NIH Public Access
Author Manuscript
Cancer Res. Author manuscript; available in PMC 2013 December 01.

Published in final edited form as:
Cancer Res. 2012 December 1; 72(23): 6183–6190. doi:10.1158/0008-5472.CAN-12-2635.

Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women

Anne F. Rositch[1], **Anne E. Burke**[2,3], **Raphael P. Viscidi**[4], **Michelle I. Silver**[1], **Kathryn Chang**[1], and **Patti E. Gravitt**[1,5,6]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[2]Department of Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD, USA

[3]Department of Population, Family, and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[4]Department of Pediatrics and Neurovirology, Johns Hopkins School of Medicine, Baltimore, MD, USA

[5]Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[6]Perdana University Graduate School of Medicine, Serdang, MY

Abstract

Understanding the fraction of newly detected human papillomavirus (HPV) infections due to acquisition and reactivation has important implications on screening strategies and prevention of HPV-associated neoplasia. Information on sexual activity and cervical samples for HPV DNA detection using Roche Linear Array were collected semi-annually for two years from 700 women age 35–60 years. Incidence and potential fraction of HPV infections associated with new and lifetime sexual partnerships were estimated using Poisson models. Cox frailty models were used to estimate hazard ratios (HR) for potential risk factors of incident HPV detection. Recent and lifetime numbers of sexual partners were both strongly associated with incident HPV detection. However, only 13% of incident detections were attributed to new sexual partners whereas 72% were attributed to ≥5 lifetime sexual partners. Furthermore, 155 out of 183 (85%) incident HPV detections occurred during periods of sexual abstinence or monogamy, and were strongly associated with cumulative lifetime sexual exposure (HR: 4.1, 95% CI: 2.0, 8.4). This association increased with increasing age. These data challenge the 20 paradigm that incident HPV detection is driven by current sexual behavior and new viral acquisition in older women. Our observation that most incident HPV infection was attributable to past, not current, sexual behavior at older ages supports a natural history model of viral latency and reactivation. As the highly exposed baby-boomer generation of women with sexual debut after the sexual revolution transition to menopause, the implications of HPV reactivation at older ages on cervical cancer risk and screening recommendations should be carefully evaluated.

Corresponding author: Anne F. Rositch, PhD, MSPH 615 N. Wolfe St., Room E6133, Baltimore, MD, 21205 Telephone: 410-614-0461; Fax: 410-614-2632; arositch@jhsph.edu.

Potential conflicts of interest: A.F. Rositch has received funding from GlaxoSmithKline within the last five years. P.E. Gravitt is a member of the Women's Health Scientific Advisory Board for Qiagen. The remaining authors have no conflicts to declare.

$watermark-text
$watermark-text
$watermark-text

Keywords

human papillomavirus; HPV; sexual behavior; older women; reactivation; incidence; acquisition; perimenopause; aging

INTRODUCTION

In natural history studies, most HPV infections in immunocompetent women are transiently detected, with loss of detection considered to represent viral eradication (1–3). However, like other human viral infections that can persist in a nonproductive phase, it is likely that at least a fraction of HPV infections are not truly cleared but rather enter a latent phase in undifferentiated basal cells of the cervical epithelium (4). Studies have consistently shown an increase in HPV detection among HIV infected women as compared to HIV negative women (5–8) and it is unlikely that the rapid and sharp increase in HPV prevalence after seroconversion in South African women (5) or the five times higher odds of multiple new HPV infections in acutely HIV infected Zimbabwean women (8) can be fully explained by sexual acquisition. A potentially more common but less pronounced form of HPV reactivation likely occurs in all women as they undergo age-related hormonal and immunological changes. For example, approximately 8% of women with carcinogenic HPV had recurrent detection after a negative test, which was associated with older age (9). Therefore, using data from a cohort of middle-aged perimenopausal women, we aimed to estimate the incidence and potential fraction of HPV infections that are associated with recent new sexual partnerships and to determine factors associated with infections not linked to new sexual partners. Understanding the sources of newly detected infection in older women has important implications on HPV screening and vaccination strategies and how the research community conceptualizes the natural history of HPV in aging women.

METHODS

Study population and data collection

Women attending outpatient OB/GYN clinics for routine examination in Baltimore, MD from March 2008 to March 2011 were recruited to participate in an ongoing prospective cohort study on the natural history of HPV infection through the perimenopausal transition (the HIP study). Women were eligible to participate if they were aged 35–60 years, had an intact cervix, and were willing and able to provide informed consent. Women were not eligible for enrollment if they were pregnant, had plans to become pregnant within the next two years, had a history of organ transplantation or were known to be HIV-positive. At baseline and at 6 month follow-up visits, questionnaires were administered either via telephone (baseline) or in face-to-face (follow-up) interviews and extensive information on women's sociodemographic characteristics and lifetime and recent sexual behavior (previous 6 months) was collected. All study procedures were approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

