New end points are needed in future human papillomavirus (HPV) vaccine efficacy studies that accurately predict disease progression. Objectives: Potential intermediate end points were analyzed in the combined New Independent States of the Former Soviet Union (NIS) and the Latin American Screening (LAMS) study cohorts. Study Design and Methods: Data files of 2 international screening trials, the NIS (n = 3187) and the LAMS (n = 12, 114) study cohorts, were combined, and a subcohort of 1865 (n = 854 and n = 1011 for the NIS and the LAMS, respectively) women prospectively followed up for 19.7 (median, 22.2) months was analyzed for different intermediate end-point markers of disease progression to squamous intraepithelial lesion (SIL), cervical intraepithelial neoplasia grade 1 and higher (CIN1+), and CIN grade 2 and higher (CIN2+) as terminal events. Results: Altogether, 131 (70%), 90 (4.8%), and 39 (2.1%) cases progressed to SIL, CIN1+, and CIN2+, respectively, progression times being equal in the NIS (11.9, 16.8, and 19.6 months) and LAMS (13.6, 14.1, and 15.4 months) cohorts (P = 0.931, P = 0.335, and P = 0.535). The 2 most powerful end-point markers of disease progression to CIN2+ were high-grade squamous intraepithelial lesions based on Papanicolaou test results at 6-month (odds ratio [OR] = 471; 95% confidence interval [CI], 173Y128.7) and 12-month (OR = 21.5; 95% CI, 5.1Y90.8) follow-up visits, with longitudinal positive and negative predictive values of 42.1% and 98.0% (6 months) and 33.3% and 97.7% (12 months). Of the virological end points, more than 6 months of persistent high-risk HPV (HR-HPV) was the most powerful predictor of progression to CIN1+ (OR = 18.6; 95%CI, 2.5Y136.5), with longitudinal positive and negative predictive values of 10.3% and 99.4%, respectively. No additional benefit was obtained using more than 12 months of persistent HR-HPV end point. Conclusions: High-grade squamous intraepithelial lesion based on a Papanicolaou test results at 6- or 12-month follow-up visits was
the most powerful end point, either considering cytological end points alone or in comparison to any of the virological end points. Of the virological end points, more than 6-month HR-HPV persistence criteria give the most powerful estimate of a progressive disease. © 2009 by IGCS and ESGO.

DOI: 10.1111/IGC.0b013e3181a834fe


ABSTRACT: Background. Currently, the German cervical cancer screening program encompasses an annual cytological Papanicolaou (Pap) smear. However, primary screening for cervical cancer using human papillomavirus (HPV) DNA testing detects cervical pre-cancerous lesions with a significantly higher sensitivity than the Pap smear-based cytology. Objectives: In order to develop viable modalities for primary cervical screening incorporating DNA testing for high-risk (HR) types of HPV, we started a pilot project in the city of Wolfsburg, Germany, in February 2006. This program provided a risk-adapted HPV testing-based strategy with defined patient pathways and extended screening intervals for women of 30 years or older. We report here the data of a 3-year follow-up. Study design: In the context of the usual routine screening at their office-based gynecologists, women were offered conventional cytology plus the Hybrid Capture 2 (HC2) HPV DNA test. Women with inconspicuous cytological findings (Pap I/II) and negative HC2 test were re-tested after 5 years but continued their annual gynecological examinations. When cytology and HC2 were positive, women were immediately referred to colposcopy. In women with a negative cytology but positive HC2 test, Pap smear was repeated after 6 mo and HC2 testing after 12 mo, and women were called for colposcopy if the HC2 test was persistently positive. Results: From February 2006 to December 2008, 16,724 women agreed to participate in the project. Overall, 906 (5.41%) had positive HC2 results and 338 (2.02%) showed atypical Pap smears at recruitment. There were 417 (2.48%) women referred for colposcopy, 104 of whom were diagnosed with cervical intraepithelial neoplasia (CIN) 3 or worse, including 8 invasive cancers and 8 adenocarcinoma in situ (ACIS). No case of CIN 3 or worse occurred in HC2 negative women. Conclusions: The presented risk-adapted Wolfsburg Cervical Cancer Prevention Project (“Wolfsburg Model”) has been shown to be effective and feasible in identifying women at risk and for avoiding unnecessary procedures for those who are double negative, thus allowing longer screening intervals and cost savings. Acceptance rates for the program were high for both participating women and gynecologists. © 2009 Elsevier B.V. DOI: 10.1016/S1386-6532(09)70294-X


HPV screening for cervical cancer in rural India. New England Journal of Medicine, 360(14), pp. 1385-1394

ABSTRACT: Background. In October 1999, we began to measure the effect of a single round of screening by testing for human papillomavirus (HPV), cytologic testing, or visual inspection of
the cervix with acetic acid (VIA) on the incidence of cervical cancer and the associated rates of death in the Osmanabad district in India. Methods: In this cluster-randomized trial, 52 clusters of villages, with a total of 131,746 healthy women between the ages of 30 and 59 years, were randomly assigned to four groups of 13 clusters each. The groups were randomly assigned to undergo screening by HPV testing (34,126 women), cytologic testing (32,058), or VIA (34,074) or to receive standard care (31,488, control group). Women who had positive results on screening underwent colposcopy and directed biopsies, and those with cervical precancerous lesions or cancer received appropriate treatment. Results: In the HPV-testing group, cervical cancer was diagnosed in 127 subjects (of whom 39 had stage II or higher), as compared with 118 subjects (of whom 82 had advanced disease) in the control group (hazard ratio for the detection of advanced cancer in the HPV-testing group, 0.47; 95% confidence interval [CI], 0.32 to 0.69). There were 34 deaths from cancer in the HPV-testing group, as compared with 64 in the control group (hazard ratio, 0.52; 95% CI, 0.33 to 0.83). No significant reductions in the numbers of advanced cancers or deaths were observed in the cytologic-testing group or in the VIA group, as compared with the control group. Mild adverse events were reported in 0.1% of screened women. Conclusions: In a low-resource setting, a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer. Copyright © 2009 Massachusetts Medical Society.

DOI: 10.1056/NEJMoa0808516


ABSTRACT: OBJECTIVE: To estimate the effectiveness of the human papillomavirus (HPV) test performed after conization in predicting residual disease in patients who subsequently underwent hysterectomy. METHODS: A total of 115 patients who underwent hysterectomy after conization caused by cervical intraepithelial neoplasia grade 3 (CIN 3) and microinvasive cervical cancer (IA1 cancer) were included in this prospective study. All patients underwent HPV testing with a liquid hybridization assay immediately before hysterectomy. Differences in sensitivity, specificity, and accuracy between resection margin and the HPV test in predicting residual disease in subsequent hysterectomy samples were estimated using the McNemar exact test. RESULTS: Univariable analysis showed that age, parity, menopausal status, glandular extension, and severity of disease were not predictive for residual disease, but positive resection margin and positive HPV tests were significant factors for predicting residual disease. These factors were also significant in a multivariable analysis (positive resection margin 45.5%, odds ratio [OR] 3.09, 95% confidence interval [CI] 1.19-8.03, P=.021; positive HPV test 57.6%, OR 11.05, 95% CI 4.01-30.49, P<.001). With resection margin, the sensitivity, specificity, and accuracy in predicting residual disease were 75%, 53%, and 61%, respectively, whereas, with the HPV test, these values were 85%, 67%, and 73%, respectively (P=.45, .08, and .044, respectively). Of patients with positive resection margins, 79% of HPV-negative patients had no residual disease. Of patients with negative resection margins, no HPV-negative patient had residual disease. CONCLUSION: The HPV test after conization was significantly more accurate than resection margin for predicting residual disease. The predictive value of resection margin for predicting...
residual disease was much improved when used in combination with the HPV test. Use of the HPV test is recommended for identifying patients for subsequent hysterectomy after conization for CIN 3 and IA1 cancer© 2009 by The American College of Obstetricians and Gynecologists.

DOI: 10.1097/AOG.0b013e3181ab6dca


**ABSTRACT:** Objectives: Conservative management of women with microinvasive cervical cancer (International Federation of Gynecologists and Obstetricians stage IA) has led to prolonged and intensive cytological follow-up. We conducted a retrospective study to assess human papillomavirus status and genotypes at diagnosis and to find out whether there is an association between the persistence of high-risk human papillomavirus during follow-up and the detection of recurrent disease. Study Design: Paraffin-embedded cervical biopsies in the pathology archives were identified from women with an initial large loop excision of the transformation zone or cone specimen diagnostic of microinvasive disease since 1991. Results: We identified 45 women with a diagnosis of microinvasive cervical cancer. Human papillomavirus was detected in 87% of the initial diagnostic specimens. Human papillomavirus testing showed a negative predictive value of 100% for recurrent disease with a sensitivity of 100%. Conclusion: Human papillomavirus testing has an important role in the follow-up of women treated conservatively for stage IA cervical cancer. Copyright © 2010 by IGCS and ESGO.

DOI: 10.1111/IGC.0b013e3181c3a6b6


**ABSTRACT:** Misclassification of exposure and surrogate endpoints of disease can obscure causal relations. Using data from the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS, 1997-2001), the authors explored the impact of exposure (human papillomavirus (HPV) detection) and endpoint (histologic cervical precancer) classification on their mutual association. Women referred into this study with an atypical squamous cells of undetermined significance Papanicolaou test with satisfactory results for all 4 HPV tests were included in this analysis (n = 3,215; 92.2%). HPV testing results were related to different definitions of cervical precancer, based on paired, worst 2-year histologic diagnoses, by calculating clinical sensitivity, specificity, and odds ratios. The authors found that HPV test sensitivity increased and specificity decreased with increasing certainty of cervical precancer, with HPV testing having the highest sensitivity (92%-98%) and lowest specificity (46%-54%) for consensus cervical intraepithelial neoplasia grade 3 (CIN 3). The overall accuracy of each HPV test, as measured by odds ratios, was greatest for consensus CIN-3 diagnoses, from 2- to 4-fold greater than for a less stringent precancer definition of any diagnosis of CIN 2 or more severe. In summary, there was convergence of greater certainty of carcinogenic HPV with
greater certainty of a precancerous diagnosis, such that all 4 HPV tests almost always tested positive in women most likely to have cervical precancer. Finding increasingly strong associations when both test and diagnostic misclassification are reduced is a useful sign of “true association” in molecular epidemiology.

