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Screening for Cervical Cancer

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HUMAN PAPILLOMAVIRUS INFECTION CAUSES CERVICAL CANCER: EPIDEMIOLOGY AND BACKGROUND

Each year in the United States, nearly 13,000 women develop cervical cancer and 4000 die from the disease.[1] However, most cases can be prevented with vaccination and screening because it is now understand that oncogenic human papillomavirus (HPV) infections cause nearly all cervical cancers.[2] Approximately 14 evolutionarily related HPV genotypes have oncogenic potential,[3,4] with HPV 16 and 18 alone being responsible for nearly 70% of cervical cancers.[3–5]

HPV is the most common sexually transmitted infection, with nearly half of Americans infected.[6,7] HPV is commonly acquired shortly after sexual debut,[8] with a peak incidence between the ages of 15 and 25 years. An estimated 80% of HPV infections that go on to cause cancer are acquired before age 26.[9] Although most infections regress spontaneously within 1 to 2 years, the longer the infection persists in a detectable state, the higher the risk of cervical precancer or cancer.[10,11] Cervical cancer precursors, or precancer, are described histopathologically as moderate to severe dysplasia, histologic high-grade squamous intraepithelial lesion (HSIL), or cervical intraepithelial neoplasia grades 2 and 3 (CIN2 or CIN3). Typically, precancers are diagnosed approximately 5 to 10 years following the initial oncogenic infection, with peak prevalence between ages 25 and 35.[12] If left untreated, approximately 30% of high-grade precancers eventually become invasive cancers.[11] Cervical cancer rates begin to rise in the mid-30s, peaking at ages 35 to 45 years, and remain high into older ages.[13,14]

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DISCLOSURE

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PRIMARY PREVENTION: HUMAN PAPILLOMAVIRUS VACCINATION

Vaccination of Adolescents Reduces Precancers and Cancers

Because the role of HPV in cervical cancer is understood, there is access to primary prevention (vaccination) and secondary prevention (screening). Extensive evidence supports the effectiveness of HPV vaccination in early adolescence for preventing vaccine-type HPV infections, precancerous lesions, and cervical cancer in young adults. If the currently available vaccines provide lifelong protection, cervical cancer rates could be reduced by 85% for those who receive vaccination before they are exposed to oncogenic HPV.[15] Studies indicate that HPV vaccination leads to reductions in rates of HPV infection and HPV-related diseases at each step along the carcinogenic pathway. First, vaccination before sexual debut reduces vaccine-type oncogenic HPV infections by more than 90% in vaccinated individuals; unvaccinated individuals begin to benefit from herd immunity when vaccination rates exceed 50%.[16–18] As vaccine programs were introduced, epidemiologic analyses demonstrated the near-disappearance of genital warts in vaccinated populations, with strong evidence for protection of nonvaccinated males when female vaccination rates were high.[19] The second piece of population-level evidence is the demonstration of decreasing rates of cervical precancers among vaccinated populations[20–22] and decreased incidence of cervical precancers in vaccinated compared with unvaccinated individuals.[23,24] The final and most important finding is the observed decline in HPV-related cancers. Reduction in HPV-related cancers was first observed in long-term follow-up studies of the original vaccine trial participants, starting an average of 7 years following vaccination.[25] More recently, invasive cancer rates have declined among the 15- to 24-year-old population in the United States from the prevaccine to the postvaccine era.[26]

Vaccination of Young Adults Has Limited Population-Level Benefit

In contrast to vaccination of adolescents, vaccination of young adults has not been associated with reductions in cervical precancer or cancer in most studies because of high rates of HPV infection. Although clinical trials indicated vaccine efficacy through age 26 among women without evidence of previous infection, when women with preexisting infections were included in the analysis, vaccine efficacy decreased with age, with a 50% reduction noted for those initiating vaccination older than age 21.[27] Because most HPV infections are acquired in early young adulthood, vaccine effectiveness at the population level is lower for this age group. Analysis of a large prepaid health plan in California (Kaiser Permanente) demonstrated a 50% reduction in cervical precancer for young women vaccinated before age 18 but no reduction for those vaccinated at ages 18 and older compared with those who were never vaccinated.[28] Similarly, population-level data in Sweden indicated that vaccine effectiveness against precancer decreased with age, declining from 64% for those vaccinated before age 17, to 25% for vaccination at ages 17 to 19, to no benefit for when vaccination occurred at ages 20 to 29.[29]