HPV DNA detection

At baseline and every 6 months for up to two years, a trained physician or nurse conducted a speculum exam to collect a cervical exfoliated cell sample for HPV DNA testing using a well-characterized conical sampling device (Digene HPV sampler, Digene, USA), which likely samples both the endo- and ecto-cervix. Pap smear data was obtained through medical records; however, if a cytology sample was clinically indicated at the time of sample collection, it was taken before the cervical brush sample. Detection and genotyping of HPV DNA from cervical specimens was performed at Johns Hopkins University in Baltimore,

$watermark-text $watermark-text $watermark-text

$watermark-text

$watermark-text

$watermark-text

MD. DNA was extracted using the QIAamp DNA Blood Kit (Qiagen, France) according to manufacturer's instructions with modification (10). An 8μl aliquot of extracted DNA was tested using the Roche HPV Linear Array polymerase chain reaction (PCR) based assay (Roche Diagnostics, USA). Detection of the presence of human DNA by beta-globin-specific PCR is a component of the LA assay and samples that were beta-globin negative were considered inadequate and were excluded. The HPV Linear Array is based on the PGMY09/11 PCR primer system that allows for high efficiency amplification of 37 distinct HPV genotypes (11, 12). For this analysis, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were classified as high-risk (carcinogenic) HPV types.

Statistical analysis

The baseline characteristics of the study population are summarized and stratified by women's sexual behavior over the course of the study: no sex reported at any time during the study, sex during the study but never with a new partner, and sex with a new partner reported at least once from the 6months prior to baseline through the end of study follow-up.

The main exposure variables of interest were evaluated as markers of two potential sources of newly detected HPV infections: recent acquisition and reactivation of latent infection. First, we assumed that true acquisition would be most strongly associated with new exposure opportunities, which we modeled using self-report of new sexual partners at 6-month intervals. At each study visit, women reported their recent sexual activity as having had no vaginal sexual intercourse with a man, having had vaginal sexual intercourse but not with a new male partner, or having had vaginal sexual intercourse with at least one new male partner in the last 6 months (baseline report) and since their last study visit (follow-up reports). Next, we assumed that reactivation risk would be strongly associated with cumulative lifetime HPV infection, which we modeled using self-report of lifetime number of sexual partners at baseline. Lifetime number of male vaginal sexual partners was collected as a categorical variable of 0, 1, 2, 3, 4, 5, 6–10, 11–20, or >20 lifetime partners. Based on the distribution of incident infections, we dichotomized lifetime number of sexual partners at 5 since women with 1 to 4 partners all had a similar risk to each other (<5 partners) whereas the risk among women with ≥5 partners was similar to each other but higher than those with <5 partners.

We modeled lifetime number of partners as a time-invariant binary variable because the risk of incident infections was similar among women with <5 partners and similar among women with ≥5 partners.

Time to first detection of a new HPV type was defined as the time from entry into the study until detection of an HPV type that had not been detected at any prior study visit. Women who did not acquire a type-specific HPV infection were censored at their last study visit; not all women had completed study follow-up at the time of analysis (median follow-up: 16.7 months, interquartile range: 11.5–23.9). If an HPV DNA test result was missing in between two non-missing results (n=39 at 6 months, n=45 at 12 months, n=22 at 18 months), the prior non-missing HPV DNA result was carried forward. Analyses were also conducted carrying the next non-missing value backwards and the results were not affected by the imputation method (e.g. <10% change in hazard ratio estimates). All results were based on women being at risk for all HPV types that were not present at baseline, with each women being at risk for a maximum of 37 HPV types. However, to compare our rates of incident HPV detection with other studies, we calculated women-level incidence rates in addition to infection-level incidence used in the main analysis. Here, incidence represents the detection of at least one new HPV type during study follow-up and time is accrued from baseline until the first new HPV type is detected, at which time the women is censored.

$watermark-text

$watermark-text

$watermark-text

To summarize the absolute number of HPV infections that were newly detected and the person-time each woman was at risk for all HPV types, incidence rates and incident rate ratios were calculated using Poisson models comparing categories of recent sexual behavior and lifetime sexual partners. Using these unadjusted rate ratios, we calculated the risk of incident detection attributable to each exposure ($AR_{EXPOSURE}$) and the attributable risk in the study population ($AR_{POPULATION}$) (13, 14). To calculate the $AR_{POPULATION}$ for recent sexual activity, which is a time-varying covariate, we assumed that cumulative recent sexual behavior represented the most extreme estimate of the prevalence of recent sexual behavior in the study population. Alternatively, we calculated the average prevalence of each category of recent sexual behavior across individual visits, which better reflects the fact that, on average, 4% of women report a new partner at any single visit, whereas the cumulative prevalence of reporting a new partner at least once in the study was 10%.

