CORRESPONDENCE

RE: Reassurance Against Future Risk of Precancer and Cancer Conferred by a Negative Human Papillomavirus Test

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With the recent approval of a human papillomavirus (HPV) test without a Pap test for cervical cancer screening, there is interest in understanding the effectiveness of HPV testing for detecting cervical precancer and cancer. Gage et al. (1) report that HPV testing alone should be considered for cervical cancer screening by comparing the 3-year risk of CIN3 following an HPV-negative or Pap-negative result. While it must be recognized that Gage et al. used a different HPV test than the one recently approved for primary screening, their study investigated a test that has shown similar sensitivity (2). They report HPV testing alone failing to identify 6.5% of 405 cancers, consistent with studies reporting that 6% to 18% of cervical cancers are HPV-negative (3-6). The Gage data add to that body of evidence, yet these findings are not discussed.

The authors state, “the 3-year risks following an HPV-negative alone result were lower than the five-year risks following a cotest negative result,” yet statistical significance was not achieved (P = .21). It would have been worthwhile to compare HPV testing with cotesting at comparable intervals. According to Figure 1 of Gage et al., the cumulative cancer risk with 3-year HPV testing (0.011%) is 57% higher than 3-year co-testing (0.007%), and the cumulative CIN3+ risk with 3-year HPV testing (0.07%) is 40% higher than 3-year co-testing (0.05%). While no P values were provided, one could extrapolate that there is a statistically significant difference in CIN3+ risk, as the 95% CIs do not overlap up to 5 years. Based upon Figure 1 of Gage et al., cotesting is better than HPV testing at 3- and 5-years for both CIN3+ and cancer.

The authors acknowledge that results are limited by the 0.44% of HPV-negative women whose Pap results were greater than or equal to low-grade squamous intraepithelial lesion (LSIL). This suggests that HPV testing alone may miss precancers and cancers that cotesting would detect. With an HPV-only screen, women with abnormal Pap results and potential underlying disease would be sent away for 3-5 years before being rescreened. The authors also acknowledge that “estimates for HPV-negative-alone results and Pap-negative-alone results likely somewhat overestimate risks of CIN2+ and CIN3+, and slightly underestimate cancer risk.” This is important for clinical practice interpretation, and it was encouraging to see the authors acknowledge these limitations.

Cotesting is effective based upon Gage et al. (1) and previous publications. Cervical cancer screening recommendations changed in 2012, and those recommendations have not been fully adopted, with less than 50% of physicians cotesting (7). Step one in HPV testing implementation should be adopting current guidelines. There is insufficient data to recommend HPV testing alone in place of cotesting, considering that the most appropriate screening interval and the age at which to initiate HPV testing remain unclear. There are also no current guidelines for managing patients with only HPV screening. With abundant data on cotesting, perhaps it’s time to reconsider cotesting intervals and expand cotesting, rather than add another less optimal option that may result in missed opportunities to prevent cervical cancer. In time, additional molecular and genomic markers may better identify personal risk for developing cervical cancer. For now, let us expand and not abandon the proven benefit of cotesting.

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References


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