Vaccination of Adults Aged 27 to 45 Does Not Have Population-Level Benefits

The Advisory Committee on Immunization Practices voted in 2019 to allow HPV vaccination of adults ages 27 to 45. They did not recommend routine vaccination for this population, but instead allowed for shared decision-making with individual patients.[30]

Review of 11 clinical trials of vaccination in midadult women demonstrated near-universal seroconversion, and reductions in combined end points, which included HPV infections, genital warts, and histopathologic changes of low grade (CIN1) or higher.[30] No benefits were noted when restricting analyses to precancer or cancer end points only. HPV vaccines seemed to be safe in midadults, and the committee voted 10 to 4 in favor of shared clinical decision-making. Because of the limited benefits, the guideline states: "Catch-up HPV vaccination is not recommended for all adults aged greater than 26 years. Instead, shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated." Because vaccination did not significantly reduce precancers and cancers in this population, guidelines further emphasize that, regardless of vaccination status, "Cervical cancer screening guidelines and recommendations should be followed."[30] Updated American Cancer Society (ACS) guidelines do not endorse vaccination of adults ages 27 to 45.[31]

SECONDARY PREVENTION: CERVICAL CANCER SCREENING

Evidence Supporting Screening in Adults

Population-level, organized screening programs have reduced cervical cancer rates by 50% to 80%.[32,33] In settings with robust screening programs, most cancers develop among those who are new to care or rarely screened.[34,35] Unequal access to screening is a key reason for the dramatic disparities in cervical cancer incidence and mortality seen between low-resource and high-resource countries,[36] and also between socially advantaged and disadvantaged individuals in the United States.[33] Cervical cancer screening programs function by identifying asymptomatic women with precancerous lesions to allow for diagnosis and treatment before cancer develops. Screening tests must be sensitive, reproducible, and easily performed and managed by primary care clinicians. Cervical cytology (Pap testing) was the mainstay of screening for decades, but HPV testing has taken on an increasingly important role as understanding of the role of HPV infection in cervical cancer development has improved.[37,38]

WHAT TESTS ARE USED FOR SCREENING?

Without question, the best screening test is the one that is performed. Cervical cytology (Pap testing), HPV primary screening, and cotesting using HPV and cytology all reduce cervical cancer incidence and mortality if guidelines are followed. However, there are advantages and disadvantages to the different screening tests.

Cervical Cytology (Pap Testing)

Cervical cytology involves a clinician performing a speculum examination and collecting a sample of cervical cells, which are either smeared onto a slide (conventional cytology) or placed into a liquid medium (liquid-based cytology), and sent to a laboratory for analysis by a cytopathologist. Examination of the cells can reveal normal-appearing cells, low-grade abnormalities, or high-grade abnormalities. Low-grade abnormalities, defined as atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL), generally indicate evidence of HPV infection but are not

immediately suggestive of a precancerous lesion. High-grade abnormalities, defined as HSIL, atypical squamous cells suggestive of high-grade, and atypical glandular cells, are highly correlated with high-grade histologic findings, which require excisional treatment to prevent the development of invasive cancer. Cytology is a specific test; if a high-grade abnormality is found, the likelihood of precancer is high. However, it is not a sensitive test; 30% to 50% of precancers are missed with each screening round.[39,40] Because of the low sensitivity, frequently repeated cytology testing over decades is needed to prevent cancer.[41,42]