DOI: 10.1093/aje/kwp390


**ABSTRACT:** Background. Human papillomavirus (HPV) testing is known to be more sensitive, but less specific than cytology for detecting cervical intraepithelial neoplasia (CIN). We assessed the efficacy of cervical-cancer screening policies that are based on HPV testing. Methods: Between March, 2004, and December, 2004, in two separate recruitment phases, women aged 25-60 years were randomly assigned to conventional cytology or to HPV testing in combination with liquid-based cytology (first phase) or alone (second phase). Randomisation was done by computer in two screening centres and by sequential opening of numbered sealed envelopes in the remaining seven centres. During phase one, women who were HPV-positive and aged 35-60 years were referred to colposcopy, whereas women aged 25-34 years were referred to colposcopy only if cytology was also abnormal or HPV testing was persistently positive. During phase two, women in the HPV group were referred for colposcopy if the HPV test was positive. Two rounds of screening occurred in each phase, and all women had cytology testing only at the second round. The primary endpoint was the detection of grade 2 and 3 CIN, and of invasive cervical cancers during the first and second screening rounds. Analysis was done by intention to screen. This trial is registered, number ISRCTN81678807. Findings: In total for both phases, 47 001 women were randomly assigned to the cytology group and 47 369 to HPV testing. 33 851 women from the cytology group and 32 998 from the HPV-testing group had a second round of screening. We also retrieved the histological diagnoses from screening done elsewhere. The detection of invasive cervical cancers was similar for the two groups in the first round of screening (nine in the cytology group vs seven in the HPV group, p=0·62); no cases were detected in the HPV group during round two, compared with nine in the cytology group (p=0·004). Overall, in the two rounds of screening, 18 invasive cancers were detected in the cytology group versus seven in the HPV group (p=0·028). Among women aged 35-60 years, at round one the relative detection (HPV vs cytology) was 2·00 (95% CI 1·44-2·77) for CIN2, 2·08 (1·47-2·95) for CIN3, and 2·03 (1·60-2·57) for CIN2 and 3 together. At round two the relative detection was 0·54 (0·23-1·28) for CIN2, 0·48 (0·21-1·11) for CIN3, and 0·51 (0·28-0·93) for CIN2 and 3 together. Among women aged 25-34 years, there was significant heterogeneity between phases in the relative detection of CIN3. At round one the relative detection was 0·93 (0·52-1·64) in phase one and 3·91 (2·02-7·57) in phase two. At round two the relative detection was 1·34 (0·46-3·84) in phase one and 0·20 (0·04-0·93) in phase two. Pooling both phases, the detection ratio of CIN2 for women aged 25-34 years was 4·09 (2·24-7·48) at round one and 0·64 (0·23-
1.27) at round two. Interpretation: HPV-based screening is more effective than cytology in preventing invasive cervical cancer, by detecting persistent high-grade lesions earlier and providing a longer low-risk period. However, in younger women, HPV screening leads to over-diagnosis of regressive CIN2. © 2010 Elsevier Ltd. DOI: 10.1016/S1470-2045(09)70360-2


What is the Role of HPV Typing in the United States Now and in the Next Five Years in a Vaccinated Population? Gynecologic Oncology, 117(3), 481-485.

ABSTRACT: Objective. To review the current state of HPV typing of the vaccinated population in the United States and potential for typing of this population over the next 5 years. Methods. An expert forum conducted on September 12–13, 2008, by the Society of Gynecologic Oncologists including 56 experts in cervical cancer and titled “Future strategies of cervical cancer prevention: what do we need to do now to prepare?” Results. In principle, screening with HPV DNA testing for oncogenic genotypes followed by cytologic triage has attractive features that may serve well the screening needs of a post-vaccination era in the US. Particularly in light of the recent FDA approval of a HPV genotyping test, the group focused on how typing could be used to assist clinical decisions and whether its implementation would be cost-effective. Furthermore, it was agreed upon that HPV typing should not be used to determine who should be vaccinated against HPV. There was considerable discussion regarding the potential misuse and overuse of HPV typing in low risk women among healthcare providers. Conclusions. As HPV typing technologies gain traction in the United States, its appropriate use will depend on the evolving natural history of the vaccinated cohort, continued educational efforts of healthcare providers, and most importantly, creating an integrated approach to cervical cancer prevention that will lead to a greater decrease in the incidence of cervical disease in the US while allowing for cost equipoise. On September 12–13, 2008, the Society of Gynecologic Oncologists (SGO) convened a symposium of 56 cervical cancer experts titled “Future strategies of cervical cancer prevention: what do we need to do now to prepare?” to discuss evidence-based strategies in cervical cancer prevention and control, including HPV vaccination. This paper is the second in a series of manuscripts which highlight concepts, information, obstacles and approaches discussed during the Forum’s sessions and focuses on the current state of HPV typing of the vaccinated population in the United States and typing of this population over the next 5 years.

DOI: 10.1016/j.ygyno.2010.01.037


A Randomized Controlled Trial of Human Papillomavirus (HPV) Testing for Cervical Cancer Screening: Trial Design and Preliminary Results (HPV FOCAL Trial). BMC Cancer 10:111.

ABSTRACT: Background. In the HPV FOCAL trial, we will establish the efficacy of hr-HPV DNA testing as a stand-alone screening test followed by liquid based cytology (LBC) triage of hr-HPV-positive women compared to LBC followed by hr-HPV triage with ≥ CIN3 as the
outcome. Methods/Design: HPV-FOCAL is a randomized, controlled, three-armed study over a four year period conducted in British Columbia. It will recruit 33,000 women aged 25-65 through the province’s population based cervical cancer screening program. Control arm: LBC at entry and two years, and combined LBC and hr-HPV at four years among those with initial negative results and hr-HPV triage of ASCUS cases; Two Year Safety Check arm: hr-HPV at entry and LBC at two years in those with initial negative results with LBC triage of hr-HPV positives; Four Year Intervention Arm: hr-HPV at entry and combined hr-HPV and LBC at four years among those with initial negative results with LBC triage of hr-HPV positive cases. Discussion: To date, 6150 participants have a completed sample and epidemiologic questionnaire. Of the 2019 women enrolled in the control arm, 1908 (94.5%) were cytology negative. Women aged 25-29 had the highest rates of HSIL (1.4%). In the safety arm 92.2% of women were hr-HPV negative, with the highest rate of hr-HPV positivity found in 25-29 year old women (23.5%). Similar results were obtained in the intervention arm. HPV FOCAL is the first randomized trial in North America to examine hr-HPV testing as the primary screen for cervical cancer within a population-based cervical cancer screening program. Trial Registration: International Standard Randomised Controlled Trial Number Register, ISRCTN79347302.

DOI: 10.1186/1471-2407/10/111

4.2 COST


**ABSTRACT:** Background. Recently published results from a large randomized trial (Canadian Cervical Cancer Screening Trial study group) suggest that human papillomavirus testing followed by Pap smear-based triage for human papillomavirus positive women may be an effective way to screen women for cervical cancer. We determined the potential cost-effectiveness of including human papillomavirus tests for cervical cancer screening for Canada and three provinces: Alberta, Newfoundland and Ontario. Methods: We developed four Markov decision models using data from relevant Canadian and provincial studies and databases. The models were used to determine the number of false positive test results, cancers, lifetime costs and life-expectancy for 27 different screening strategies that varied by age to begin screening (18 or 25 years), screening interval (one, two, three, or five years) and whether the currently recommended strategy (screening every year from age 18 until 21 and then every three years afterwards with conventional Pap tests) was conducted prior to age 25. Strategies were compared using incremental cost-effectiveness ratios. Results: Screening strategies beginning at age 18 were associated with a substantial increase in the number of false-positive test results but only small differences in the number of cancers compared to the same strategy conducted beginning at age 25. Strategies of human papillomavirus testing first, followed by triage with Pap smears were associated with lower costs and greater increases in life-expectancy than the currently recommended screening strategy in Canada. Conclusion: A strategy of human papillomavirus testing beginning at age 25, with Pap triage for women with positive human papillomavirus results may be more effective.
at reducing cervical cancer at a lower cost than the current recommended strategy for screening in Canada. © 2009 Kulasingam et al; licensee BioMed Central Ltd.
DOI: 10.1186/1741-7015-7-69


ABSTRACT: Objective: To determine the cost effectiveness of several cervical cancer screening strategies utilizing HPV testing in South Africa. Methods: We developed a lifetime Markov model of the costs, quality of life, and survival associated with screening and treating cervical cancer and its precursors. Screening strategies evaluated included: 1) conventional cytology, 2) cytology followed by HPV testing for triage of equivocal cytology, 3) HPV testing, 4) HPV testing followed by cytology for triage of HPV-positive women, and 5) co-screening with cytology and HPV testing. Primary outcome measures included quality-adjusted life-years saved (QALYs), incremental cost-effectiveness ratios, and lifetime risk of cervical cancer. Costs are in 2006 South African Rand (R). Results: In a cohort of 100,000 women, starting at age 30 and screening once every 10 years reduced the lifetime risk of cervical cancer by 13-52% depending on the screening strategy used, at an incremental cost of R13,000-R42,000 per QALY. When strategies were compared incrementally, cytology with HPV triage was less expensive and more effective than screening using cytology alone. HPV testing with the use of cytology triage was a more effective strategy and costs an additional R42,121 per QALY. HPV testing with colposcopy for HPV-positive women was the next most effective option at an incremental cost of R1541 per QALY. Simultaneous HPV testing and cytology co-screening was the most effective strategy and had an incremental cost of R25,414 per QALY. Conclusions: In our model, HPV testing to screen for cervical cancer and its precursors is a cost-effective strategy in South Africa. © 2008 Elsevier Inc.
DOI: 10.1016/j.ygyno.2008.08.030


ABSTRACT: This study assessed the cost-effectiveness of a new, rapid human papillomavirus (HPV)-DNA screening test for cervical cancer prevention in the high-risk region of Shanxi, China. Using micro-costing methods, we estimated the resources needed to implement preventive strategies using cervical cytology or HPV-DNA testing, including the Hybrid Capture 2 (hc2) test (QIAGEN Corp., Gaithersburg, MD) and the rapid HPV-DNA careHPVTM test (QIAGEN). Data were used in a previously published model and empirically calibrated to country-specific epidemiological data. Strategies differed by initial test, targeted age, frequency of screening, number of clinic visits required (1, 2 or 3) and service delivery setting (national, county and township levels). Outcomes included lifetime risk of cancer, years of life saved (YLS), lifetime costs and incremental cost-effectiveness ratios (cost per YLS). For all screening frequencies, the most efficient strategy used 2-visit rapid HPV-DNA testing at the county level, including screening and diagnostics in the first
visit, and treatment in the second visit. Screening at ages 35, 40 and 45 reduced cancer risk by 50% among women compliant with all 3 screening rounds, and was US$ 150 per YLS, compared with this same strategy applied twice per lifetime. This would be considered very cost-effective evaluated against China's per-capita gross domestic product (US$ 1,702). By enhancing the linkage between screening and treatment through a reduced number of visits, rapid HPV-DNA testing 3 times per lifetime is more effective than traditional cytology, and is likely to be cost-effective in high-risk regions of China.

