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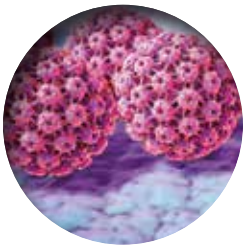
The current state of HPV vaccination, cervical cancer screening guidelines that consider age plus immune status and prior abnormality, and guidance on individualized risk-based management

IN THIS ARTICLE

Infection with high-risk human papillomavirus (hrHPV) is an essential step in the development of cervical cancer and its precursors, as well as in several other cancers, including oropharyngeal, vulvar, vaginal, anal, and penile cancers. At least 13 HPV strains, known collectively as hrHPV, have been associated with cervical cancer, in addition to more than 150 low-risk HPV types that have not been associated with cancer (for example, HPV 6 and 11).[1] Up to 80% of women (and most men, although men are not tested routinely) will become infected with at least one of the high-risk HPV types throughout their lives, although in most cases these infections will be transient and have no clinical impact for the patient. Patients who test positive consecutively over time for hrHPV, and especially those who test positive for one of the most virulent HPV types (HPV 16 or 18), have a higher risk of developing cervical cancer or precancer. In addition, many patients who acquire HPV at a young age may "clear" the infection, which usually means that the virus becomes inactive; however, often, for unknown reasons, the virus can be reactivated in some women later in life.

This knowledge of the natural history of HPV has led to improved approaches to cervical cancer prevention, which relies on a combined strategy that includes vaccinating as many children and young adults as possible against hrHPV, screening and triaging approaches that use HPV-based tests, and applying risk-based evaluation for abnormal screening results. New guidelines and information address the best approaches to each of these aspects of cervical cancer prevention, which we review here.



HPV vaccination: Recommendations and effect on cervical cancer rates

Meites E, Szilagyi PG, Chesson HW, et al. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019;68:698-702.

Lei J, Ploner A, Elfstrom KM, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 2020;383;1340-1348.

The Advisory Committee on Immunization Practices (ACIP) recommends HPV vaccination for both males and

females through age 26.[2] Routine vaccination is recommended at ages 11 and 12, but it may be given as young as age 9. Vaccination for children through age 14 can be given as 2 doses 1 year apart.[3] Starting at age 15, and for those who are immunocompromised, 3 doses at 0, 1 to 2, and 6 months are recommended. Catch-up vaccination is recommended through age 26.

Vaccination at ages 27 to 45, although approved by the US Food and Drug Administration, is recommended only in a shared decision-making capacity by ACIP and the American College of Obstetricians and Gynecologists (ACOG) due to the vaccine's minimal effect on cancer prevention in this age group. The ACIP and ACOG do not recommend catch-up vaccination for adults aged 27 to 45 years, but they recognize that some who are not adequately vaccinated might be at risk for new HPV infection and thus may benefit from vaccination.[4]

In contrast, the American Cancer Society (ACS) does not endorse the 2019 ACIP recommendation for shared clinical decision making in 27- to 45-year-olds because of the low effectiveness and low cancer prevention potential of vaccination in this age group, the burden of decision making on patients and clinicians, and the lack of sufficient guidance on selecting individuals who might benefit.[5]

Decline in HPV infections

A study in the United States between 2003 and 2014 showed a 71% decline in vaccine-type HPV infections among girls and women aged 14 to 19 in the post–vaccine available era as compared with the prevaccine era, and a lesser but still reasonable decline among women in the 20- to 24-year-old age group.[6] Overall, vaccine-type HPV infections decreased 89% for vaccinated girls and 34% for unvaccinated girls, demonstrating some herd immunity.[6] Ideally, the vaccine is given before the onset of skin-to-skin genital sexual activity. Many studies have found the vaccine to be safe and that immunogenicity is maintained for at least 9 years.[7-11]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Despite the well-established benefits of HPV vaccination, only 57% of women and 52% of men in the recommended age groups have received all recommended doses.[13] Based on these findings, we need to advocate to our patients to vaccinate all children as early as recommended or possible and to continue catch-up vaccination for those in their 20s, even if they have hrHPV, given the efficacy of the current nonvalent vaccine against at least 7 oncogenic types. It is not at all clear that there is a benefit to vaccinating older women to prevent cancer, and we should currently focus on vaccinating younger people and continue to screen older women as newer research indicates that cervical cancer is increasing among women older than age 65.[14]

Decrease in invasive cervical cancer

Recently, Lei and colleagues published a study in the *New England Journal of Medicine* that reviewed outcomes for more than 1.6 million girls and women vaccinated against HPV in Sweden between 2006 and 2017.[12] Among girls who were vaccinated at younger than 17 years of age, there were only 2 cases of cancer, in contrast to 17 cases among those vaccinated at age 17 to 30 and 538 cases among those not vaccinated.

This is the first study to show definitively the preventive effect of HPV vaccination on the development of invasive cancer and the tremendous advantage of vaccinating at a young age. Nonetheless, the advantage conferred by catch-up vaccination (that is, vaccinating those at ages 17–30) also was significant.

