Human Papillomavirus in Older Women: New Infection or Reactivation?

Darron R. Brown and Bree Weaver

Human papillomavirus (HPV) can be detected in exfoliated cervical cells or vaginal swab samples from approximately 25%–50% of young, sexually active women, according to cross-sectional studies, and from a higher percentage, according to longitudinal studies. In up to 90% of cases, the infection “clears” within 1 or 2 years, meaning that specific HPV types cannot be detected by polymerase chain reaction (PCR) assays of cervical or vaginal swab samples [1]. “Clearance” implies that the individual is no longer infected and does not need to worry about possible long-term sequelae of the infection. Proving that HPV is absolutely gone is, of course, impossible. An alternative hypothesis is that HPV can exist in a low-level persistent state and can reactivate later in life and cause disease.

Determining that an HPV infection has cleared should not be based on 1 or 2 negative test results, as nearly all studies have done [2–5]. Several studies involving younger women indicate that type-specific HPV can be detected again after a long period of apparent clearance, but it has not been established whether type-specific HPV redetection is due to reactivation of a low-level persistent infection or the result of a new infection [6–9]. The questions of why and how low-level persistence happens are not understood. A small focus of infected cells may simply be inadequately sampled, or the HPV load may drop to only a few copies per cell at the time of HPV integration into the host genome, making detection unlikely. The resulting low viral copy number may be below the lower limit of detection of standard HPV PCR assays, resulting in falsely negative HPV testing results. This small focus of cells could persist under immunologic control until waning control later in life allows lesion expansion and subsequent HPV redetection.

Although our understanding of HPV is incomplete, relatively more is known about early events (at the time of initial infection) and late events (the malignancies associated with oncogenic HPV), compared with the long period between initial infection and the diagnosis of cervical cancer. The prevalence of HPV infection peaks in the early 20s, and after a gradual decline, a second peak in HPV prevalence occurs in the fifth or sixth decades of life in North American, European, and Central/South American women [10]. Cervical cancer, essentially all of which is caused by infection with oncogenic HPV types, also peaks around the fifth or sixth decades of life.

Many studies have demonstrated that persistent oncogenic HPV detection is associated with cervical cancer. “Persistence” in these studies was generally defined as 2–4 semiannually collected cervical swabs positive for the same HPV type, just prior to the diagnosis of the high-grade cervical lesion. The question remains of when this infection initially occurred: is it the same HPV isolate acquired in the woman’s teens or early 20s, or does it involve a new infection acquired later in life (during ages 45–60 years), in the years immediately prior to the diagnosis of cancer?

A study by Gravitt et al in this issue of the Journal was performed to address these and other questions about HPV detection and possible reactivation of a preexisting or “prevalent” HPV infection in older women [11]. This study involved cohort analysis, a method used to identify birth cohorts at increased risk for specific outcomes (such as detection of oncogenic HPV) and risk factors for those outcomes. Cohort effects are variations in the risk of a health outcome according to birth year (or years) that are related to differences in the exposure of the cohort to risk factors for that particular outcome [12]. The authors enrolled a cohort of 843 women aged 35–60 years...
and stratified these women into 2 groups: those with <5 lifetime sex partners (and, thus, at a lower risk of oncogenic HPV acquisition), and those with ≥5 lifetime sex partners (and, thus, at a higher risk of oncogenic HPV infection). The age-specific HPV prevalence was estimated in these 2 groups of women.

The age-specific prevalence of oncogenic HPV declined among women with <5 lifetime sex partners but not among those with ≥5 lifetime sex partners. Additionally, the population attributable risk for oncogenic HPV infection due to ≥5 lifetime sex partners was higher among older women (87.2%), compared with younger woman (28.0%). In contrast, the population attributable risk associated with a new sex partner was 28% among younger women, compared with 7.7% among older women. The authors concluded that there might be an interaction of age and lifetime number of sex partners on oncogenic HPV infection. The authors also concluded that this interaction of age and lifetime number of sex partners on oncogenic HPV infection suggested that older women might be at risk for HPV “reactivation.”

Thus, the older women in the study, who were likely infected with oncogenic HPV during the interval spanning the late 1960s through the 1970s—the period of the US sexual revolution—had a lower overall risk of HPV infection, because they reported a lower overall number of lifetime number of sex partners. However, oncogenic HPV prevalence declined with age only among older women with <5 lifetime sex partners. One can conclude from this study that the risk of oncogenic HPV reactivation may increase after the age of 50 years and that reactivation contributes to a large fraction of HPV detection at older ages, compared with the fraction resulting from new HPV infections.

What is the importance of HPV reactivation? What is the cause of reactivation? Among immunosuppressed individuals, oncogenic HPV present for many years at very low levels may be responsible for the high rate of HPV-related disease. The high rate of disease among these individuals may result from reactivation of low-level persistent HPV as immunity wanes [13]. What about the phenomenon known as immunosenescence, which involves a reduction in many aspects of immune system function and naturally occurs during the aging process? Immunosenescence leading to reactivation of HPV has been hypothesized as an explanation for higher prevalence proportions among older women [14].

In summary, although we now have safe and effective vaccines to prevent infection and disease with the 2 most important oncogenic HPV types (HPV 16 and HPV 18) in younger women, it will be decades before reductions in cervical cancer will be seen. Women >30 years old who are unvaccinated today are at continued risk of cervical cancer for the next 20–30 years. The questions asked by Gravitt et al have great importance from epidemiologic, behavioral, and clinical perspectives. Older women should not be told that detection of HPV always indicates a new infection, but rather that detection of HPV could result from an infection acquired many years ago. Further research is needed to help better understand the natural history of HPV infection in older women and to understand the importance of HPV persistence and reactivation in all women.

**Notes**

**Financial support.** This work was supported by the National Institutes of Health.

**Potential conflicts of interest.** D. R. B. has received honoraria from Merck for lectures related to HPV vaccines. Indiana University and Merck have a confidential agreement that pays the university on the basis of certain landmarks related to intellectual property and development of the HPV vaccine, and D. R. B. receives a portion of these funds as income. All other authors report no conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References