Human Papillomavirus Primary Screening

HPV primary screening involves collection of a cervical or vaginal sample to detect the presence of an oncogenic HPV infection. Currently, available HPV tests in the United States involve clinician-collected cervical samples obtained via a speculum examination. However, the ability to detect an oncogenic HPV infection is similar when using a self-collected vaginal swab or a clinician-collected sample, making self-sampling a possible option for the future. A meta-analysis of 56 studies found that HPV assays using polymerase chain reaction technology were as sensitive with self-samples as with clinician-collected samples, although assays based on signal amplification were less sensitive.[43] mRNA assays also seems to be less sensitive when obtained via self-collection compared with clinician collection.[44] Trials are currently underway to define the parameters for broader use of self-collected samples. One advantage to self-sampling is the potential to increase screening participation in populations that currently experience high cancer rates because of lack of screening, specifically those living in low-resource settings either in low-income countries[45] or in low-resource settings within high-income countries.[46]

HPV testing, whether clinician-collected or self-collected, is more sensitive than cytology. A single HPV test detects 90% of precancers and cancers.[47] Thus, the negative predictive value (reassurance) of HPV testing is far better than cytology and allows safe extension of screening intervals.[48,49] Testing using HPV assays at 5-year intervals results in a lower risk of cancer and precancer than cytology testing at 3-year intervals.[49] Sequential negative HPV tests provide extensive protection, yielding a risk for high-grade precancer of fewer than 1 case per 1000 patients screened.[50,51]

Another advantage of HPV testing is superior detection of adenocarcinoma and its precursors compared with cytology.[52] Cytologic specimens often appear normal even when adenocarcinoma and adenocarcinoma in situ (AIS) are present, with the consequence that cytology-based screening programs that effectively reduce rates of squamous cancers do not reduce rates of adenocarcinomas and AIS.[47,53,54] Because HPV testing leads to earlier detection of squamous and glandular precancers (CIN3/AIS), incorporating HPV testing into cervical cancer screening programs reduces cancer incidence within 5 years and mortality within 8 years compared with cytology screening alone.[41,55]

Although randomized trials of Pap and HPV testing consistently demonstrate that HPV testing identifies precancers earlier, the proportion of abnormal results is higher when screening with HPV tests compared with cytology alone: 10% and 6%, respectively.[56] However, recommendations for repeat testing in 1 year rather than immediate colposcopic

referral for HPV-positive tests with normal cytology results lead to similar or only marginally higher rates of referral to colposcopy.[38] Adhering to recommended screening intervals is important when using HPV testing for screening, because repeating the test too soon is more likely to detect transient HPV infections than precancer. This can increase emotional distress and financial burden without decreasing cancer incidence and mortality, so adherence to recommended intervals is important for realizing the benefits of HPV screening.[57] Of note, some HPV tests may be used alone, whereas others may only be used with concurrent cytology (cotesting).

Cotesting

Cotesting involves taking a cervical cytology sample and HPV test during the same examination. Samples are collected by a clinician during a speculum examination. Depending on which tests are used, cytology and HPV tests may be collected separately or both tests may be performed from a single liquid-based cytology sample. Similar to HPV testing alone, cotesting detects greater than 90% of precancers and cancers with a single screen.[47] Serial negative screens confer increasing protection, with one study of 990,013 women finding no cervical cancers and few precancers after two negative cotests.[51] Screening with cotesting slightly increases the sensitivity for detecting high-grade cervical precancers (CIN3 and AIS) and invasive cervical cancers compared with HPV testing alone, detecting approximately five additional cancers per million women screened.[47,58,59] Abnormal cytologic findings with negative HPV tests may also occur in advanced cancers, often caused by an abundance of necrotic tissue in the sample that obscures HPV test results. However, most advanced cancers are detected because of symptoms and are thus not preventable via screening of asymptomatic populations. A disadvantage of screening with cytology in addition to HPV testing is the number of abnormal results without a substantial reduction in the cancer burden. Modeling studies indicate that 640 colposcopies would be performed per cancer prevented when using HPV testing alone, compared with almost 1000 colposcopies per prevented cancer using cotesting.[60] Modeling a population of 100,000 individuals screened over their lifetimes, cotesting would prevent five additional cervical cancers and two deaths compared with HPV testing, but with about 50% more false-positive results and colposcopies.[60]