In order to estimate the relative risk of new HPV DNA detection by recent and lifetime sexual behavior and investigate other potential risk factors, Cox proportional hazards frailty models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) (15, 16). The frailty model adjusts for the correlations within women that arise from repeated measurements and analysis of 37 distinct HPV types. Since report of a new partner in the previous 6–12 months, but not in the previous 0–6 months, was associated with an increased risk of incident detection, we modeled time-varying recent sexual behavior with a 6-month lag. All potential risk factors that we examined were included in the final multivariate model. In addition, we investigated a potential interaction (*a priori* p-value for significant interaction=0.10) between age and lifetime number of sexual partners on incident detection of HPV because we previously observed evidence of effect measure modification of baseline HPV prevalence and lifetime sexual partners by age [Gravitt *et al.*, under review]. All analyses were conducted in SAS version 9.3 (Cary, NC).

RESULTS

Study population

Of the 885 women in the study cohort, 700 (79%) women were included in this analysis of incident detection of HPV. Three women were excluded because they provided no information on recent and lifetime sexual partners or hadn't had vaginal sex with a man, 3 were excluded because they did not have HPV DNA results at baseline, and 179 women did not have at least one follow-up HPV DNA result. The women without follow-up HPV data did not differ from the full population in age, marital status, or lifetime number of sexual partners. The median age of the study population was 47 years (interquartile range: 42–52). Women in the youngest age category, 35–39 years, were most likely to ever report new sexual partners during the study (17%; Table 1) and women age 55–60 years were most likely to report no sexual activity for the study duration (7%). The majority of women were married at baseline (64%). Divorced or separated women had the highest proportion of new sexual partners (27%) compared to single (16%) and married women (4%). Black women, women with less than a college education and women in the two lowest earning categories were more likely to report new sexual partners as compared to women of other races, with more education or in higher income categories. Recent sexual behavior was correlated with lifetime sexual behavior. A higher proportion of women with 5 or more lifetime sexual partners, previous sexually transmitted infections (STI), or a previous abnormal Pap smear reported new recent sexual partners (14%, 13%, and 13%, respectively).

Contribution of recent and lifetime sexual activity to incident HPV detection

The prevalence of any-HPV at baseline was 19%. Over study follow-up, 186 type-specific incident infections were detected in 122 women, for a women-level incidence rate of 11.7

$watermark-text

$watermark-text

$watermark-text

per 1,000 women-months and an infection-level rate of 0.44 per 1,000 infection-months. The rate of type-specific incident HPV DNA detection was highest in women reporting new sexual partners (1.7 per 1,000 infection-months) compared to women reporting sex but with no new partners (0.4 per 1,000 infection-months) and women reporting no sex in the previous 6 months (0.3 per 1,000 infection-months; Table 2). The relative rate of incident HPV DNA detection among women with ≥5 vs. <5 lifetime partners (incidence rate ratio (IRR) of 5.1 (95% confidence interval (CI): 2.2, 8.1)) was almost identical to the relative rate of incident HPV detection in women who reported new sex partners compared to women reporting no sex in the previous 6 months (IRR: 5.6, 95% CI: 3.6, 8.7). Among the exposed, the fraction of incident HPV attributable to new sexual partners (82%) and for ≥5 lifetime partners (81%) was high. However, since the average (4%) and cumulative prevalence of new partners (10%) was relatively small, only 13–27% of incident infections in the entire study population could be attributed to new sexual partners. On the other hand, having 5 or more lifetime sexual partners was more common (62%), so 72% of incident HPV infections in the study population could be attributed to a higher lifetime number of sexual partners. To understand if male partners were potentially contributing to detection of incident HPV infections, we compared women who reported having sex but not with a new partner to women reporting no sex in the previous 6 months and found little difference in the rate of detection (IRR: 1.3, 95% CI: 0.9, 2.0). When restricting to incident detection of HR-HPV types, all findings were similar (e.g. $AR_{POPULATION}$ for (average) new partners=13% and $AR_{POPULATION}$ for ≥5 lifetime partners=74%).

Risk factors for HPV incident detection

In the total cohort, new sexual partners, five or more lifetime sexual partners, unmarried status, and previous abnormal Pap smear were associated with an increased risk of incident HPV detection (Table 3). In order to better understand the risk factors that were associated with the 155 newly detected HPV infections that could not be attributed to a new sexual partnership, we restricted the remaining analyses to women who never reported having a new sex partner during follow-up (n=629; Table 3). Women with five or more lifetime partners had 4 times the risk of incident HPV detection compared to women with fewer than five lifetime partners (restricted adjusted hazard ratio (aHR): 4.1, 95% CI: 2.0, 8.4), and women who were not married had nearly 5 times the risk of incident HPV detection as compared to married women (restricted aHR: 5.7, 95% CI: 3.1, 10.4). Having no sex vs. sex with no new partners, age, race and ever previous abnormal Pap smear were not significantly associated with incident HPV detection in this analysis.