DOI: 10.1002/ijc.25150


ABSTRACT: Objectives: Human papillomavirus (HPV) testing is not widely used for triage of equivocal Pap smears or primary screening in Québec, Canada. Our objective was to evaluate the cost-effectiveness of cervical cancer screening strategies utilizing HPV testing. Methods: We used a lifetime Markov model to estimate costs, quality of life, and survival associated with the following strategies: 1) cytology; 2) cytology with HPV testing to triage equivocal Pap smears; 3) HPV testing followed by colposcopy for HPV-positive women; 4) HPV testing with cytology to triage HPV-positive women; and 5) simultaneous HPV testing and cytology. Cytology was used in all strategies prior to age 30. Outcome measures included disease incidence, quality-adjusted life-years saved (QALYs), lifetime risk of cervical cancer, and incremental cost-effectiveness ratios. Results: All strategies incorporating HPV testing as a primary screening test were more effective and less expensive than annual cytology alone, while HPV testing to triage equivocal Pap smears annually was very cost-effective ($2,991 per QALY gained compared to annual cytology alone). When compared to cytology every three years, HPV-based strategies cost an additional $8,200 to $13,400 per QALY gained. Conclusion: Strategies incorporating HPV testing are not only more effective than screening based on cytology alone but are also highly cost-effective. Provincial policymakers should evaluate incorporating HPV-based strategies into current cervical cancer screening guidelines. © Canadian Public Health Association, 2010.

4.3 SELF-SAMPLING


ABSTRACT: Background. Around 65% of women with cervical carcinoma in Sweden have not attended an organised screening. We therefore investigated the value of using self-sampling at home in combination with a test for high-risk human papilloma virus (HPV) to increase participation. Methods: A total of 2829 women 30-58 years old, who had not attended the organised screening for 6 years, were recruited. They were offered self-sampling at home (Qvintip) and recommended to send the collected vaginal fluid to a laboratory for analysis of the presence of high-risk HPV (Hybrid Capture 2 method). Results: A total of 39.1% of the women accepted home sampling. These women disclosed
a relatively high prevalence of high-risk HPV, which decreased with age, from 11.1% in women 30-39 years old to 2.9% in women 50 years. Follow-up disclosed histological cervical intraepithelial neoplasm (CIN) 2-3 lesions in 43.2% of the women with a persistent HPV infection, corresponding to 2.0% of the total number of participating women. The sensitivity of a single smear to detect the histological CIN 2-3 lesions were only 52.6%, even if all abnormal smears (atypical squamous cells of unknown significance (ASCUS)-CIN 3) were included. Conclusion: The use of self-sampling at home in combination with testing for high-risk HPV increases the participation rate of the organised screening and detects almost twice as many women with pre-malignant cell alterations (CIN 2-3) in comparison those with a single cytological smear. © 2009 Cancer Research UK. DOI: 10.1038/sj.bjc.6605194


ABSTRACT: Objectives: Immigrant and low socio-economic (SES) women in North America underutilize Papanicolaou screening. Vaginal swab self-sampling for oncogenic human papillomavirus (HPV) has the potential to increase cervical cancer screening participation. The purpose of this qualitative study was to understand the perceptions of lower SES and immigrant women regarding self-sampling for HPV. Methods: Eleven focus-group interviews were conducted: one with Canadian-born English-speaking lower SES women, and two groups each with Arabic, Cantonese, Dari (Afghani), Somali and Spanish (Latino)-speaking women (one group conducted in English, the other in the native language) recently immigrated to Canada. Five to nine women aged 35 to 65 years and married with children participated in each group. Results: Themes included 1) who might use self-sampling and why; 2) aversion to self-sampling and reasons to prefer physician; 3) ways to improve the appeal of self-sampling. Women generally perceived benefits of self-sampling and a small number felt they might use the method, but all groups had some reservations. Reasons included: uncertainty over performing the sampling correctly; fear of hurting themselves; concern about obtaining appropriate material; and concerns about test accuracy. Women preferred testing by a health care professional because they were accustomed to pelvic examinations, it was more convenient, or they trusted the results. Conclusions: Perceptions of self-sampling for HPV were similar across cultures and pertained to issues of confidence in self-sampling and need for physician involvement in care. These findings can inform programs and studies planning to employ self-sampling as a screening modality for cervical cancer. © Canadian Public Health Association, 2009.


Can human papillomavirus DNA testing of self-collected vaginal samples compare with physician-collected cervical samples and cytology for cervical cancer screening in developing countries? Cancer Epidemiology, 33(6), pp. 446-450.

ABSTRACT: Background. To determine human papillomavirus (HPV) types by polymerase
chain reaction (PCR)-reverse line blot assay and examine the concordance between HPV by Hybrid Capture 2 (HC2) and PCR on self-collected vaginal and physician-collected cervical samples and cytology. Methods: This was a cross-sectional study of 546 sexually active women aged ≥30 years with persistent vaginal discharge, intermenstrual or postcoital bleeding or an unhealthy cervix. Participants self-collected vaginal samples (HPV-S) and physicians collected cervical samples for conventional Pap smear and HPV DNA (HPV-P) testing and performed colposcopy, with directed biopsy, if indicated. HPV testing and genotyping was done by HC2 and PCR reverse line blot assay. Concordance between HC2 and PCR results of self- and physician-collected samples was determined using a Kappa statistic (κ) and Chi-square test. Results: Complete data were available for 512 sets with 98% of women providing a satisfactory self-sample. PCR detected oncogenic HPV in 12.3% of self- and 13.0% of physician-collected samples. Overall, there was 93.8% agreement between physician-collected and self-samples (κ = 76.31%, 95% confidence interval [CI]: 64.97-82.29%, p = 0.04)-complete concordance in 473 cases (57 positive, 416 negative), partial concordance in seven pairs and discordance in 32 pairs. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of self-sampling for detection of cervical intraepithelial neoplasia (CIN)2+ disease were 82.5%, 93.6%, 52.4% and 98.4%, respectively; for physician-sampling they were 87.5%, 93.2%, 52.2% and 98.9%, respectively; and for cytology they were 77.5%, 87.3%, 34.1% and 97.9%, respectively. Concordance between HC2 and PCR was 90.9% for self-samples (κ = 63.7%, 95% CI: 55.2-72.2%) and 95.3% for physician-collected samples (κ = 80.4%, 95% CI: 71.8-89.0%). Conclusions: Self-HPV sampling compares favourably with physician-sampling and cytology. A rapid, affordable, HPV self-test kit can be used as the primary method of cervical cancer screening in low-resource situations. © 2009 Elsevier Ltd.

DOI: 10.1016/j.canep.2009.10.013


ABSTRACT: Objectives: Our aim was to determine if (1) Hybrid Capture 2 and a PCR-based method were comparable for detection of high-risk human papillomavirus (HPV) clinician-collected and self-collected samples were equally efficient to detect HPV and cervical cancer precursor lesions, and (3) if participation rates improved with home-based versus clinic-based self collection. Methods: Samples were selected from women participating in a cervical cancer screening study according to HPV, visual inspection with acetic acid, or Pap smear screening results. From 432 of 892 selected women, split sample aliquots were tested for HPV DNA using both the Hybrid Capture 2 assay and the Roche prototype line blot assay. Women from a subset of villages were recruited at two separate time points for clinic-based self-collection and home-based self-collection, and participation rates were compared. Results: Pairwise agreement between self- and clinician-collected samples was high by both Hybrid Capture 2 (90.8% agreement, κ = 0.7) and PCR (92.6% agreement, κ = 0.8), with
significantly increased high-risk HPV detection in clinician-collected specimens (McNemar’s P < 0.01). Ability to detect precursor lesions was highest by PCR testing of clinician-collected samples and lowest by Hybrid Capture 2 testing of self-collected samples (11 of 11 and 9 of 11 cases of cervical intraepithelial neoplasia grade 2/3 and cancer detected, respectively). Participation in home-based screening was significantly higher than clinic-based screening (71.5% and 53.8%, respectively; P < 0.001) among women ages 30 to 45 years. Conclusion: The combination of improved screening coverage and a high single test sensitivity afforded by HPV DNA testing of home-based self-collected swabs may have a greater programmatic effect on cervical cancer mortality reduction compared with programs requiring a pelvic exam. Copyright © 2009 American Association for Cancer Research. DOI: 10.1158/1055-9965.EPI-08-1171


ABSTRACT: The Mexican Cervical Cancer Screening (MECCS) study took place in the State of Michoacán. Primary screening was by self-sampling for high-risk human papillomavirus (HR-HPV). The objectives were to increase the specificity of primary HPV screening by requiring 2 positive HPV tests 1 year apart in women whose secondary screen was negative according to an acetic acid aided visual inspection (VIA). In addition, we postulated that the sensitivity of VIA would be sufficient to identify large preinvasive lesions and cancers unsuitable for cryotherapy if applied in a see-and-treat algorithm. A total of 8621 women (aged 30-50 years) were screened, and 14.3% were positive for HR-HPV. In phase 1, 11.9% of the HPV-positive women were VIA-positive and were referred for colposcopy with directed and random biopsies. If VIA-negative, women repeated the self-sample 1 year later to detect persistent HR-HPV (25.2% were positive). If persistently HR-HPV positive in phase 2, patients again had VIA, then all women (both VIA-positive and -negative) received directed and random biopsies. If cryotherapy had been used to treat HPV- and VIA-positive women in phase 1 or persistent HR-HPV positive (phase 2), the potential risk of undertreatment would have been 4.1%, and 66.4% of the treated patients would have had normal or cervical intraepithelial neoplasia I on biopsy. The VIA triage would refer 0.73% of the patients to colposcopy owing to the lesion size, location, or the presence of a cancer. On the basis of this pilot study, we are encouraged to explore and evaluate a rapid, more sensitive, and more specific self-test. ©2009 by IGCS and ESGO. DOI: 10.1111/IGC.0b013e318197f479