Screening Test Summary

The goal of a screening test is to accurately separate individuals at high risk of disease from those at low risk of disease, and to minimize false-negative results. By these parameters, HPV testing is clearly superior to cytology testing alone as a screening test for cervical cancer, because it detects far more precancerous lesions per screen. Adding cytology to HPV testing alone (cotesting) slightly increases the number of cases detected, but at the cost of more false-positive results and more invasive procedures (colposcopy with biopsy).

WHO SHOULD BE SCREENED?

Although there some areas of disagreement, most cervical cancer screening guidelines agree on which individuals should and should not be screened for cervical cancer (Table 1).[37,38,61,62]

Individuals Who Should Be Screened

- All individuals with a cervix (women who have not undergone hysterectomy with removal of the cervix and trans-men) ages 25 to 65 regardless of sexual history or sexual orientation.
- Individuals who have undergone hysterectomy with removal of the cervix only if they had a diagnosis of precancer or cancer before hysterectomy.
- Individuals older than age 65 who do not meet exit criteria. To fulfill exit criteria, a patient must have medical record documentation of two consecutive negative HPV tests or cotests or three consecutive negative Pap tests between ages 55 and 65 years, with no abnormal screening within that time, and no history of precancer (CIN2, CIN3, or AIS) within the past 25 years.

Screening applies only to asymptomatic individuals. Cervical cytology (Pap testing) should be performed as part of the work-up of abnormal uterine bleeding even if the patient is not due for a “screening” test.

Individuals Who Should Not Be Screened

- Individuals aged less than 21 years
- Individuals who have undergone hysterectomy for benign indications
- Individuals older than age 65 who fulfilled exit criteria

Age Less Than 21

All guidelines agree that screening should not occur before age 21 (unless the individual is human immunodeficiency virus positive) because the rates of HPV infection and minor cellular abnormalities are high, leading to the potential for overtreatment of lesions never destined to go on to become cancer. HPV infection rates peak shortly after sexual debut.[63] Most HPV infections and low-grade cytologic abnormalities (ASC-US, LSIL) regress within 1 to 2 years in young women[64,65] and even many high-grade lesions regress over time without treatment.[66,67]

Ages 21 to 24

Screening is recommended starting at age 21 in the 2016 American College of Obstetricians and Gynecologists (ACOG) and 2018 US Preventive Services Task Force (USPSTF) guidelines, but it is recommended starting at age 25 in the 2020 ACS guidelines.[62] Between 2012 and 2018, initiating screening at age 21 was believed to represent the best balance of the benefits of screening and harms of overtreatment. However, as HPV vaccination rates rise, the balance is shifting toward initiating screening later. ACS cites three primary reasons for raising the screening initiation age to 25 years. First, individuals who received on-time HPV vaccination are aging into this cohort, leading to a decline in precancers and cancers that is independent of screening.[26,28] Because vaccination has reduced rates of HPV 16/18 infections,[17] most abnormal cytology results represent transient infections with less aggressive oncogenic HPV types, which can lead to invasive diagnostic tests (eg, colposcopy with biopsy) but are unlikely to cause cancer.[28] Second, many high-grade lesions

diagnosed at ages less than 25 are destined to regress without treatment.[67,68] Deferring unnecessary treatment in young women is important because some data indicate that treatment may lead to future pregnancy complications,[69,70] although other studies do not show this association.[71] Finally, initiating treatment at age 25 allows HPV testing at 5-year intervals to be recommended for all individuals, simplifying guidelines for clinicians.