FAST TRACK

The study by Lei and colleagues is the first to show definitively the preventive effect of HPV vaccination on the development of invasive cervical cancer

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Updated guidance on cervical cancer screening for average-risk women

US Preventive Services Task Force; Curry SJ, Frist AH, Owens DK, et al. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;320:674-686.

Fontham ET, Wolf AM, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin. 2020;70:321-346.

FAST TRACK

The USPSTF guidelines focus not only on the best test but also on what is feasible and likely to benefit public health

As more is understood about the natural history of HPV and its role in the development of cervical cancer and its precursors, refinements and updates have been made to our approaches for screening people at risk. There is much evidence and experience available on recommending Pap testing and HPV cotesting (testing for HPV along with cytology even if the cytology result is normal) among women aged 30 to 65 years, as that has been an option since the 2012 guidelines were published.[15]

We know also that HPV testing is more sensitive for detecting cervical intraepithelial neoplasia grade 3 (CIN 3) or greater at 5 years and that a negative HPV test is more reassuring than a negative Pap test.[16]

Primary HPV tests

HPV tests can be used in conjunction with cytology (that is, cotesting) or as a primary screening that if positive, can reflex either to cytology or to testing for the most oncogenic subtypes. Currently, only 2 FDA-approved primary screening tests are available, the cobas 4800 HPV test system (Roche Diagnostics) and the BD Onclarity HPV assay (Becton, Dickinson and Company).[17] Most laboratories in the United States do not yet have the technology for primary testing, and so instead they offer one of the remaining tests (Hybrid Capture 2 [Qiagen] and Cervista and Aptima [Hologic]), which do not necessarily have the same positive and negative predictive value as the tests specifically approved for primary testing. Thus, many clinicians and patients do not yet have access to primary HPV testing.

In addition, due to slow uptake of the HPV vaccine in many parts of the United States,[13] there is concern that adding HPV testing in nonvaccinated women under age 30 would result in a surge of unnecessary colposcopy procedures for women with transient infections. Thus, several large expert organizations differ in opinion regarding screening among certain populations and by which test.

Screening guidance from national organizations

The US Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS) differ in their recommendations for screening women in their 20s for cervical cancer.[18,19] The USPSTF guidelines, which were published first, focus not only on the best test but also on what is feasible and likely to benefit public health, given our current testing capacity and vaccine coverage. The USPSTF recommends starting screening at age 21 with cytology and, if all results are normal, continuing every 3 years until age 30, at

WHAT THIS EVIDENCE MEANS FOR PRACTICE

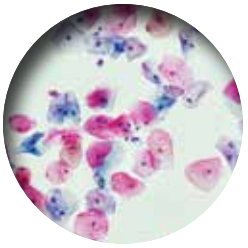
Notably, the newest guidelines for cervical cancer screening essentially limit "screening" to low-risk women who are immunocompetent and who have never had an abnormal result, specifically high-grade dysplasia (that is, CIN 2 or CIN 3). Guidelines for higher-risk groups, including the immunosuppressed, and surveillance among women with prior abnormal results can be accessed (as can all the US guidelines) at the American Society for Colposcopy and Cervical Pathology (ASCCP) website (http://www.asccp.org/).

which point they recommend cytology every 3 years or cotesting every 5 years or primary HPV testing alone every 5 years (if all results are normal in each case).

In contrast, the ACS published "aspirational" guidelines, with the best evidence-based recommendations, but they acknowledge that due to availability of different testing options, some patients still need to be screened with existing modalities. The ACS recommends the onset of screening at age 25 with either primary HPV testing every 5 years (preferred) or cotesting every 5 years or cytology every 3 years.

Both the USPSTF and ACS guidelines state that if using cytology alone, the screening frequency should be every 3 years, and if using an HPV-based test, the screening interval (if all results are normal) can be extended to every 5 years.

New ASCCP management guidelines focus on individualized risk assessment



Perkins RB, Guido RS, Castle PE, et al; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2020;24:102-131.

The ASCCP risk-based management guidelines introduce a paradigm shift from managing a specific cervical cancer screening result to using a clinical action threshold based on risk estimates that use both current and past test results to determine frequency and urgency of testing, management, and surveillance (**FIGURE**).[20] The individualized risk estimate helps to target prevention for those at highest risk while minimizing overtesting and overtreatment.

Estimating risk and determining management

The new risk-based management consensus guidelines use risk and clinical action thresholds to determine the appropriate management course for cervical screening abnormalities.[20] New data indicate that a patient's risk of developing cervical precancer or cancer can be estimated using current screening results and previous screening test and biopsy results, while considering personal factors such as age and immunosuppression.[20] For each combination of current test results and screening history (including unknown history), the immediate and 5-year risk of CIN 3+ is estimated.

With respect to risk, the following concepts underlie the changes from the 2012 guidelines:

- Negative HPV tests reduce risk.
- Colposcopy performed for low-grade abnormalities, which confirms the absence of CIN 2+, reduces risk.
- A history of HPV-positive results increases risk.
- Prior treatment for CIN 2 or CIN 3 increases risk, and women with this history need to be followed closely for at least 25 years, regardless of age.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Using the ASCCP risk thresholds, most patients with a history of an abnormal result, especially CIN 2+, likely will need more frequent surveillance testing for the foreseeable future. As increasing cohorts are vaccinated and as new biomarkers emerge that can help triage patients into more precise categories, the current risk categories likely will evolve. Hopefully, women at high risk will be appropriately managed, and those at low risk will avoid overtreatment.