4.3 Self-Sampling

ABSTRACT: This study assesses human papillomavirus (HPV) detection and genotyping in self-sampled genital smears applied to an indicating FTA elute cartridge (FTA cartridge). The study group consisted of 96 women, divided into two sample sets. All samples were analyzed by the HPV SPF10-Line Blot 25. Set 1 consisted of 45 women attending the gynecologist; all obtained a self-sampled cervicovaginal smear, which was applied to an FTA cartridge. HPV results were compared to a cervical smear (liquid based) taken by a trained physician. Set 2 consisted of 51 women who obtained a self-sampled cervicovaginal smear at home, which was applied to an FTA cartridge and to a liquid-based medium. DNA was obtained from the FTA cartridges by simple elution as well as extraction. Of all self-obtained samples of set 1, 62.2% tested HPV positive. The overall agreement between self- and physician-obtained samples was 93.3%, in favor of the self-obtained samples. In sample set 2, 25.5% tested HPV positive. The overall agreement for high-risk HPV presence between the FTA cartridge and liquid-based medium and between DNA elution and extraction was 100%. This study shows that HPV detection and genotyping in self-obtained cervicovaginal samples applied to an FTA cartridge is highly reliable. It shows a high level of overall agreement with HPV detection and genotyping in physician-obtained cervical smears and liquid-based self-samples. DNA can be obtained by simple elution and is therefore easy, cheap, and fast. Furthermore, the FTA cartridge is a convenient medium for collection and safe transport at ambient temperatures. Therefore, this method may contribute to a new way of cervical cancer screening. Copyright © 2009, American Society for Microbiology.

DOI: 10.1128/JCM.00285-09


ABSTRACT: Objectives: We explored Muslim women’s attitudes to self-sampling for human papillomavirus (HPV) in the context of cervical cancer screening and their responses to two self-sampling devices. Setting: A Muslim community centre in north-east London. Methods Following a talk given on the subject of cervical cancer and HPV at the community centre, 28 women were recruited to take part in three focus group discussions. The discussion covered cervical screening, self-sampling and HPV testing. Women were also asked for their responses to a swab self-sampling kit and a cervico-vaginal lavage device. Discussions were recorded and transcribed verbatim and the qualitative data were analysed using Framework Analysis. Results: Participants were generally positive about cervical screening but acknowledged that some women in their community were reluctant to attend because of embarrassment, language difficulties, fear or because they were unmarried and did not want to communicate implicit messages about being sexually active. Self-sampling met a mixed response – women were concerned about not doing the test correctly, but thought that it might overcome barriers to screening for some women. HPV testing itself was thought to raise potentially difficult issues relating to trust and fidelity within marriages. Although most women said they would prefer to continue to have screening by a health professional, if they were to perform self-sampling, there was overwhelming preference for the swab over the lavage kit. Conclusions: There was limited enthusiasm for self-sampling in this group of
Muslim women who had mostly attended for cervical screening, but a clear preference for a swab rather than a cervico-vaginal lavage.

DOI: 10.1258/jms.2009.009069


**ABSTRACT:** Background. We assessed the accuracy of self-collected human papillomavirus (HPV) specimens in men compared with clinician-collected specimens from men in British Columbia and determined the prevalence of HPV subtypes at different male genital sites. Methods: Heterosexual men were recruited at the Provincial Sexually Transmitted Infection (STI) Clinic in Vancouver, Canada. Participants were randomly assigned to conduct self-collection or clinician-collected specimens first. Clinicians obtained specimens using emery paper followed by saline-moistened Dacron swab from three genitourinary sites: glans penis/foreskin, penile shaft (ventral and dorsal surfaces) and scrotum. Participants received written instructions and took specimens from one of the three sites using the same technique as clinicians. HPV testing was performed with the Roche Amplicor HPV test and samples found to be reactive were tested with the Roche Linear Array HPV typing assay to establish the HPV genotype(s) in the sample. Results: Overall prevalence of any HPV genotype from any site was 69.8% in clinician-collected specimens and 55.3% in self-collected specimens. Order of collection (clinician vs self-collected) did not impact on the prevalence of HPV in the specimens. The $\kappa$ scores for agreement between clinician-collected and self-collected specimens ranged from fair to excellent. Overall, there was better agreement between self-collected and clinician-collected specimens for HPV-18 (range: $\kappa = 0.88$ to $0.92$) than for HPV-16 (range: $\kappa = 0.36$ to $0.62$). Conclusion: HPV is a prevalent genital tract infection in men. Site-specific agreement for specific HPV genotypes between clinician-collected and self-collected specimens varied broadly and neither clinicians nor patients routinely obtained samples with consistently higher or lower prevalence at specific genital sites, indicating there are continued opportunities to improve techniques for clinician-collected and self-collected male specimens for HPV.

DOI: 10.1136/sti.2008.033068


**ABSTRACT:** Objective: To determine whether pairing self-sampling for HPV with community health workers (CHWs) is a culturally acceptable method for cervical cancer screening among Haitian immigrant women residing in Little Haiti, the predominately Haitian neighborhood in Miami, FL. Methods: As part of a larger, ongoing community-based participatory research (CBPR) initiative in Little Haiti, Haitian CHWs recruited 246 eligible women to this study. Participants provided self-collected cervical specimens for HPV testing and answered a series of questions about their experience with self-sampling for HPV. Results: The vast majority of women (97.6%) was comfortable using the self-sampler at...
home, would recommend this screening method to their friends and/or family members (98.4%), and described the sampler as easy to use (95.1%). Additionally, 97% of all self-collected specimens were deemed adequate for HPV testing. Conclusions: When paired with CHWs, who are of Haitian descent and well respected in Little Haiti, self-sampling is a highly acceptable method of cervical screening for Haitian women in this ethnic enclave. This approach addresses critical access barriers, including poverty, language difficulties, and sociocultural concerns about modesty, that may similarly affect Pap smear utilization among other immigrant or medically underserved population sub-groups. Coupled with generally positive reviews of the device, the low rate of insufficient specimens for testing suggests that this device is promising for use in non-clinical settings. © 2009 Springer Science+Business Media B.V.
DOI: 10.1007/s10552-009-9474-0
Section 5.
Data Management and Linkages
SUMMARY

One of the critical elements of a successful immunization program is the surveillance of vaccine coverage. In one report, the evaluation of the immunization program in Manitoba was facilitated by the availability and linkage of information systems to measure vaccine coverage and evaluate reduction of disease incidence.


The Manitoba Human Papillomavirus Vaccine Surveillance and Evaluation System. Health Reports, 21(2). Statistics Canada, Catalogue no. 82-003-XPE.

ABSTRACT: Background. With the recent introduction of a human papillomavirus (HPV) vaccine in Canada, it is important to establish surveillance and evaluation programs that not only track the uptake of the vaccine, but also assess its safety and its impact on: distribution of HPV type, cervical cancer screening programs, the incidence of anogenital warts, precancerous lesions and various cancers, and sexual behaviour. Data sources and methods Administrative databases, registries and questionnaire information are being linked to identify people receiving the HPV vaccine and to develop an evaluation system. Interpretation: The availability of extensive linkable databases in Manitoba allows for the development of a comprehensive HPV vaccine surveillance and evaluation system that can address many of the questions related to the HPV vaccine. Aspects of the Manitoba surveillance and evaluation system could be implemented in other provinces that have similar databases.
Section 6.
Therapeutic Use of Vaccine
SUMMARY
Therapeutic vaccine development in early clinical trials with HIV-infected men demonstrated positive results for an HPV 16 (E6E7) ISCOMATRIX adjuvant vaccine (96% 4-fold increase in HPV 16 antibody response). In another study of HspE7 vaccination of women with CIN III, a modest increase in HPV16 E7 specific serum IgG levels were maintained for at least 12 months.


ABSTRACT: OBJECTIVE: Study aimed to assess safety, tolerability, and immunogenicity of novel therapeutic HPV-16 E6E7 ISCOMATRIX vaccine for treatment of human papilloma virus (HPV)-related anal intraepithelial neoplasia in HIV-infected men who have sex with men with moderate immunosuppression. DESIGN: Randomized, multicenter, blinded, placebo-controlled, dose-escalating study investigating 3 different doses of vaccine and different dose schedule. Primary objective to determine safety and tolerability, including clinical status, maintenance of virological control, and CD4 cell count for more than 252 days. RESULTS: Thirty-five men who have sex with men enrolled; median age 47 years; current CD4 count 627 cells per milliliter; nadir CD4 count 154 cells per milliliter; 94% current antiretrovirals; 100% high-risk HPV types; 69% abnormal anal cytology; and 34% anal intraepithelial neoplasia 1-3 on high-resolution anoscopy. No dose-limiting toxicities or serious adverse events in HPV-16 vaccine recipients. Most HPV-16 vaccine recipients reported moderate/severe short-term injection site reactions and systemic reactions including headache, myalgia, and fatigue. CD4 cell counts remained stable. Five participants had transiently detectable viral loads. Ninety-six percent of vaccine recipients had at least a 4-fold increase in HPV-16 antibody from prevaccination levels. Seventy-one percent had at least a 3-fold increase in interferon-gamma responses to E6E7 peptides. CONCLUSIONS: The novel therapeutic HPV-16 E6E7 ISCOMATRIX vaccine seemed safe and reasonably well tolerated. The therapeutic vaccine induces strong and durable antibody responses and moderate interferon-γ levels that fell to prevaccination levels by week 24. Copyright © 2009 by Lippincott Williams & Wilkins. DOI: 10.1097/QAI.0b013e3181b7354c


ABSTRACT: Purpose: Infection with oncogenic human papillomaviruses has been linked to the development of cervical neoplasia and cancer. The exclusive expression of E7, a viral oncogene, in infected cells makes this protein an ideal target for immunotherapy.
We recently reported on the results of a trial in women with cervical carcinoma-in-situ using HspE7, a protein vaccine consisting of full length HPV16 E7 linked to a heat shock protein from M. bovis. The stimulating effects of HspE7 on specific cytotoxic T lymphocytes have been demonstrated in vitro and in (pre-)clinical trials. The induction of a B-cell response by HspE7 and its association with clinical outcome is unknown, and is the purpose of this study. Experimental design: We measured the serum IgG levels against HPV16 E7 and HPV16 and -18 VLPs using a multiplexed Luminex based assay in 57 women with CIS who received the HspE7 vaccine. Results: Vaccination with HspE7 results in a modest, yet maintained increase in HPV16 E7 specific IgG levels. While not significant, increased HPV16 E7 IgG levels appear to be correlated with a positive therapeutic effect. Women who were previously treated for recurrent disease (by LEEP) had significantly higher HPV16 E7 IgG levels compared with subjects without recurrent disease (p = 0.01). In women with recurrent disease, higher IgG levels correlated with complete pathological response. Conclusions: This study suggests that IgG levels could potentially be used as a marker for response to a therapeutic vaccine. Further translational investigations of the ‘priming’ of local immune responses using extirpative procedures should be explored. © 2009 Elsevier Inc. DOI: 10.1016/j.ygyno.2009.05.044
SECTION 7 - HPV TESTING TECHNOLOGY

WHAT IS THE CURRENT STATUS OF HPV TESTING TECHNOLOGY?