Ages 25 to 65

All guidelines agree that screening is beneficial for this age group because organized screening programs consistently lead to decreases in cancer incidence and mortality.[37,38,61]

Age Greater Than 65

Women older than age 65 represent 20% of cervical cancers and have excess mortality compared with younger women.[14,72] However, studies indicate that many individuals diagnosed with cancer older than age 65 did not fulfill exit criteria as defined previously.[73,74] In addition, the sensitivity of cytology and HPV screening tests seems to decrease in older women,[34] and colposcopy also becomes more difficult because more lesions are found inside the endocervical canal after menopause, which are less amenable to colposcopic detection.[75] Therefore, emphasis is placed on ensuring adequate screening between ages 45 and 65, rather than continuing screening later in life. Note that women with screening test abnormalities must continue to screen until exit criteria are met.[76]

Hysterectomy with Removal of the Cervix

Because individuals without a cervix are at extraordinarily low risk for cervical cancer, screening should be discontinued following hysterectomy with removal of the cervix when performed for benign indications.[77] Following treatment of high-grade cervical precancer, individuals remain at risk of recurrent disease at the vaginal cuff, and should undergo screening for 25 years following their treatment (which may be <25 years after hysterectomy if they were treated with an excisional procedure and then went on to have a hysterectomy for another indication later).[76]

HOW SHOULD INDIVIDUALS BE FOLLOWED AFTER ABNORMAL RESULTS?

Surveillance: Interplay of Management and Screening

A substantial minority of women do not qualify for routine screening intervals. Up to 20% of women report at least one prior abnormal screening result,[78] and a cross-sectional analysis of a population screened with cotesting demonstrated that approximately 10% of women had an abnormal result.[56] Surveillance at shorter intervals is now recommended for a minimum of 10 years (four consecutive negative tests) after most abnormalities, which means that in any given primary care population, 10% to 20% of patients may not qualify for routine screening.[76] The 2019 ASCCP Risk-Based Management Consensus Guidelines[76] recommend follow-up surveillance at 1 year for abnormalities with an immediate risk of precancer (CIN3+) less than 4%, but a 5-year risk greater than 0.55%. Results that fall into the 1-year surveillance category include low-grade results not requiring colposcopy

(eg, normal cytology with a positive HPV test), follow-up after a colposcopy confirming low-grade abnormalities (CIN1), or during the initial period of intensive follow-up after treatment of a high-grade lesion (histologic HSIL or CIN2/CIN3).

Surveillance at 3 years is recommended for individuals whose cumulative 5-year CIN3+ risk falls between 0.015% and 0.054%.[76] Surveillance with HPV testing or cotesting at 3-year intervals is recommended for long-term surveillance following initial resolution of most abnormalities. At this time, even after three consecutive negative follow-up HPV tests or cotests, data indicate that risks remain in the range for which 3-year follow-up is recommended. With currently available data, return to routine screening is currently recommended for only two scenarios:

1. HPV-negative ASC-US followed by a negative HPV test or cotest, and
2. Minimally abnormal screening results (HPV-positive negative for intraepithelial lesion or malignancy [NILM], HPV-positive ASC-US, HPV-positive LSIL), with low-grade disease confirmed at colposcopy (biopsy of CIN1 or normal) followed by three consecutive negative HPV tests or cotests.

PRACTICAL IMPLICATIONS

Because routine screening intervals do not apply to up to 20% of individuals, risk-stratification and long-term tracking of primary care populations is crucial. When annual well-woman examinations were the standard of care, visits could easily be scheduled by office staff, and patients could easily remember when their next visit was due. With more nuanced approaches to cervical cancer screening and surveillance following abnormal results, use of population management strategies within clinical care settings is necessary to ensure that patients receive indicated follow-up. To facilitate tracking and management of cervical cancer screenings, clinical practices should take several steps:

1. Decide as a practice whether USPSTF, ACS, or ACOG screening guidelines will be followed.
2. Determine whether HPV primary screening, cotesting, or cytology-only screening will be performed.
3. Operationalize tracking systems for providers and patients to ensure that tests are performed when needed. This can use personnel, such as a dedicated nurse, to review and triage all cervical cancer screening results, or other methods, such as electronic health record prompts, or a combination of various tools.
4. Ensure that the strategy for population health management includes the goal of measuring and achieving high rates of recommended screening so that progress can be tracked.