Interaction between age and lifetime sexual partners on incident detection

The effect of lifetime number of sexual partners on the hazard of incident detection of HPV was different across age categories (p-interaction=0.06), with a stepwise increase in the relative risk of incident HPV detection among women with ≥5 lifetime partners compared to less than 5 partners with increasing age (Table 4). After adjustment for time-varying no sex vs. sex with no new partners and marital status, the relative risk ranged from 1.8 (95% CI: 0.6, 5.3) among 35-39 year old women, 3.0 (95% CI: 1.4, 6.4) among 40–44 year olds, 4.8 (95% CI: 2.3, 10.0) among 45–9 year olds, 7.8 (95% CI: 2.9, 21.0) among 50–54 year olds, and 12.7 (95% CI: 3.2, 50.7) among 55–60 year olds, although data were sparse in the oldest age category.

DISCUSSION

Recent and lifetime sexual partnerships were both strongly associated with incident HPV detection in women age 35–60 years. However, 85% of incident HPV infections occurred in women who reported no new recent sexual partners. Thus, while women appear to remain at

$watermark-text

$watermark-text

$watermark-text

risk for HPV acquisition at all ages given a new sexual exposure, this exposure alone does not appear to account for the majority of new HPV detections. On the other hand, 72% of newly detected HPV infections in the HIP cohort were attributed to having 5 or more lifetime sex partners. The strong association with lifetime sex partners, which increased with age, suggests that reactivation of previously undetectable latent infections is likely a common source of newly detected HPV in this age group.

Similar to previous studies (17, 18), we observed an increased risk of incident HPV detection among women reporting recent new sexual partners, confirming that women remain at risk of acquiring HPV at all ages. Trottier, *et al.*, argued that HPV infections among older and pre-exposed women were mostly due to new sexual partnerships, with an estimated relative risk of 2.5 (17). However, high relative risks do not necessarily translate to a high attributable fraction. In the HIP cohort, we estimated that only 13–27% of incident HPV infections could be attributed to new sexual partners. Although the fraction of incident infections in the population attributed to recent sexual partners in the Brazilian study was not reported, it was presumably quite low since only 19% of all women reported new partners over 7 years of follow-up. We recognize that new exposure opportunities are a function of both the female's and her partner's behavior, the latter of which we did not collect. Based on our analysis of women's report of new partners only, it is possible that we underestimated new exposure opportunities since we could not account for new infections in the male partner. For example, it could be argued that male partners of unmarried women have a higher number of concurrent sexual partnerships compared with the male partners of married women, and thus the higher HPV incidence observed in unmarried women could be due to residual confounding of the unmeasured behavior of the male sexual partners. However, because we saw only a minimal increase in HPV detection among women with non-new partners compared with women who were sexually inactive, it is unlikely that the excess risk from unmeasured male partner behavior fully explains our findings. In fact, the attributable risk for new sexual partners alone may actually be an overestimate because women with new sexual partners would still be at risk for HPV reactivation and re-detection.

In this study, we found that incident detection was greatly increased among women with a higher lifetime number of sexual partners, consistent with previous studies (18, 19). However, Munoz, *et al.*, did not find HPV incidence to increase with increasing lifetime number of partners among Colombian women with no new partners (20). Although it is difficult to discern between truly new sexually acquired HPV infections, intermittently detectable infections with fluctuating viral load, and reactivated infections in epidemiological studies, the risk of recurrent detection of periodic undetectable infection, rather than new infection, would be conditional on previous sexual exposure and infection with HPV (21). Therefore, assuming that an association between HPV incidence and high lifetime sex partner reflects either reactivation or an increase in viral load above detection limits in women with higher cumulative exposure, the ability to observe an increased risk will depend on the reliability of a woman's lifetime number of sexual partners to adequately characterize her past probability of infection. In some populations, male partner behavior may contribute significantly to a women's risk of sexually transmitted infections and HPV (22, 23), such that her own number of partners may not adequately capture her lifetime HPV exposure.

Few studies have been conducted to evaluate disease risk specifically in older women. Rodriguez, *et al.*, estimated the risk of high grade neoplasia following incident HPV detection in the Guanacaste Natural History Study and found similar risks of progression in older and younger women in this cohort(9). While they argue that reactivation of HPV at older ages is not associated with a greater risk of high grade neoplasia, it must be noted that if the risk is the same and the fraction of menopausal women at risk of HPV reactivation

$watermark-text

$watermark-text

$watermark-text

may be 2-fold higher in the current generation of menopausal women [Gravitt *et al.*, under review], the risk of high grade neoplasia may be predicted to double as well. It is possible, in fact, that pre-invasive disease in older women may be underestimated in studies (24, 25) because of anatomic differences in the pre- and postmenopausal cervix. While the decrease in Pap and HPV performance in screening at older ages has long been recognized (26–28), little effort has been extended to understand the performance decrement because of a perceived low-risk of disease at this age.