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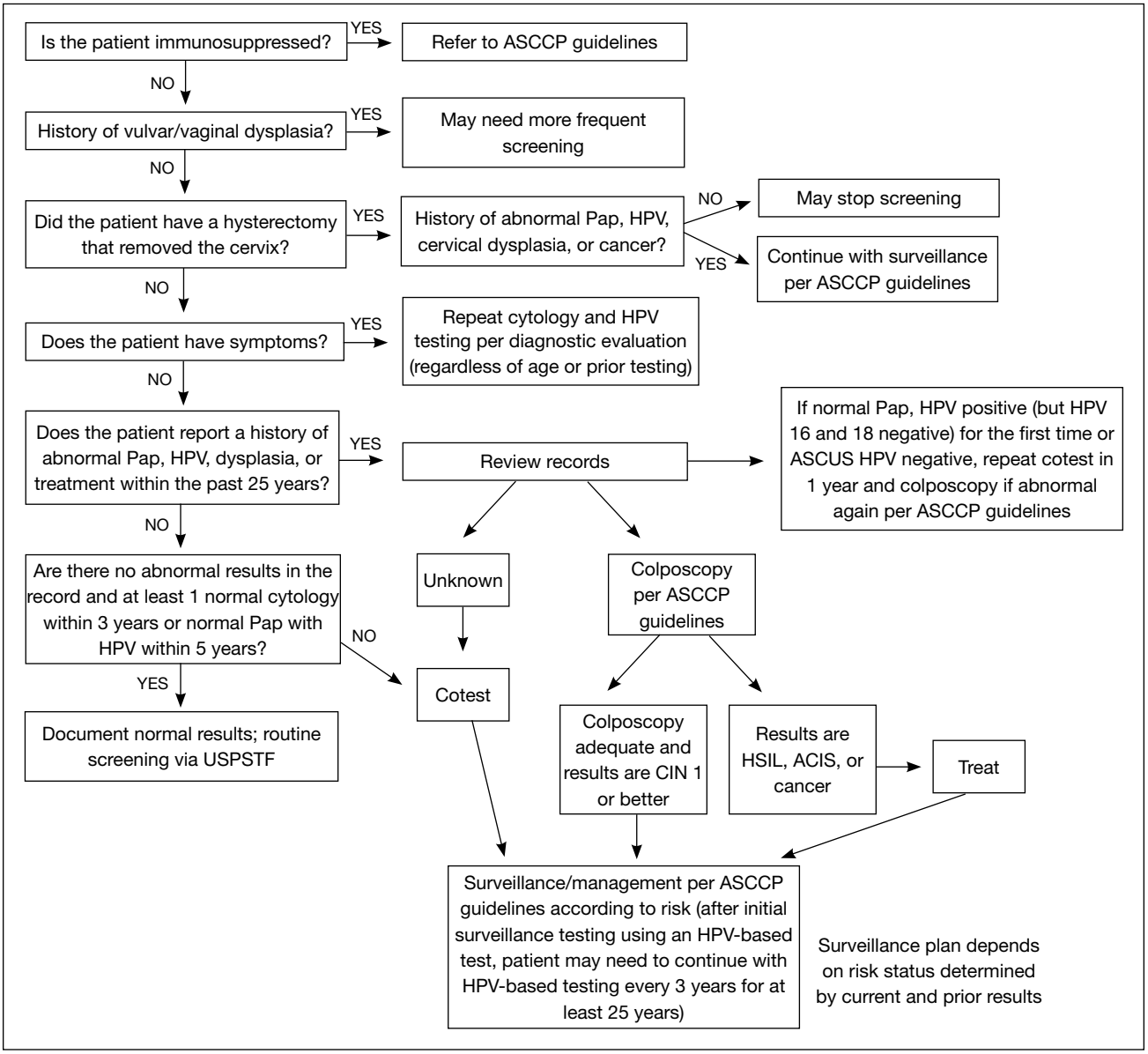
FIGURE Cervical cancer screening and management[20]



Abbreviations: ACIS, adenocarcinoma in situ; ASCCP, American Society for Colposcopy and Cervical Pathology; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; USPSTF, US Preventive Services Task Force.

Once an individual's risk is estimated, it is compared with 1 of the 6 proposed "clinical action thresholds": treatment, optional treatment or colposcopy/biopsy, colposcopy/biopsy, 1-year surveillance, 3-year surveillance, or 5-year return to regular screening (<0.15% 5-year CIN 3+ risk).

Key takeaways

Increasing knowledge of the natural history of HPV has led to improved approaches to prevention, including the nonvalent HPV vaccine, which protects against 7 high-risk and 2 low-risk HPV types; specific screening guidelines that take into consideration age, immune status, and prior abnormality; and risk-based management guidelines that use both current and prior results as well as age to recommend the best approach for managing an abnormal result and providing surveillance after an abnormal result. ●

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