Note that the ASCCP Risk-Based Management Consensus guidelines are the only national guidelines directing management of abnormal screening test results.[76] These guidelines give management recommendations for practices using primary HPV testing, cotesting, or cytology for screening. However, because cytology is substantially less sensitive than HPV testing for detecting precancer, cytology is recommended more frequently than HPV testing

in follow-up of abnormal results. Specifically, cytology is recommended every 6 months when HPV testing or cotesting is recommended annually, and cytology is recommended annually when HPV testing or cotesting is recommended every 3 years. The increased frequency of required follow-up visits for 10% to 20% of the population may be an important factor when practices are considering the costs and benefits of different screening strategies. HPV testing or cotesting may be especially advantageous for practices whose patients are less able to comply with frequent follow-up visits, because negative HPV test results are more reassuring than negative cytology results and thus can be performed less frequently, allowing the clinical practices to focus their limited outreach resources on the highest-risk patients.

DISCUSSION

What Is the Most Effective Strategy for Cervical Cancer Prevention Throughout the Lifespan?

The most effective strategy for cervical cancer prevention evolves directly from understanding of the role of HPV in cervical carcinogenesis. Most oncogenic HPV infections are acquired between the ages of 18 and 26,[9] precancers peak between ages 25 and 35,[12] and cancer rates begin to rise at age 40 and remain elevated throughout the remaining years of life.[13,14] Thus primary prevention of HPV infections in adolescence followed by screening for and treatment of precancers in adults are the keys to cancer prevention.[26,79]

Ages 9 to 18

The first step is primary prevention: universal HPV vaccination of the current adolescent population. This is estimated to prevent up to 85% of cervical cancers, even in the absence of screening.[80]

Ages 18 to 24

Both screening and HPV vaccination are recommended for portions of this age group, yet neither is optimally effective. Because HPV infections accrue rapidly following sexual debut, HPV vaccine effectiveness decreases substantially when the series is initiated greater than ages 18 to 20.[28,29] However, although the prevalence of HPV infection is high in this age group, most infections and cervical lesions are destined to regress, such that treating precancers younger than age 25 is discouraged in all but the highest-risk cases.[76] Thus, this population derives limited benefit from screening. Screening guidelines universally state that the risks of screening outweigh benefits in immunocompetent individuals younger than age 21 years, and the 2020 ACS guidelines recommend initiating screening at age 25 years.[37,38,61,62]

Ages 25 to 65

All experts agree that screening is the key to cervical cancer prevention for this age group.[37,38,61,62] Experts also concur that clinical trials of HPV vaccination older than age 26 have demonstrated limited evidence for prevention of cervical cancer precursors; therefore, routine vaccination of this age group is not recommended.[30] Examination of the

characteristics of cervical cancer screening tests conclusively demonstrate that HPV testing or cotesting detects more precancers per screening round than cytology screening alone.[48,49] Screening with HPV testing or cotesting can be performed less frequently than cytology alone with superior cancer prevention,[37,38,61,62] and HPV tests or cotests are preferred to cytology alone for surveillance following screening test abnormalities.[76] Cotesting detects approximately 5% more precancers per screening round than does HPV testing alone, but results in a substantial increase in cost and false-positive testing rates (defined as abnormal results that lead to additional diagnostic testing without detecting a precancer).[47,56,58] Data indicate that screening at ages 45 to 65 is crucial to preventing cancer among women older than age 65[73,74]; however, screening rates are low in this age group.[81] Therefore ensuring adequate screening at ages 45 to 65 should be an important goal of screening programs.