SUMMARY
Numerous clinical trials have proven the utility of HPV DNA testing for cervical cancer screening. HPV DNA testing was used with success for ASCUS triage and for monitoring cervical lesions after treatment. Most of the clinical work was based on one type of test, Hybrid Capture II, but many commercial and in-house testing methods were available. Many of these methods had an equivalent, or better, analytical performance compared to HCII, but their clinical utility requires evaluation. Testing for tumour markers (HPV E6 RNA and p16 host proteins) has demonstrated utility in cervical cancer screening, but their superiority compared to HPV DNA testing remains to be determined.

Priority Research

1) Clinical evaluation of alternative HPV DNA testing technologies, other than Hybrid Capture II, are required to establish test specificity in detecting high grade lesions and utility for cervical cancer screening.

2) The development of a truly point-of-care HPV test would revolutionize the approach to cervical cancer screening.

3) The development of a test based on tumour markers that could detect high grade lesions with the sensitivity of HPV DNA testing and the specificity of Pap testing would be valuable.

7.1 REVIEWS AND META-ANALYSIS


ABSTRACT: Excellent recommendations exist for studying therapeutic and diagnostic questions. We observe that good guidelines on assessment of evidence for screening questions are currently lacking. Guidelines for diagnostic research (STARD), involving systematic application of the reference test (gold standard) to all subjects of large study populations, are not pertinent in situations of screening for disease that is currently not yet present. A five-step framework is proposed for assessing the potential use of a biomarker as a screening tool for cervical cancer: i) correlation studies establishing a trend between the rate of biomarker expression and severity of neoplasia; ii) diagnostic studies in a clinical setting where all women are submitted to verification by the reference standard; iii) biobank-based studies with assessment in archived cytology samples of the biomarker in cervical cancer cases and controls; iv) prospective cohort studies with baseline assessment of the biomarker and monitoring of disease; v) randomised intervention trials aiming to observe reduced incidence of cancer (or its surrogate, severe dysplasia) in the experimental arm at subsequent screening rounds. The 5-phases framework should guide researchers and test developers in planning assessment of new biomarkers and protect clinicians and stakeholders against premature claims for insufficiently evaluated products. © 2009 UICC.

DOI: 10.1002/ijc.24774


**ABSTRACT:** Human papillomaviruses (HPV) are the etiologic agents of cancer of the uterine cervix and several other neoplasias. Detection of HPV infection will improve the sensitivity of primary and secondary screening of cervical cancer. The clinical indications for the use of HPV tests will have to consider the natural history of HPV infection and diseases, and the multiplicity of types involved. Signal amplification HPV DNA tests detect several high-risk HPV types, are standardized, commercialized and approved for clinical use. Nucleic acid amplification techniques are ideal methods for epidemiologic purposes since they minimize misclassification of HPV infection status and allow detection of infection with low viral burden. They are currently under evaluation for clinical use. PCR is the most widespread method for HPV typing, especially with the use of consensus primers and typing with reverse hybridization techniques. Novel promising HPV detection strategies are now proposed, such as HPV mRNA detection, and suspension or solid phase arrays. These novel techniques will have to be evaluated as stringently as actual assays in clinical studies. Although assays have been developed for the evaluation of viral load, viral integration and HPV polymorphism in molecular epidemiological studies, their role in clinical practice is not currently defined. Copyright © 2009 S. Karger AG. DOI: 10.1159/000214921


**ABSTRACT:** Background. p16<sup>INK4a</sup> is a biomarker for transforming HPV infections that could act as an adjunct to current cytological and histological assessment of cervical smears and biopsies, allowing the identification of those women with ambiguous results that require referral to colposcopy and potentially treatment. Material and methods: We conducted a systematic review of all studies that evaluated the use of p16<sup>INK4a</sup> in cytological or histological specimens from the uterine cervix. We also estimated the mean proportion of samples that were positive for p16<sup>INK4a</sup> in cytology and histology, stratified by the grade of the lesion. Results: Sixty-one studies were included. The proportion of cervical smears overexpressing p16<sup>INK4a</sup> increased with the severity of cytological abnormality. Among normal smears, only 12% (95% CI: 7-17%) were positive for the biomarker compared to 45% of ASCUS and LSIL (95% CI: 35-54% and 37-57%, respectively) and 89% of HSIL smears (95% CI: 84-95%). Similarly, in histology only 2% of normal biopsies (95% CI: 0.4-30%) and 38% of CIN1 (95% CI: 23-53%) showed diffuse staining for p16<sup>INK4a</sup> compared to 68% of CIN2 (95% CI: 44-92%) and 82% of CIN3 (95% CI: 72-92%). Conclusion: Although there is good evidence that p16<sup>INK4a</sup> immunostaining correlates with the severity of cytological/histological abnormalities, the reproducibility is limited due to insufficiently standardized interpretation of the immunostaining. Therefore, a consensus needs to be reached regarding the evaluation of p16<sup>INK4a</sup> staining and the biomarker needs to be assessed in various clinical settings addressing specific clinical questions. © 2008 Elsevier Ltd. DOI: 10.1016/j ctrv.2008.10.005
SECTION 7 - HPV TESTING TECHNOLOGY

7.2 HPV SCREENING AND GENOTYPING AMONG COMMERCIAL METHODS

7.2.1. METHODS FOR DETECTION OF DNA


**ABSTRACT:** Cervical intraepithelial neoplasia (CIN) 2 is used as the threshold for treatment decisions. This study was conducted to evaluate the clinical efficacy of the Hybrid Capture II assay (HC2) and the human papillomavirus (HPV) DNA chip test (HDC) for detecting HPV in high-grade cervical lesions CIN2 or greater, including adenocarcinoma (CIN2+). Seven hundred forty-one women with abnormal cervical cytology were evaluated with the HC2, the HDC, and histological assessment of the cervix. The overall agreement of the 2 HPV tests was 88.8% (J value, 0.61). Of 615 high-risk HPV-positive specimens by the HC2, 571 (92.8%) were HDC-positive. Both tests were performed similarly on CIN2+ samples; the sensitivities of the HC2 and HDC as predictors of CIN2+ were 93.4 and 92.6%, respectively. In 83 cases of discrepancies between the HC2 and HDC, genotyping of 39 HC2-negative/HDC-positive cases revealed 13 HPV-53, 8 HPV-58, 7 HPV-16, 6 HPV-18, 2 HPV-68, 1 HPV-31, 1 HPV-45, and 1 HPV-66. In 515 patients with CIN2+, HPV-16 (45.0%) was the most common type; the next most common types were HPV-58 (20.8%), HPV-18 (16.1%), HPV-31 (6.6%), and HPV-33 (6.6%). Human papillomavirus types 16, 58, and 18 were more likely associated with CIN2+ (P < 0.05). In conclusion, the HDC is a reliable diagnostic tool for the detection of CIN2+. In addition, the HDC provides useful information regarding viral genotypes. © 2009 by IGCS and ESGO.

DOI: 10.1111/IGC.0b013e3181a832a2


Evaluation of a prototype real-time PCR assay for carcinogenic human papillomavirus (HPV) detection and simultaneous HPV genotype 16 (HPV16) and HPV18 genotyping. *Journal of Clinical Microbiology, 47*(10), pp. 3344-3347.

**ABSTRACT:** Results from a prototype real-time PCR assay that separately detected human papillomavirus genotype 16 (HPV16), HPV18, and 12 other carcinogenic HPV genotypes in aggregate (cobas 4800 HPV test) and results from a PCR assay that detects 37 HPV genotypes individually (Linear Array) were compared using a convenience sample of cervical specimens (n = 531). The percentage of total agreement between the two assays was 94.7% (95% confidence interval, 92.5 to 96.5%). The Linear Array test was more likely than cobas 4800 HPV test to test positive for the 12 other carcinogenic HPV genotypes among women without evidence of cervical disease (P = 0.004). Copyright © 2009, American Society for Microbiology.

DOI: 10.1128/JCM.00725-09


**ABSTRACT:** Background. Epidemiologic studies have classified 18 genotypes of the human papillomavirus (HPV) as (probably) high-risk (HR) based on their association with cervical cancer, i.e., HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82. Given the fact that certain HR HPV types confer an increased risk of cervical (pre)cancer, type-specific identification might aid clinical management of women tested positive for HR HPV. Therefore, the development of robust, high-throughput genotyping assays is important. Objectives: An analytical comparison of the digene HPV Genotyping LQ Test (digene LQ Test), capable of identifying 18 HR types using bead-based xMAP suspension array technology, with the established Reverse Line Blot (RLB) genotyping assay was carried out on amplimers generated with the clinically validated GP5+/6+-PCR method. Study design: GP5+/6+ amplimers, generated from 434 digene High Risk HPV HC2 DNA Test (HC2)-positive and 95 HC2-negative cervical smears, were genotyped by both the digene LQ Test and the RLB genotyping assay. Results: The genotyping assays revealed high agreement for overall HR HPV detection (u = 0.884) and type-specific identification of the 18 HR HPV types (overall u = 0.958, individual u range 0.795 to 1.000). The digene LQ Test demonstrated a very good inter-laboratory reproducibility (u = 0.987). Among the HC2-positive women, the digene LQ Test revealed positivity for one or more HR HPV type(s) in 85.9%, and negativity was observed in 97.9% of the HC2-negative women. Conclusions: The digene LQ Test demonstrated a high genotyping agreement with the established RLB genotyping assay on GP5+/6+ amplimers. This novel assay allows for high-throughput genotyping following HR HPV testing by HC2. © 2009 Elsevier B.V.