The HIP cohort is made up of middle-aged women who obtain routine cervical cancer screening. Since these are relatively low-risk, well-screened women, the results from this study may not be generalizable to all women at risk of incident HPV infection. Estimates of the fraction of HPV infections related to lifetime sexual partners are likely conservative and are expected to be higher in more highly exposed cohorts of women [Gravitt, *et al.*, under review]. However, these women likely represent a majority of older women currently receiving HPV testing during routine screening. Women in this study had an average of 3 visits and a median of 17 months of follow-up. Though we observed strong associations between the main variables of interest, power may have been limited for some analyses. We found that sexual behavior reported at the current visit was at most weakly associated with incident detection at that same visit, but sexual behavior at the prior study visit was strongly associated with incident HPV detection, similar to previous studies (29). Based on this observation, we used time-lagged recent sexual behavior in our regression models. The time between report of new partners and HPV detection may account for time to HPV transmission or the time between infection of the basal cells and productive infection at the mucosal surface. Also, we did not examine re-detection of prevalent or incident infections, as these would have likely been underestimated without extended follow-up. Additional follow-up of this cohort is ongoing and will clarify the associations between age, exposure history and re-detection of type-specific HPV infections, which were not the focus of the current analysis.

There is now sufficient evidence for a latent state in the natural history of cervical HPV infection to warrant consideration of the clinical implications of viral reactivation. Because so little newly detected HPV in older women is attributed to new sexual acquisition, our data are consistent with previous recommendations that vaccination of older women will be of little benefit (9). Furthermore, the risk associated with a negative HPV DNA test at older ages (e.g., >45 years) should also be reconsidered in the context of a possible age-dependent increased relative risk of HPV reactivation. Most of our natural history data from menopausal women in the United States derive from cohorts of women with sexual debut before the sexual revolution. The baby-boomer generation of women, with sexual debut after the sexual revolution, are entering the menopausal transition with substantially more lifetime exposure to HPV compared with previous generations, and thus may be more likely to be latently infected and at risk of HPV reactivation. This raises questions as to whether the long term negative predictive value of a single negative HPV test in women over age 45(30, 31) will be applicable to aging cohorts with post-sexual revolution sexual debut. New studies are needed to evaluate the risk of disease following HPV reactivation in these women , and such studies must exercise caution when making inferences solely on detection of preinvasive disease, since the cells most susceptible to transformation following incident HPV detection are localized deep in the endocervical canal of postmenopausal women and may be missed in screening (32, 33). Given the number of women currently transitioning through menopause and at risk of HPV reactivation, it is critical to ensure that potentially outdated paradigms do not cloud our rationale for cervical cancer screening recommendations or appropriate design and analysis of prospective studies in the coming decades.

$watermark-text

$watermark-text

$watermark-text

Acknowledgments

We would like to thank Yolanda Eby, Roslyn Howard, and Aleksandra Ogurtsova for laboratory testing, Lori Hackett for research administration, Emily Seay, Rebecca Redett, and Jean Murphy for study recruitment and follow-up, the clinical providers and support teams at Johns Hopkins Women's Health Center at Green Spring Station, Johns Hopkins Women's Services at the Bayview Medical Offices, and Johns Hopkins Women's Services at White Marsh. Finally, we would like to thank the women who generously volunteered their time as participants in the HIP Cohort for their invaluable contributions and commitment to this study.

Financial support: This work was supported by the US National Cancer Institute R01 CA123467 and the Institutional Research Cancer Epidemiology Fellowship funded by the National Cancer Institute T32 CA0009314.

REFERENCES

1. Rodriguez AC, Burk R, Herrero R, Hildesheim A, Bratti C, Sherman ME, et al. The natural history of human papillomavirus infection and cervical intraepithelial neoplasia among young women in the Guanacaste cohort shortly after initiation of sexual life. Sexually transmitted diseases. 2007; 34:494–502. [PubMed: 17237737]
2. Giuliano AR, Harris R, Sedjo RL, Baldwin S, Roe D, Papenfuss MR, et al. Incidence, prevalence, and clearance of type-specific human papillomavirus infections: The young women's health study. Journal of Infectious Diseases. 2002; 186:462–9. [PubMed: 12195372]
3. Moscicki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. The Journal of pediatrics. 1998; 132:277–84. [PubMed: 9506641]
4. Maglennon GA, McIntosh P, Doorbar J. Persistence of viral DNA in the epithelial basal layer suggests a model for papillomavirus latency following immune regression. Virology. 2011; 414:153–63. [PubMed: 21492895]
5. Wang C, Wright TC, Denny L, Kuhn L. Rapid rise in detection of human papillomavirus (HPV) infection soon after incident HIV infection among South African women. The Journal of infectious diseases. 2011; 203:479–86. [PubMed: 21216869]
6. Theiler RN, Farr SL, Karon JM, Paramsothy P, Viscidi R, Duerr A, et al. High-risk human papillomavirus reactivation in human immunodeficiency virus-infected women: risk factors for cervical viral shedding. Obstetrics and gynecology. 2010; 115:1150–8. [PubMed: 20502284]
7. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. Journal of the National Cancer Institute. 2005; 97:577–86. [PubMed: 15840880]
8. Nowak RG, Gravitt PE, Morrison CS, Gange SJ, Kwok C, Oliver AE, et al. Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe. The Journal of infectious diseases. 2011; 203:1182–91. [PubMed: 21451006]
9. Rodriguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, et al. Low risk of type-specific carcinogenic HPV re-appearance with subsequent cervical intraepithelial neoplasia grade 2/3. International Journal of Cancer. 2012; 131:1874–81.
10. Marks MA, Viscidi RP, Chang K, Silver M, Burke A, Howard R, et al. Differences in the concentration and correlation of cervical immune markers among HPV positive and negative perimenopausal women. Cytokine. 2011; 56:798–803. [PubMed: 22015106]
11. Gravitt PE, Peyton CL, Alessi TQ, Wheeler CM, Coutlee F, Hildesheim A, et al. Improved amplification of genital human papillomaviruses. J Clin Microbiol. 2000; 38:357–61. [PubMed: 10618116]
12. Coutlee F, Gravitt P, Kornegay J, Hankins C, Richardson H, Lapointe N, et al. Use of PGMY primers in L1 consensus PCR improves detection of human papillomavirus DNA in genital samples. J Clin Microbiol. 2002; 40:902–7. [PubMed: 11880413]
13. Walter SD. The estimation and interpretation of attributable risk in health research. Biometrics. 1976; 32:829–49. [PubMed: 1009228]
14. Hanley JA. A heuristic approach to the formulas for population attributable fraction. Journal of epidemiology and community health. 2001; 55:508–14. [PubMed: 11413183]