Ages 65 and Older

Individuals in this age group represent a conundrum in care. Although routine screening is not recommended,[47,56,58] they represent 20% of cervical cancers, and have excess mortality compared with younger women.[14,72] In addition, performing screening, diagnostic, and treatment procedures in individuals more than 10 years past menopause is more difficult and less likely to yield accurate results because of vaginal atrophy and, in some cases, physical mobility issues. Therefore, the key to preventing cervical cancer in individuals older than age 65 may be ensuring adequate screening at ages 45 to 65. Many patients who develop cervical cancer at age greater than 65 did not fulfill exit criteria before cessation of screening.[73,74] In contrast, the rate of cervical cancer following multiple rounds of HPV testing or cotesting is extremely low.[51] Yet, 12% to 18% of women age 45 to 65 report no cervical cancer screening in greater than 5 years.[82] Thus, encouraging women to engage in cervical cancer screening around and through the menopausal transition has the potential to dramatically decrease cancer rates older than age 65.

SUMMARY

Because of decades of important research on the relationship of HPV and cervical cancer, the tools are now in hand to prevent nearly all cases of the disease.[83] Cervical cancer prevention is no longer “one size fits all” with annual examinations for all adult women. Primary prevention of cervical cancer begins in adolescence with universal vaccination to prevent infection with HPV in the future. Most adults have been exposed to oncogenic HPV, therefore secondary prevention with screening becomes the primary mode of prevention for adults. The increased precision afforded by incorporating HPV testing into screening algorithms allows providers and healthcare systems to focus resources on high-risk individuals and reduce unnecessary screening and diagnostic procedures in low-risk individuals. This is efficient and effective, but requires investment of time and resources into the development of robust population management systems to appropriately track and recall patients for needed screenings and interventions. Finally, cervical cancer continues to occur most frequently in un-screened and underscreened patients, so ensuring that all adolescents receive HPV vaccinations and that all adults with a cervix receive screening and follow-up are most crucial to decreasing rates of cervical cancer.

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KEY POINTS

- HPV vaccination in adolescence is critical to preventing cervical cancer in young adults; screening is the key to preventing cervical cancer in adult patients.
- Achieving and maintaining high rates of cervical cancer screening in the 25- to 65-year-old population is the key to cervical cancer prevention.
- HPV testing detects more disease and achieves higher rates of cancer prevention than Pap testing; it can also be performed less frequently with superior results.
- Ensuring adequate screening between ages 45 and 65 is critical to preventing cervical cancer after age 65.
- Reminder/recall/tracking systems are necessary to ensuring that testing occurs when needed for individuals undergoing routine screening and for those undergoing surveillance after abnormalities.

Table 1

Comparison of ACS 2020, USPSTF 2018, and ACOG 2016 screening guidelines

Guideline Author	American Cancer Society (ACS) 2020	US Preventive Services Task Force (USPSTF) 2018	American College of Obstetricians and Gynecologists 2016
Age to start screening	25	21	21
Age to end screening	65[a]	65[a]	65[a]
Screening test options	HPV primary screening preferred for all ages; co-testing and cytology (Pap test) acceptable during transition	Cytology (Pap test) ages 21–29; HPV primary screening, co-testing, and cytology all equally acceptable ages 30–65	Cytology (Pap test) ages 21–29; HPV primary screening, co-testing, and cytology all equally acceptable ages 30–65; HPV primary screening every 3 y for ages 25–65 can be considered
Testing interval	5 y	3 y for cytology (Pap test); 5 y for HPV primary screening and co-testing	3 y for cytology (Pap test); 5 y for co-testing; 3 y for HPV primary screening
Individuals who have undergone hysterectomy with removal of the cervix for benign indications	Do not screen	Do not screen	Do not screen
Exclusions from screening guidelines	Screening guidelines do not apply to individuals with a history of cervical cancer or pre-cancer, DES in utero exposure, or immunocompromised, including HIV infection, as more frequent testing is typically recommended.		

[a]Criteria to end screening: 3 consecutive negative cytologies (Pap tests) or 2 negative screening HPV or co-tests within the past 10 y, without abnormal results during that time, with the most recent within the past 5 y and no history of pre-cancer (defined as CIN2 or higher) within the past 25 y.

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