DOI: 10.1016/S1386-6532(09)70297-5


**ABSTRACT:** Background. Abbott RealTime High Risk (HR) HPV is a recently developed test for the detection of 14 high-risk oncogenic HPV types combined with the ability to concurrently identify genotypes 16 and 18. Objectives: The clinical performance of the Abbott RealTime HR HPV test was evaluated in comparison with the Hybrid Capture 2 (HC2) test for the detection of cervical intraepithelial neoplasia 2 or worse (CIN2+). The relative accuracy of the Abbott RealTime HR HPV to detect high-risk HPV was also determined. Study design: Cervical specimens were collected from 702 patients with abnormal cytology who were referred for colposcopy, and were tested with liquid based cytology (LBC), Abbott RealTime HR HPV and HC2. Genotyping was done using the Linear Array (LA) method. Histological assessment was used as the gold standard for disease status. Clinical performance for detection of disease was evaluated for Abbott RealTime HR HPV in comparison with HC2.
in the overall population and in each cytological grade. The relative accuracy for detection of high-risk HPV was assessed by concordance between the two tests and based on LA genotyping. Results and Conclusions: The Abbott RealTime HR HPV showed similar clinical performance for detection of CIN2+ when compared with HC2, for both the overall population and those with a cytological grade of atypical squamous cells of undetermined significance (ASC-US). The accuracy for detection of high-risk HPV was significantly higher with Abbott RealTime HR HPV than with HC2. © 2009 Elsevier B.V. DOI: 10.1016/S1386-6532(09)70004-6


The clinical performance of Invader® technology and SurePath® when detecting the presence of high-risk HPV cervical infection. Journal of Clinical Virology, 45 (SUPPL. 1), pp. S79-S83.

ABSTRACT: Background. Testing for high-risk genotypes of the human papillomavirus (HR HPV) has been fully integrated into the management algorithms for the prevention of cervical cancer. The literature is limited with regard to the evaluation of the clinical performance of laboratory-developed tests (LDT) utilizing Invader® V2.0 assay (ThirdWave/Hologic, Madison, WI, USA) for the detection of HR HPV. Objectives: To evaluate the clinical performance of Invader V2.0 LDT by determining its sensitivity, negative predictive value (NPV), specificity and positive predictive value (PPV). Study Design: This study evaluated Invader V2.0 assay results from 12,490 SurePath® Pap specimens and 1,931 cervical biopsies in order to assess the clinical performance of the Invader V2.0 assay. The cervical biopsy results were correlated with Invader V2.0 results to determine clinical sensitivity, NPV, clinical specificity, and PPV. Results: The clinical sensitivity and NPV of Invader V2.0 LDT for cervical intraepithelial neoplasia 3 (CIN 3) or higher were 97.4% and 99.1% respectively. The clinical specificity and PPV for CIN 3 were 10.3% and 3.7% respectively. Conclusions: The results support the use of the Invader V2.0 in identifying patients who are at low risk for CIN 3 or higher. The power of the assay implies that it could be used as a primary screening tool for prevention of cervical cancer if a paradigm shift in cervical screening ever occurs. © 2009 Elsevier B.V. DOI: 10.1016/S1386-6532(09)70012-5


Comparison of the PapilloCheck® DNA micro-array Human Papillomavirus detection assay with Hybrid Capture II and PCR-enzyme immunoassay using the GP5/6+ primer set. Journal of Clinical Virology, 45 (2), pp. 100-104.

ABSTRACT: Background. Cervical screening detects precancerous cells and routine screening could be improved by testing for Human Papillomavirus (HPV), the virus that causes cervical cancer. HPV infection is common and the benefit of HPV testing would be identification of women who are HPV negative and at low risk of developing cancer. Study design: The aim of this study was to evaluate the Greiner Bio-one PapilloCheck® micro-array assay (PapilloCheck) for detection of HPV in comparison with Hybrid Capture II (hc2) and PCR-enzyme immunoassay (PCR-EIA) using the GP5/6+ primers. Results: Samples from a cytologically defined population (n = 878) were analysed and 187 samples also had histology
information. Overall, 674 out of 878 samples gave a consistent result (76.8%; 95% CI 73.83-79.52%) on all three platforms. The genotype results obtained by PapilloCheck and PCR-EIA were compared and 94% were consistent (95% CI 92.1-96.4%). The main difference was the poor Kappa agreement for detection of high risk (HR) type 35 (Kappa = 0.190) with all inconsistent results being HR positive by PCR-EIA assay but negative on the PapilloCheck platform. There was no statistically significant difference between the performance of each assay when HR HPV positive samples were linked with clinical result (cytology and histology grade). PapilloCheck detected the highest number of HR HPV infections in samples with histology confirmed as CIN1, CIN2 and CIN 3 (76.6%, 85% and 91.7%, respectively). Conclusions: Overall, PapilloCheck proved to be a sensitive, reproducible, robust molecular assay for HPV genotyping with the potential for high throughput of specimens in a clinical setting. © 2009 Elsevier B.V.

DOI: 10.1016/j.jcv.2009.02.013


ABSTRACT: The INFINITI HPV-QUAD assay is a commercially available genotyping platform for human papillomavirus (HPV) that uses multiplex PCR, followed by automated processing for primer extension, hybridization, and detection. The analytical performance of the HPV-QUAD assay was evaluated using liquid cervical cytology specimens, and the results were compared with those results obtained using the digene High-Risk HPV hc2 Test (HC2). The specimen types included SurePath and PreservCyt transport media, as well as residual SurePath and HC2 transport media from the HC2 assay. The overall concordance of positive and negative results following the resolution of indeterminate and intermediate results was 83% among the 197 specimens tested. HC2 positive (+) and HPV-QUAD negative (-) results were noted in 24 specimens that were shown by real-time PCR and sequence analysis to contain no HPV, HPV types that were cross-reactive in the HC2 assay, or low virus levels. Conversely, HC2 (+) and HPV-QUAD (-) results were noted in four specimens and were subsequently attributed to cross-contamination. The most common HPV types to be identified in this study were HPV16, HPV18, HPV52/58, and HPV39/56. We show that the HPV-QUAD assay is a user friendly, automated system for the identification of distinct HPV genotypes. Based on its analytical performance, future studies with this platform are warranted to assess its clinical utility for HPV detection and genotyping. Copyright © American Society for Investigative Pathology and the Association for Molecular Pathology.

DOI: 10.2353/jmoldx.2009.080154


ABSTRACT: Human papillomavirus (HPV) testing using molecular methods in liquid based cytology (LBC) specimens may be useful as an adjunct to cervical screening by cytology. We
compared the positivity rate of the commercially available HPV DNA method hybrid capture 2 (hc2) and the commercially available E6/E7 mRNA method PreTect™ HPV-Proofer in cytological specimens (n = 299). LBC specimens collected (n = 299) represented the following cervical cytological disease categories: Normal (n = 60), borderline nuclear abnormalities (BNA) (n = 34), CIN1 (n = 121), CIN2 (n = 60), CIN3 (n = 24). Overall, 69% (205/299) of the cases were positive by hc2 and 38% (112/299) of the cases were positive by PreTect™ HPV-Proofer.

Concordance rates between the two tests were highest in the high-grade cytology cases (CIN2: 67% and CIN3: 83%) and the normal cytology cases (88%) and lowest in the BNA and CIN1 categories (56% and 52%). HPV DNA viral load analyses were carried out on HPV16 (n = 55), HPV18 (n = 9) and HPV33 (n = 13) samples that were positive by PreTect™ HPV-Proofer.

The sensitivity and specificity of PreTect™ HPV-Proofer and the hc2 DNA test for the detection of high-grade cytology (i.e. CIN2+) were 71.4% and 75.8% vs 100% and 43.7%, respectively. The relatively low detection rate observed by PreTect™ HPV-Proofer in the whole range of cytological positive cases, combined with a relatively higher specificity and PPV, suggests that PreTect™ HPV-Proofer may be more useful than hc2 for triage and in predicting high-grade disease. © 2008 Elsevier B.V.

DOI: 10.1016/j.jviromet.2008.09.027


ABSTRACT: In efforts to improve service, we compared the performance of four methods of HPV detection: Invader® HPV (Hologic), Hybrid Capture 2® (Qiagen), Inform® HPV detection (Ventana), and standard PCR. Using blinded/de-identified cervical samples in Preservcyt® (Hologic), we compared Ventana’s Inform® HPV Test, against Hologic’s HPV Invader® and PCR. In a separate evaluation, we compared Inform® versus Invader versus hc2®. Ventana employs in situ hybridization; Hologic’s technology uses three specifically designed oligonucleotides and a fluorescent signal for detection. Qiagen’s hc2® method incorporates enzyme-linked antibody detection of RNA-DNA hybrids. PCR testing was provided by Access Genetics (Minneapolis, MN). The United States Food and Drug Administration recently approved the Third Wave/Hologic Invader HPV high-risk test (rebranded as Cervista™ HPV HR Test). In this small study, involving a few hundred tests, Third Wave, Qiagen, and PCR tests were comparable. Kappa statistics comparing Third Wave to PCR and Third Wave to Qiagen were 0.88 and 0.74, respectively. Ventana’s method did not correlate well with any of the other methods with Kappa ranging from a low of 0.25 versus Qiagen to 0.31 versus PCR. Kappa statistics measure correlation and not accuracy of measurement. Although we felt that the specificity of our original HPV method, Ventana Inform® was satisfactory and lowered our subsequent colposcopy rate, worries about its lower sensitivity caused us to look at other techniques. Other methods, PCR, hc2, and Invader®, appeared comparable with one another in our series. We chose to implement the Third Wave test in our laboratory.