$watermark-text

$watermark-text

$watermark-text

15. Klein JP. Semiparametric estimation of random effects using the Cox model based on the EM algorithm. Biometrics. 1992; 48:795–806. [PubMed: 1420842]
16. Vaida F, Xu R. Proportional hazards model with random effects. Statistics in medicine. 2000; 19:3309–24. [PubMed: 11122497]
17. Trottier H, Ferreira S, Thomann P, Costa MC, Sobrinho JS, Prado JC, et al. Human papillomavirus infection and reinfection in adult women: the role of sexual activity and natural immunity. Cancer research. 2010; 70:8569–77. [PubMed: 20978200]
18. Gonzalez P, Hildesheim A, Rodriguez AC, Schiffman M, Porras C, Wacholder S, et al. Behavioral/lifestyle and immunologic factors associated with HPV infection among women older than 45 years. Cancer Epidemiology Biomarkers and Prevention. 2010; 19:3044–54.
19. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Thompson PJ, et al. Prevalence, acquisition, and clearance of cervical human papillomavirus infection among women with normal cytology: Hawaii Human Papillomavirus Cohort Study. Cancer research. 2008; 68:8813–24. [PubMed: 18974124]
20. Munoz N, Mendez F, Posso H, Molano M, van den Brule AJ, Ronderos M, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. The Journal of infectious diseases. 2004; 190:2077–87. [PubMed: 15551205]
21. Gravitt PE. The known unknowns of HPV natural history. The Journal of clinical investigation. 2011; 121:4593–9. [PubMed: 22133884]
22. Vaccarella S, Franceschi S, Herrero R, Munoz N, Snijders PJ, Clifford GM, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. Cancer Epidemiology Biomarkers and Prevention. 2006; 15:326–33.
23. Bosch FX, Castellsague X, Munoz N, de Sanjose S, Ghaffari AM, Gonzalez LC, et al. Male sexual behavior and human papillomavirus DNA: key risk factors for cervical cancer in Spain. J Natl Cancer Inst. 1996; 88:1060–7. [PubMed: 8683637]
24. Han MA, Choi KS, Lee HY, Jun JK, Jung KW, Kang S, et al. Performance of papanicolaou testing and detection of cervical carcinoma in situ in participants of organized cervical cancer screening in South Korea. PloS one. 2012; 7:e35469. [PubMed: 22530028]
25. Rebolj M, van Ballegooijen M, Lynge E, Looman C, Essink-Bot ML, Boer R, et al. Incidence of cervical cancer after several negative smear results by age 50: prospective observational study. BMJ. 2009; 338:b1354. [PubMed: 19395420]
26. Rositch AF, Silver MI, Burke A, Viscidi R, Chang K, Duke CMP, et al. The correlation between HPV positivity and abnormal cervical cytology differs by age among perimenopausal women. Journal Lower Genital Tract Diseases. 2012 In press.
27. Castle PE, Fetterman B, Thomas Cox J, Shaber R, Poitras N, Lorey T, et al. The age-specific relationships of abnormal cytology and human papillomavirus DNA results to the risk of cervical precancer and cancer. Obstetrics and gynecology. 2010; 116:76–84. [PubMed: 20567171]
28. Stoler MH, Wright TC Jr, Sharma A, Zhang G, Apple R, Wright TL, et al. The interplay of age stratification and HPV testing on the predictive value of ASC-US cytology. Results from the ATHENA HPV study. American journal of clinical pathology. 2012; 137:295–303. [PubMed: 22261457]
29. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. American journal of epidemiology. 2003; 157:218–26. [PubMed: 12543621]
30. Castle PE, Glass AG, Rush BB, Scott DR, Wentzensen N, Gage JC, et al. Clinical human papillomavirus detection forecasts cervical cancer risk in women over 18 years of follow-up. Journal of clinical oncology. 2012; 30:3044–50. [PubMed: 22851570]
31. Clinical Review of Biologics License Application Supplement STN# 125126/773 – Mid-adult Women Indication for GARDASIL. Food and Drug Administration. 2010
32. Gage JC, Duggan MA, Nation JG, Gao S, Castle PE. Detection of cervical cancer and its precursors by endocervical curettage in 13,115 colposcopically guided biopsy examinations. American journal of obstetrics and gynecology. 2010; 203:481, e1–9. [PubMed: 20800216]

