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EDITORIAL COMMENTARY

Human Papillomavirus DNA Detection in Older Women—Implications for Cancer Screening and Prevention

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(See the major article by Winer et al on pages 665–75.)

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In this era of declining marriage rates and increasing divorce rates, women are increasingly likely to acquire new sex partners at older ages. In this issue of *The Journal of Infectious Diseases*, Winer et al [1] present an interesting look at the incidence of high-risk human papillomavirus (HR-HPV) type DNA detection in a group of mid-adult women, defined as those aged 25–65 years, exhibiting "high-risk" sexual behaviors. The investigators collected behavioral data, including the lifetime number of male sex partners, age at first intercourse, smoking history, and, specifically, sex with ≥1 male partner within the preceding 6 months. They used these data in an attempt to characterize whether detection of HR-HPV DNA by type-specific polymerase chain reaction represented true incident infection or redetection of a previously acquired infection. This study provides insight into this subgroup of women who generally are well studied but do not constitute a large portion of the participants in trials of cervical cancer screening methods. The findings that the cumulative incidence of HR-HPV DNA detection was relatively high in a cohort of mid-adult women and that nearly one third of cases of incident HR-HPV DNA detection were not attributable to the acquisition of new sex partners raise certain questions that may influence our understanding of the natural history of HR-HPV infections, cervical cancer screening of mid-adult women, and how we use HPV vaccines.

The pattern of detection of HR-HPV DNA and its significance has been investigated in longitudinal cohorts [2] or among mid-adult women [3]. The factors leading to persistent detection of HR-HPV DNA are not clearly understood, and in some cases, HR-HPV redetection cannot always be attributed to the acquisition of a new partner [4, 5]. Attempts to properly elucidate whether type-specific HPV DNA detection represents a new infection or redetection have been hampered by a lack of long-term follow-up data, a lack of detailed behavioral data, biases (usually recall bias) associated with the collection of behavioral data, and the lack of a reliable serological marker of past infection to determine whether detection of a HR-HPV type represented new infection or redetection of previously acquired infection. The women included in the study by Winer et al were separated into 3 groups based on their sexual activity during the preceding 6 months. The investigators noted that nearly two thirds of the incident HR-HPV detection events were attributable to the acquisition of a new partner. However, a significant portion of these women who had newly detected HR-HPV DNA did not report a new partner, reinforcing the concept that episodic detection of HR-HPV may be responsible for this paradox. This is further supported by the increased risk attributed to lifetime number of sex partners prior to the study period (adjusted hazard ratio, 2.56; 95% confidence interval, 1.15–2.83), which remained an independent predictor even in the multivariate analysis. The behavioral data suggest that the majority of these infections are truly incident, but this cannot be determined with certainty.

The significance of episodic detection of HR-HPV will become more relevant as the use of HPV DNA testing increases [6]. The results of the ATHENA trial [7] indicate a high negative predictive value (99.3%) for the presence of cervical intraepithelial neoplasia grade ≥2 (CIN2+), when testing specifically for HPV 16/18, and a relatively high positive predictive value for the presence of precancerous lesions, based on HPV 16/18 genotyping. This led to the recommendation that women with HPV 16/18–positive results undergo colposcopy without by cytologic testing. The study cohort in the ATHENA trial and participants in the National Health and Nutrition Examination Survey (NHANES) [8] had lower overall prevalence proportions of HR-HPV DNA detection (12.6% and 15.2%, respectively). These prevalence values are lower than that in the group studied by Winer et al, which had a cumulative incidence of HR-HPV DNA detection of 25.4%. This could make findings of larger screening trials less generalizable for certain subgroups of the population who may be at higher risk for recent HR-HPV acquisition later

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in life. The risk of subsequent CIN2+ lesions in these instances is less clear, and HPV DNA testing without cytologic analysis may be of reduced usefulness. This leads to the question of how we accurately identify women who engage in such high-risk behaviors and whether screening them for cervical cancer should be done differently.

The study evaluated the incidence of 19 HPV types that are classified as carcinogenic, probably carcinogenic, or possibly carcinogenic. Two of these HR-HPV types are covered by the quadrivalent HPV vaccine (Gardasil) and the bivalent HPV vaccine (Cervarix), and an additional 5 of these HR-HPV types are covered by the 9-valent HPV vaccine (Gardasil 9). The cumulative incidence of HPV 16 or HPV 18 DNA detection was found to be 6.1%, and the other 5 HR-HPV types included in Gardasil 9 (31, 33, 45, 52, and 58) had a cumulative incidence ranging from 0.7% to 3.7%.

The recently published seroprevalence of these same 9 HPV types, as evaluated by an NHANES study from 2005 to 2006 [9], noted that 40% of women aged 14–59 years tested positive for any one of the 9 HPV types. In their report, published in the *Journal*, Liu et al [9] also found that lifetime number of partners significantly influenced the seropositivity to all 9 HPV types. In their study, seroprevalence peaked in the group aged 30–39 years but began to decrease rather precipitously with increasing age. This fact could represent 2 possibilities: (1) natural immunity to HPV infection wanes over time, and (2) cohort effects and differences in behavior and new partner acquisition have influenced the seroprevalence of HR-HPV types [10].

The implication that waning natural immunity later in life could lead to increased HR-HPV DNA detection, whether it be related to true incident infection or redetection due to lack of immune control, is particularly important when considering the high-risk behaviors of the mid-adult women studied by Winer et al and their relatively high incidence of HR-HPV detection. The protection offered by natural immunity appears to be relatively insignificant, and the data regarding the protective effects of naturally acquired immunity are conflicting [11]. This and the increasing evidence of continued HR-HPV DNA detection in mid-adult women [12] may support vaccination of subgroups such as the one included in the current report.

The implementation of cervical cytology screening, HPV DNA detection, and vaccines targeting HR-HPV types represent major advances in public health. We now face the challenge of adapting these to all segments of the population at risk. Indeed, longitudinal cohort studies, in particular those that provide long-term follow-up from near the age of acquisition to mid-adulthood, are necessary to fully understand the impact of changing behaviors on screening and prevention.

Notes

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