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**ABSTRACT:** Background. The low sensitivity of cytology and low specificity of human papillomavirus testing prompts searching for more accurate cervical cancer screening strategies. Our goal was to evaluate an ELISA-based test for p16INK4a. Methods: 1,781 women undergoing routine screening provided cervical specimens for p16INK4a ELISA (original and enhanced versions of a prototype), liquid-based cytology, and Hybrid Capture II (hc2) testing. All women with a positive result and a random sample of those with negative results on all tests were referred for histologic diagnosis. Cervical intraepithelial neoplasia grade ≥3 (≥CIN3) was the main outcome. The original analysis included all ≥CIN3 outcomes (n = 28). The a posteriori analysis was used to represent clinically relevant results with ≥CIN3 as outcomes only when detected after a positive screening test (n = 27). Results: Participants had a median age of 23 years. The prevalence of high-risk human papillomavirus DNA was 30.6%. In a posteriori analyses, the sensitivity and specificity for p16INK4a ELISA (≥8 pg/mL cut-point), cytology, and hc2 were 50.9%, 58.1%, and 100.0%, respectively, and 90.4%, 89.3%, and 69.2%, respectively. Referral to colposcopy of women with positive results for hc2 and p p16INK4a (enhanced ELISA, ≥6 pg/mL cutpoint) had a sensitivity of 91.8% (95% confidence interval, 79.1-100.0%) and specificity of 86.0% (95% confidence interval, 82.0-89.0%). Results of the original analyses had similar specificity but substantially lower sensitivity due to the strong influence of the single CIN3 case with completely negative screening results. Conclusions: An enhanced version of this prototypic p16INK4a ELISA showed promise in screening, particularly when combined with hc2.

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DOI: 10.1158/1055-9965.EPI-09-0328


**ABSTRACT:** Background. The Abbott RealTime High Risk HPV test (RealTime) is a novel assay designed to detect 14 high-risk human papillomavirus genotypes (hr-HPV) and concurrently distinguish HPV-16 and HPV-18 from other hr-HPV within a single test. OBJECTIVE: To evaluate analytical specificity and clinical sensitivity for cervical carcinoma and cervical intraepithelial neoplasia grade 3 (CIN3) of the RealTime test in comparison with the Digene Hybrid Capture II Test (hc2). Materials and methods: Analytical specificity of the RealTime assay was evaluated on 37 samples with previously determined hc2 false-positive results due to cross-reactivity of the hc2 high-risk probe cocktail with untargeted low-risk HPV genotypes. All 37 samples were negative for 14 hr-HPV using the RealTime test. Clinical sensitivity of RealTime was evaluated in comparison to hc2 on 95 and 267 archived routine
cervical specimens collected from women with histologically confirmed cervical carcinoma and CIN3 lesions, respectively. Archived specimens were selected for the present study after linkage with the Slovenian national registry of CIN3 and cervical cancer to obtain histology data. Results: Concordant results between RealTime and hc2 were obtained in 90/95 cervical cancer samples (94.7% agreement) and in 250/267 CIN3 samples (93.6% agreement). Clinical sensitivity of RealTime and hc2 for cervical cancer in the total study cohort was 88.4% (95% confidence interval (CI): 80.3-93.6%) and 873% (95% CI: 79.0-92.8%), respectively, and analytical sensitivity for samples containing at least one targeted hr-HPV was 98.8% (95% CI: 93.0-100.0%) and 95.3% (95% CI: 88.2-98.5%), respectively. Clinical sensitivity of RealTime and hc2 for CIN3 lesions of the total study cohort was 91.8% (95% CI: 87.8-94.5%) and 89.1% (95% CI: 84.8-92.3%), respectively, and analytical sensitivity for samples containing at least one targeted hr-HPV was 96.4% (95% CI: 93.3-98.2%) and 92.5% (95% CI: 88.5-95.2%), respectively. Conclusion: The RealTime test showed excellent analytical specificity and no cross-reactivity with low risk HPV genotypes that tested positive with hc2. Clinical sensitivity of the RealTime assay using archived routine cervical specimens was comparable to hc2. The RealTime test is an important new method applicable to cervical carcinoma screening and management of cervical precancerous lesions.


ABSTRACT: Objective: To compare a recently developed fluorescence in situ hybridization (FISH) high-risk human papillomavirus (HR-HPV) assay to Hybrid Capture 2 (HC2) (Digene Corporation, Gaithersburg, Maryland, U.S.A.) and polymerase chain reaction (PCR) for the detection of HR-HPV subtypes in cervical cytology specimens. STUDY DESIGN: One hundred forty-one liquid-based cytology specimens were used to produce a thin-layer slide for FISH analysis. The remaining material was sent for HC2 and PCR HR-HPV testing. Thin-layer slides were hybridized with a FISH probe set containing a biotin-labeled HR-HPV cocktail and were manually screened for HR-HPV-infected cells. Specimens with ≥ 1 HPV-positive cell by FISH were considered positive for HR-HPV infection. RESULTS: There was complete concordance between HC2, FISH and PCR in 104 (75%) specimens. FISH was concordant with HC2 and PCR in 120 (85%) and 115 (82%) specimens, respectively. HC2 and PCR were concordant in 118 (84%) specimens. CONCLUSION: The concordance of HR-HPV detection between FISH and HC2/PCR appears similar to concordances between HC2 and PCR. This suggests that FISH may be another method of detecting HR-HPV while having the potential to add additional information such as integrated/episomal staining and the ability to detect chromosomal abnormalities in individual cells. © Science Printers and Publishers, Inc.


ABSTRACT: Background. The APTIMA® HPV Assay (AHPV) is designed to detect HPV E6/E7 mRNA from 14 high-risk types in Cytoc PreservCyt liquid-based cytology specimens.

Objectives: To compare AHPV analytical sensitivity for RNA and DNA; to compare the sensitivity of AHPV and Hybrid Capture® 2 (HC2) assays for HPV DNA detection; to compare assay performance with and without sample denaturation; to compare assay results with cytology. Study design: Analytical sensitivity of AHPV for detecting E6/E7 RNA was assessed by spiking samples with various quantities of HPV 16 E6/E7 in vitro RNA transcript or HPV 16-positive SiHa cells. AHPV and HC2 analytical sensitivity for HPV 16 DNA was evaluated by spiking samples with various quantities of a plasmid vector containing cloned HPV 16 DNA, or with purified SiHa cell genomic DNA containing integrated HPV 16 genome. Samples were tested using standard AHPV and HC2 protocols. Endocervical samples from 568 women were collected in Digene Specimen Transport Medium. Non-denatured and denatured samples were tested in AHPV and denatured samples with HC2. Assay results were compared to each other, and to cytology. Results: AHPV had substantially higher (2-4 log10) analytical sensitivity for HPV 16 RNA than for HPV 16 DNA. AHPV also had substantially lower (3 log10) analytical sensitivity for HPV 16 DNA compared to HC2. The overall agreement between assay results in clinical specimens was 94.2%, but AHPV had fewer positives than HC2 (48.4% positive agreement).

In denatured samples, the number of samples testing positive in AHPV increased two-fold, yielding a positive agreement rate of 88.7%. When assay results were compared with cytology, AHPV had fewer positives in samples with normal or ASC-US diagnoses than did HC2. Conclusions: AHPV is much more efficient at detecting HPV 16 RNA than DNA. Selective capture, amplification, and detection of HPV RNA by AHPV may improve the specificity of molecular HPV testing. © 2009 Elsevier B.V.

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ABSTRACT: Background. Analytical sensitivity of DNA-based assays to detect infection with human papillomaviruses is very high, but clinical specificity for cervical cancer strongly depends on the age of the patient and case classification. To solve the dilemma between sensitivity and specificity, a new generation of assays focuses on the pathogenic factors that underlie the development of HPV-associated tumors: the expression of the viral oncogenes E6 and E7. Demonstration of persistent expression of these mRNAs or expression in the context of relevant clinical symptoms has a strong positive predictive value for the development of HPV-associated carcinomas and strongly warrants further diagnostic action. Objectives: The NucliSENS® EasyQ® HPV v1 test was designed to test cervical scrapes for the expression of the oncogenic E6/E7 mRNA from the five most common carcinogenic HPV types (16, 18, 31, 33 and 45). The test can be used for confirmation and risk stratification of individuals with proven infection with high risk papillomaviruses. Study design: In order to establish performance of the assay, sensitivity, specificity, repeatability, and reproducibility were determined with artificial and clinical specimens. Further, a total of 420 cervical scrapes were tested and the results directly compared to the CE-market device.
PreTect HPV-Proofer assay (NorChip, Klokkarstua, Norway). For arbitration of discordant clinical results, the specimens were rated according to Pap-classification and the presence of HPV DNA was determined. Results: The limit of detection for the five HPV types 16, 18, 31, 33, and 45 ranged from $2.3 \times 10^2$ to $3.0 \times 10^4$ copies/mL on a background of $5 \times 10^3$ HPV-negative HS67 cells. No cross-reactivity for other viral, bacterial, or fungal agents known to be potentially present in cervical fluids was detected. Repeatability and reproducibility were shown by testing panels of HPV-spiked artificial and clinical samples. A comparative analysis of 420 cervical scrapes demonstrated an overall concordance of >90% between the NucliSENS EasyQ HPV test and the technologically related PreTect HPV-Proofer assay. © 2009 Elsevier B.V.

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Comparison of human papillomavirus genotyping using commercial assays based on PCR and reverse hybridization methods. APMIS, 117(10), pp. 708-715.

ABSTRACT: Different tests for human papillomavirus (HPV) screening are commercially available, detecting high-risk oncogenic HPV types with a pool of genotype-specific probes. However, it is necessary to establish reliable methods for the identification of individual genotypes. The purpose of this study was to compare three different commercial methods for HPV genotyping: INNO-LiPA HPV Genotyping v2 (LiPA), Linear Arrays HPV Genotyping Test (LA) and Clinical Arrays Human Papillomavirus (CA). A total of 83 HPV DNA-positive samples by hybrid capture method were genotyped (82, 78 and 81 by LiPA, LA and CA, respectively). Comparison analysis was limited to the HPV genotypes common to the three assays. There were concordant results (absolute agreement between assays) in 31 samples (39.7%) and compatible results (correspondence for some but not all genotypes) were found in 44 samples (56.4%). Only three samples (3.8%) were considered as discordant (did not show any similarity between the tests). Analyzing kappa values we have a very good agreement (>0.8) for HPV16 and HPV31 and good agreement (0.6-0.8) for HPV types 6, 18, 53 and 66 when all methods are compared. We conclude that all genotyping methods tested are highly comparable and suitable for clinical and epidemiological studies. © 2009 The Authors. Journal Compilation © 2009 APMIS.