33. Solomon D, Stoler M, Jeronimo J, Khan M, Castle P, Schiffman M. Diagnostic utility of endocervical curettage in women undergoing colposcopy for equivocal or low-grade cytologic abnormalities. Obstetrics and gynecology. 2007; 110:288–95. [PubMed: 17666602]

$watermark-text
$watermark-text
$watermark-text

$watermark-text
$watermark-text
$watermark-text

Table 1

Baseline characteristics according to cumulative sexual behaviors over follow-up: women who report never having sex, having sex but never with a new partner, and ever having sex with a new partner from 6 months prior to baseline through follow-up (N=700)

	No sex (n=27)	Sex with no new partners (n=602)	Sex with new partners (n=71)
	N (%)	N (%)	N (%)
Age in years			
35–39	2 (1.5%)	107 (81.0%)	23 (17.4%)
40–44	7 (4.8%)	127 (87.0%)	12 (8.2%)
45–49	6 (3.5%)	146 (85.8%)	18 (10.6%)
50–54	5 (3.3%)	133 (85.5%)	14 (9.2%)
55–60	7 (7.0%)	89 (89.0%)	4 (4.0%)
Marital status			
Married	6 (1.3%)	426 (94.9%)	17 (3.8%)
Divorced/Separated/Widowed	10 (7.8%)	84 (65.6%)	34 (26.6%)
Single	11 (9.0%)	91 (74.6%)	20 (16.4%)
Race			
White/Caucasian	25 (4.7%)	456 (86.5%)	46 (8.7%)
Black/African-American	2 (1.6%)	100 (80.7%)	22 (17.7%)
Other	0 (0.0%)	46 (93.9%)	3 (6.1%)
Education completed			
High School	3 (2.7%)	97 (86.6%)	12 (10.7%)
Post high school	5 (3.1%)	135 (83.9%)	21 (13.0%)
College	7 (3.4%)	178 (87.3%)	19 (9.3%)
Post graduate	12 (5.4%)	192 (86.1%)	19 (8.5%)
Yearly Income			
<40,000	2 (4.3%)	37 (78.7%)	8 (17.0%)
40–80,000	12 (7.3%)	124 (75.2%)	29 (17.6%)
80–120,000	2 (1.4%)	133 (89.9%)	13 (8.8%)
>120,000	10 (4.5%)	203 (90.1%)	10 (4.5%)
Unknown	1 (0.9%)	105 (89.7%)	11 (9.4%)
Smoking history			
Never	20 (4.1%)	420 (85.7%)	50 (10.2%)
Former	6 (4.3%)	123 (87.7%)	11 (7.9%)
Current smoker	1 (1.4%)	59 (84.3%)	10 (14.3%)
Menopausal status			
Premenopausal	8 (2.8%)	242 (83.5%)	40 (13.8%)
Perimenopausal	8 (3.9%)	186 (89.4%)	14 (6.7%)
Postmenopausal	11 (5.9%)	161 (86.1%)	15 (8.0%)
Lifetime sexual partners			
< 5 partners	14 (5.2%)	243 (90.7%)	11 (4.1%)
≥ 5 partners	13 (3.0%)	359 (83.1%)	60 (13.9%)

$watermark-text

$watermark-text

$watermark-text

	No sex (n=27)	Sex with no new partners (n=602)	Sex with new partners (n=71)
	N (%)	N (%)	N (%)
Ever STI			
No	15 (3.4%)	393 (88.1%)	38 (8.5%)
Yes	12 (4.8%)	205 (82.0%)	33 (13.2%)
Ever abnormal Pap			
No	13 (3.5%)	325 (88.6%)	29 (7.9%)
Yes	13 (4.0%)	270 (83.1%)	42 (12.9%)

Abbreviations: N (number); % (percentage); STI (sexually transmitted infection

Missing data: marital status (1); menopausal status (15); ever abnormal Pap prior to baseline (8); ever STI prior to baseline (4)

$watermark-text $watermark-text $watermark-text

Cancer Res. Author manuscript; available in PMC 2013 December 01.

