Duration of Anal Human Papillomavirus Infection among Immunocompetent Women: Clues to Anal Cancer Epidemiology and Possible Prevention Strategies

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(See the article by Shvetsov et al. on pages 536–46)

Squamous cell cancer of the anus (SCCA) is a rare malignancy in the general US population; however, the incidence of SCCA has increased significantly in the past decade among both men and women, especially among individuals aged 35–54 years [1]. SCCA, like invasive squamous cell cancer of the cervix, has been etiologically linked to human papillomavirus (HPV) infection; thus, the increased incidence of anal cancer likely reflects the changing epidemiology of HPV infection [2].

Although the increased incidence of SCCA among the growing population of immunosuppressed individuals in the United States accounts for some of the overall increased incidence [3], immunocompetent women with cervical disease [4, 5] and men who have sex with men [6] are also at an elevated risk for SCCA. Although several studies have evaluated anal cancer precursors and HPV infection among HIV-infected cohorts [7, 8], there have been fewer studies evaluating immunocompetent populations. The Hawaii HPV cohort study is one of the largest cohort studies that has evaluated the epidemiology of HPV disease in healthy, immunocompetent women and has provided valuable epidemiological information regarding the incidence, prevalence, and duration of cervical and anal HPV infection among these women. In this issue of Clinical Infectious Diseases, Shvetsov et al. [9] used the Hawaii HPV cohort study to determine the patterns of duration and clearance of anal HPV infection among women. Their findings add important insights into risk factors for persistent anal HPV infection and into the improvement of strategies for SCCA screening.

In previous studies, the investigators of the Hawaii HPV cohort study evaluated the prevalence [10] and incidence [11] of anal HPV infections. In the first study of the cohort, Hernandez et al. [10] found a prevalence of anal HPV infection of 27% among 1363 immunocompetent women. They found that women with cervical infection had a &gt;3-fold increased risk for anal HPV infection and that although the prevalence of concurrent cervical and anal HPV infection decreased with increasing age, the prevalence of anal HPV infection only (without concurrent cervical infection) remained constant among the women. They hypothesized that these findings may be related to initiation of anal sex practices at an older age among women in their cohort or to the fact that anal HPV infection is a more persistent infection in the anus, compared with the cervix. However, they acknowledge that their findings may have been biased because women who agreed to provide anal samples were significantly more likely to have engaged in anal intercourse and were more likely to be older than were women who did not provide specimens.

Goodman et al. [11] found that new HPV infection was a relatively common event and that 70% of a cohort of 431 women had &gt;1 HPV infection during the follow-up period of average duration 1.3 years. They reported that the incidence of new HPV infection was almost 50 cases per 1000 woman-months and that the incidence of high-risk (HR) HPV infections was 19.5 cases per 1000 woman-months, which was comparable to that reported in previous studies that evaluated cervical HR HPV infections. The most common incident anal HR HPV types were HPV-53, HPV-52, and HPV-16. Baseline cer-
vical and anal HR HPV infection significantly increased the risk of an incident anal infection. In addition, they found that younger age, white ethnicity, lower socioeconomic status, greater lifetime number of sexual partners, past estrogen use, and condom use but not anal sex were associated with increased risk of acquiring anal HR HPV infection.

The present study conducted by Shvetsov et al. [9] focuses on the duration and clearance of anal HPV infection among the same cohort of 431 women studied by Goodman et al. [11], who evaluated the incidence of HPV infection. The cohort of healthy women who attended 5 clinics in Oahu, Hawaii, from 1998 through 2003 underwent follow-up visits every 4 months. Shvetsov et al. [9] found that incident HPV infection was relatively common, with 50% of the cohort experiencing ≥1 incident anal HPV infection. In addition, they found that anal HPV infections had relatively short duration; 87% of anal HPV infections cleared within 1 year. They also found that the median duration of anal HR HPV infection was 5 months, which was shorter than the median duration of 8 months for cervical HR HPV infection in the same cohort. In contrast to most studies of cervical HPV infection, their study found that low-risk (LR) HPV infections had higher clearance rates than did HR HPV infections. The authors also conducted a relatively novel analysis by evaluating the effect of multiple HPV genotypes on the clearance of anal HPV. In a previous article about the same cohort, Goodman et al. [12] found that clearance times for cervical HPV were faster among older women and women with multiple HPV genotypes. In contrast, this study found that the rate of clearance of anal HR and LR HPV infections was not significantly increased in the presence of ≥1 other HPV genotype. Also, coinfection with specific HPV genotypes did not appear to have a significant effect on the clearance of HR HPV infection, although Shvetsov et al. may have had only enough power to detect large changes, because of the sample size. Finally, they also reported nonviral factors associated with clearance of anal HPV. They found that age did not significantly affect clearance of HR HPV infection but that long-term tobacco smoking, douching, and the current practice of anal sex reduced clearance rates of anal HPV.