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ABSTRACT: Purpose: This study was performed to evaluate the compatibility of the Digene media when performing the Roche linear array human papillomavirus (HPV) genotyping test. Methods: A total of 258 samples from 166 women were tested using the Hybrid Capture 2 (HC2) assay, the Cytyc media-based linear array test, and the Digene media-based linear array test. Results: The results between the HC2 assay and the Digene media-based linear array test were highly concordant (kappa = 0.78). The Cytyc media-based linear array test and Digene media-based linear array test exhibited substantial agreement in 207/249 cervical
The two genotyping tests showed substantial agreement for the detection of HPV genotypes 16, 18, 52, 58 and for 18 HPV genotypes including both high-risk, and possible high-risk genotypes (kappa = 0.74, 0.69, respectively). Conclusions: We found Digene media to be interchangeable with Cytyc media when performing the Roche linear array genotyping test. This may be clinically meaningful in that we could perform the Roche linear array genotyping test with the same Digene media among women, positive for HC2 assay without the need for a return visit. © 2009 Springer-Verlag.

7.3 NOVEL TECHNOLOGY


**ABSTRACT:** We describe a novel array for accurate and reliable genotyping of human papillomavirus (HPV) using peptide nucleic acid (PNA) probes. In order to exploit the superior hybridization properties of PNA with target HPV DNAs, we developed a novel PNA array (PANArray HPV). PANArray HPV enables the detection and genotyping of HPVs using 32 type-specific PNA capture probes for medically important HPVs. All tested HPV types showed highly unique hybridization patterns with type-specific PNA probes. PNA array results showed stable specificities and sensitivities after up to 13 months of storage at room temperature. Also, we demonstrated the superior specificity, sensitivity, and stability of PNA arrays for HPV genotyping. We compared the genotyping results of the PNA array to sequencing with MY09/11 PCR products derived from 72 clinical samples. The results showed excellent agreement between the PNA array and sequencing, except for samples reflecting multiple infections. The results from the PNA array were compared with those of type-specific PCR when discrepant results occurred owing to multiple infections. The results for the PNA array matched those of type-specific PCR in all cases. Newly developed PNA arrays show excellent specificity and sensitivity and long shelf life. Our results suggest that the PNA array represents a reliable alternative to conventional DNA arrays for HPV genotyping, as well as for diagnostics. Copyright © 2009, American Society for Microbiology. DOI: 10.1128/JCM.01398-08


**ABSTRACT:** Human papillomavirus (HPV) plays a key role in the development of cervical and laryngeal cancers. The aim of our study was to compare the performance of a new hydrogel-based HPV genotyping biochip assay (Biochip) to a commercially available and CE-marked conventional PCR followed by reverse hybridization (GenID-PCR). One hundred twenty-three samples were available for the study. Of these samples, 101/123 were gynecological swabs, 8/123 were swabs or biopsy samples of genital warts, 7/123 were biopsy samples of oropharyngeal lesions, 5/123 were samples of skin warts, and 2/123 were samples of orolabial abnormalities. These molecular methods for HPV genotyping showed comparable
sensitivity and specificity. However, 19/123 of the results were discrepant. Specifically, Biochip showed better performance in the detection of multiple infections, especially when more than one high-risk genotype was present. Due to the different probe configurations used in the two assays, GenID-PCR achieves only group-specific detection of many HPV genotypes, whereas Biochip allows for specific identification. Overall, the newly developed HPV chip system (Biochip) proved to be a suitable tool for HPV detection and genotyping; it also proved to be superior for establishing HPV genotyping methods. Copyright © 2009, American Society for Microbiology.


**ABSTRACT:** Background. Human papillomavirus (HPV) infection is a necessary event in the development of cervical carcinoma. High risk (HR) HPV genotypes, however, may progress differentially from low grade lesions to malignancy. Objectives: The necessity to genotype and quantify HPV-DNA in cervical screening programs, in the follow up post-surgical treatments and in monitoring the effectiveness of HPV vaccination programs, requires access to economical, high-throughput and flexible molecular technologies. Study design: A high-throughput two-step LNA real time PCR assay was developed consisting of real time PCR reactions with fluorescent Locked Nucleic Acid (LNA) probes. The first step permits classification into three prognostic-risk groups of nine HR HPV genotypes (16, 18, 31, 33, 35, 45, 52, 56 and 58) most frequently found associated with cervical lesions in Europe. The second step allows us to genotype/quantify the HPV-DNA only when clinical, epidemiological or prophylactic aims exist. Results: The specificity, repeatability, detection and quantitation limit, and linearity of the assay were evaluated and appear to be in agreement with guidelines for the validation of analytical procedures. The overall genotype concordance on cervical samples between our assay and INNOLiPA test was 94% (k 0.83) indicating good agreement. Conclusions: The two-step PCR assay can give much information relative to the predictive value of different HR HPV types and can quantify the genotype-specific viral load. In particular, its ability to detect and quantify nine HR HPV genotypes can help provide more efficient and successful patient care and may be useful for the monitoring of the efficacy of HPV vaccines. © 2009 Elsevier B.V.

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**ABSTRACT:** Background. High-risk HPV DNA detection has become a valuable tool for the triage of borderline, questionable and abnormal cytologic findings in cervical carcinoma screening programs. This knowledge is largely based on studies which could only discriminate between low-risk (LR-) and high-risk (HR-) HPV groups. However, it is becoming increasingly clear that HPV genotyping may allow further risk stratification and may offer
7.3 Novel Technology

different treatment options in the future. Objectives: To establish a fast and cost-effective system not only for genotyping but also for quantification of viral DNA. Study design: Development and validation of a 5′ exonuclease fluorescent probe multiplex real-time PCR assay (TaqMan format) for the detection and quantification of the 7 most frequent HR-HPV types (16, 18, 31, 33, 45, 52 and 58) which account for over 87% of cervical carcinomas world-wide. Two PCR reactions are required to detect the designated HPV types. Results: Experiments with plasmid constructs of all 18 HR-HPV DNA showed that the multiplex real-time PCR assay was highly sensitive and specific. Evaluation of DNA extracted from archived cell pellets of cervical scrapes by the multiplex assay and the GP5+/6+-EIA showed identical genotyping for 234 of 261 (89.6%) samples and an almost perfect agreement when considering all typing results (kappa 0.901). Viral load did not correlate with disease progression within the CIN spectrum but significant differences were evident when comparing all CIN with the group lacking CIN (p = 0.0028) or with the cancer group (p = 0.0001). Conclusion: Our multiplex assay will be useful to address questions related to viral persistence at the genotype level, the kinetics of viral load and disease recurrence. © 2009 Elsevier B.V.
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Dramatic increase in signal by integration of polymerase chain reaction and hybridization on surface of DNA microarray. Analytical Biochemistry, 396(1), pp. 139-145.

ABSTRACT: The cumbersome process required for diagnosis by DNA microarray can be simplified by simple extraction of nucleic acid from cells and by integration of liquid-phase polymerase chain reaction (PCR) and hybridization on the surface of a microarray slide. An unexpected benefit was the large (five- to sixfold) increase in detection signal that also is translated into an increase in sensitivity and the confidence level of diagnosis. The large increase in the detection signal appears to be due to participation of PCR primers as well as to extension of the immobilized capture probes during the hybridization process. The reason for the large increase in signal is not clear in view of only one round of DNA synthesis during the hybridization step. The integrated process correctly identified various genotypes of human papillomavirus (HPV) in the infected clinical human cervical specimens with specificity and efficiency. The process described in this article saves labor, time, and cost and should be applicable for automation of diagnosis by DNA microarray. © 2009 Elsevier Inc.
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ABSTRACT: In this article, we report the design and development of a plastic modular chip suitable for one-shot human papillomavirus (HPV) diagnostics, namely detection of the viral presence and relative genotyping, by two sequential steps performed directly on the same device. The device is composed of two modular and disposable plastic units that can be assembled or used separately. The first module is represented by a polydimethylsiloxane
(PDMS) microreactor that is exploited for real-time polymerase chain reaction (PCR) and, thus, is suitable for detecting the presence of virus. The second unit is a PDMS microwell array that allows virus genotyping by a colorimetric assay, based on DNA hybridization technology developed on plastic, requiring simple inspection by the naked eye. The two modules can be easily coupled to reusable hardware, enabling the heating/cooling processes and the real-time detection of HPV. By coupling real-time assay and colorimetric genotyping on the same chip, the assembled device may provide a low-cost tool for HPV diagnostics, thereby favoring the prediction of cancer risk in patients. © 2009 Elsevier Inc.

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**ABSTRACT:** Oncogenic human papillomavirus (HPV) is the most important risk factor for cancer of the uterine cervix and a subgroup of head and neck cancers. Viral load has been associated with persistence of infection, whereas integration of HPV into the host cell genome is associated with transition to invasive disease. Viral integration is frequently correlated with loss of viral E2 and gain of the telomerase-related genes TERC and TERT. The objective of this study was to develop a rapid and sensitive multiplex ligation-dependent probe amplification (MLPA) assay for the simultaneous analysis of viral load, integration and copy number gain of TERC and TERT in HPV16/18-associated lesions. The performance of the assay was tested for HPV vs. human gene copy number ratios ranging from 0.1 to 100 and for percentages of integration ranging from 0 to 100%. The model systems used include plasmid mixtures and the HPV-positive cell lines SiHa, HeLa and CaSki described to contain a range of 2-600 viral copies per cell. In samples with low-viral load, viral integration can be reliably determined when more than 30% of the virus is integrated. Gain of the telomerase-related genes in the cell lines as determined by our MLPA assay was in accordance with data reported in the literature. Our study demonstrates that within a single MLPA-reaction viral type, load, integration and gain of TERC and TERT can be reliably determined, which will improve risk assessment for patients suspected for HPV infection. © 2009 UICC.

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