Table 2

Incident detection of 37 HPV types by recent and lifetime sexual activity

	Incident infections	Person-time[a]	Incidence rate[b]	Rate ratio	Attributable risk$_{EXPOSURE}$	Cumulative Attributable risk$_{POPULATION}$[c]	Average Attributable risk$_{POPULATION}$[c]
Recent sexual behavior[d]							
No recent sexual activity	28	90.3	0.3 (0.2, 0.5)	REF			
Recent activity, no new partners	127	309.2	0.4 (0.4, 0.5)	1.3 (0.9, 2.0)	24.2%	14.9%	16.0%
Recent activity, new partners	28	16.1	1.7 (1.2, 2.5)	5.6 (3.6, 8.7)	82.1%	26.9%	13.0%
Lifetime sexual partners							
<5 Partners	21	166.1	0.1 (0.1, 0.2)	REF			
≥5 Partners	162	249.6	0.7 (0.6, 0.8)	5.1 (3.3, 8.1)	80.5%	71.7%	71.7%

[a] Person-time (units are 1,000 infection-months) is at the infection level since women who acquired one HPV type infection were at risk of acquiring a different incident type infection.

[b] Rate is expressed as the number of incident detections of infections per 1,000 women months

[c] Attributable risk in the population is calculated as the prevalence of exposure in the population*(attributable risk of the exposure). For recent sexual behavior, the exposure prevalence was either cumulative sex behavior (no sex over follow-up, sex but with no new partners or ever a new partner over follow-up) or the average of sexual behavior across individual visits (average prevalence of no sex, sex with no new partners, sex with new partners). Lifetime sexual partners was collected at baseline only.

[d] Recent refers to the 6 month period before each study visit, including baseline. Women can contribute infections and person-time to more than one category since this is a time-varying variable.

$watermark-text

$watermark-text

$watermark-text

Table 3

Recent and lifetime sexual activity and other potential risk factors for incident HPV DNA detection among all women and restricted to women reporting no new sexual partners in the 6 months prior to baseline through study follow-up

	All women Unadjusted HR (95% CI)	All women[a] Adjusted HR (95% CI)	Restricted[b] Adjusted HR (95% CI)
Recent sexual activity[c]			
No sex	REF	REF	REF
No new partners	0.9 (0.5, 1.4)	1.5 (0.9, 2.7)	1.7 (0.9, 3.4)
New partners	3.3 (1.5, 7.4)	2.5 (1.1, 5.7)	N/A
Lifetime number partners			
< 5	REF	REF	REF
≥ 5	4.8 (3.0, 7.9)	3.4 (1.9, 6.2)	4.1 (2.0, 8.4)
Age in years			
< 50	REF	REF	REF
≥ 50	0.7 (0.5, 1.0)	0.8 (0.5, 1.2)	0.7 (0.4, 1.3)
Marital status			
Married	REF	REF	REF
Divorced/Separated/Widowed/Single	4.8 (3.3, 6.9)	4.3 (2.7, 7.0)	5.7 (3.1, 10.4)
Race			
White/Caucasian	REF	REF	REF
Black/African-American	1.1 (0.7, 1.8)	1.4 (0.8, 2.3)	0.7 (0.3, 1.4)
Other	1.0 (0.5, 2.0)	0.9 (0.3, 2.5)	0.7 (0.2, 2.4)
Ever abnormal Pap			
No	REF	REF	REF
Yes	2.1 (1.5, 3.0)	1.6 (1.0, 2.5)	1.6 (0.9, 2.7)

Abbreviations: HR (hazard ratio); CI (confidence interval)

[a] Mutually adjusted for all other variables in the table

[b] Excludes women (n=71) who reported a new sexual partner within the 6 months prior to baseline through the end of study follow-up. Mutually adjusted for all other variables in the table and time-varying no sex vs. sex but no new partners

[c] Recent sexual activity included as a time-varying variable, lagged by one visit

$watermark-text
$watermark-text
$watermark-text

Table 4

Incident detection of HPV associated with lifetime number of sexual partners stratified by age at study baseline among women reporting no new sexual partners in the 6 months prior to baseline through study follow-up[a]

	N women	N infections	Unadjusted HR (95%CI)	Adjusted HR (95% CI)[b]
Age 35–39				
<5 partners	42	3	REF	REF
≥ 5 partners	67	19	2.6 (1.1, 6.2)	1.8 (0.6, 5.3)
Age 40–44				
<5 partners	42	3	REF	REF
≥ 5 partners	92	24	3.5 (1.9, 6.3)	3.0 (1.4, 6.4)
Age 45–49				
<5 partners	65	9	REF	REF
≥ 5 partners	87	30	4.7 (2.7, 8.1)	4.8 (2.3, 10.0)
Age 50–54				
<5 partners	64	2	REF	REF
≥ 5 partners	74	16	6.2 (2.9, 13.4)	7.8 (2.9, 21.0)
Age 55–60				
<5 partners	44	0	REF	REF
≥ 5 partners	52	15	8.3 (2.7, 24.9)	12.7 (3.2, 50.7)

Abbreviations: N (number); HR (hazard ratio); CI (confidence interval)

[a]Excludes women who reported a new sexual partner within the 6 months prior to baseline through the end of study follow-up (N=71)

[b]Adjusted for time-varying no sex and sex with no new partners lagged by one visit and time-invariant marital status