The results of the findings by Shvetsov et al. [9] need to be interpreted in light of several important caveats: (1) the collection of anal specimens was optional for patients, and the 66% of the cohort who did provide anal samples were significantly older and were more likely to have engaged in anal sex, compared with the rest of the Hawaii HPV cohort; (2) the authors defined clearance by a single visit with negative findings after a positive finding (other investigators have recommended a definition that includes 2 visits with negative findings); and (3) the authors assumed that the same genotype detected at consecutive visits represented the same persistent infection, not repeat infection, and thus clearance rates may have been underestimated.

Despite the limitations of the present study, the published findings from multiple studies of anal HPV infection produced from the Hawaii HPV cohort suggest that incident anal HPV infection is relatively common but that anal HPV infection is cleared quickly, with a short duration of infection. This may explain in part why, despite a similar incidence of HR HPV infection at cervical and anal sites, the incidence of anal cancer is much lower than that of cervical cancer. The findings also may explain why the prevalence of anal HPV infection and, consequently, the incidence of anal dysplasia and SCCA are higher among immunocompromised individuals. For example, Palfsky et al. [8] evaluated anal HPV infection and results of anal Papnicolaou (pap) smear tests for 223 HIV-infected women and 57 HIV-uninfected women. Of the HIV-infected women, 76% had anal HPV detected, compared with 42% of HIV-uninfected women. In addition, 26% of the HIV-infected women had abnormal anal pap smear test results, compared with 8% of the HIV-uninfected women. Although there have been no studies directly comparing the HPV clearance rate between HIV-infected and HIV-uninfected women, the results from the Hawaii HPV cohort study suggest that, because anal HPV infection is common among presumed HIV-uninfected women, the higher prevalence of anal HPV infection among HIV-infected women, compared with among HIV-uninfected women, may be because immunocompromised women have slower anal HPV clearance rates.

The present study is significant because the findings highlight the specific importance not only of evaluating the incidence and prevalence of anal HPV infection but also of carefully studying anal HPV clearance. The findings provide evidence that anal HPV clearance might differ from cervical HPV clearance and that factors that decrease anal HPV clearance rates may be important for development of neoplasia and may partially explain the differences in epidemiology between squamous cell cancer of the cervix and SCCA. For example, it is interesting to note that, in this study, the nonviral factors associated with anal HPV clearance (long-term tobacco smoking and anal intercourse) are factors that have been associated with SCCA. In contrast, these factors are different from the factors associated with cervical HPV clearance identified by Goodman et al. [12]. In addition, they are different from the factors that Goodman et al. [11] identified as related to the incidence of anal HPV infection (younger age, lower socioeconomic status, greater lifetime number of sexual partners, past use of hormones, and condom use), which are not as closely linked to SCCA risk factors. Thus, although the present study did not evaluate the correlation between HPV clearance and anal histology, it appears that anal HPV clearance may be an important factor in determining the risk for anal dysplasia.

In the past decade, stronger links be-
tween HPV infection and noncervical squamous cancers, including anal, vaginal, vulvar, and oropharyngeal cancers, have been established as a result of improved techniques for HPV detection. This and the increasing incidences of these cancers (and the coincident US Food and Drug Administration approvals of HPV vaccines) have led to an increased interest in HPV epidemiology and the initiation of screening protocols for HPV-related cancers. Shvetsov et al. [9] have provided important epidemiological information regarding anal HPV infection, and although they provide a reasonable argument against the use of detection of anal HR HPV infection as a screening tool for SCCA in women, several questions remain unanswered. For instance, it will be important to determine whether delayed HPV clearance is associated with development of high-grade anal dysplasia. In addition, evaluation of the effect of cervical HR HPV infection and dysplasia on anal HPV clearance will help to determine the efficacy of screening for anal dysplasia among these women. Finally, SCCA screening programs using anal pap smear tests have been shown to be cost-effective for HIV-infected men who have sex with men [13]. Even if women who are at higher risk for SCCA can be identified, the cost-effectiveness and clinical efficacy of such screening programs will need to be evaluated.

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