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Cervical Cancer Screening
A Review

Rebecca B. Perkins, MD, MSc; Nicolas Wentzensen, MD, PhD, MS; Richard S. Guido, MD; Mark Schiffman, MD, MPH

IMPORTANCE Each year in the US, approximately 100 000 people are treated for cervical precancer, 14 000 people are diagnosed with cervical cancer, and 4000 die of cervical cancer.

OBSERVATIONS Essentially all cervical cancers worldwide are caused by persistent infections with one of 13 carcinogenic human papillomavirus (HPV) genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. HPV vaccination at ages 9 through 12 years will likely prevent more than 90% of cervical precancers and cancers. In people with a cervix aged 21 through 65 years, cervical cancer is prevented by screening for and treating cervical precancer, defined as high-grade squamous intraepithelial lesions of the cervix. High-grade lesions can progress to cervical cancer if not treated. Cervicovaginal HPV testing is 90% sensitive for detecting precancer. In the general population, the risk of precancer is less than 0.15% over 5 years following a negative HPV test result. Among people with a positive HPV test result, a combination of HPV genotyping and cervical cytology (Papanicolaou testing) can identify the risk of precancer. For people with current precancer risks of less than 4%, repeat HPV testing is recommended in 1, 3, or 5 years depending on 5-year precancer risk. For people with current precancer risks of 4% through 24%, such as those with low-grade cytology test results (atypical squamous cells of undetermined significance [ASC-US] or low-grade squamous intraepithelial lesion [LSIL]) and a positive HPV test of unknown duration, colposcopy is recommended. For patients with precancer risks of less than 25% (eg, cervical intraepithelial neoplasia grade 1 [CIN1] or histologic LSIL), treatment-related adverse effects, including possible association with preterm labor, can be reduced by repeating colposcopy to monitor for precancer and avoiding excisional treatment. For patients with current precancer risks of 25% through 59% (eg, high-grade cytology results of ASC cannot exclude high-grade lesion [ASC-H] or high-grade squamous intraepithelial lesion [HSIL] with positive HPV test results), management consists of colposcopy with biopsy or excisional treatment. For those with current precancer risks of 60% or more, such as patients with HPV-16–positive HSIL, proceeding directly to excisional treatment is preferred, but performing a colposcopy first to confirm the need for excisional treatment is acceptable. Clinical decision support tools can facilitate correct management.

CONCLUSIONS AND RELEVANCE Approximately 100 000 people are treated for cervical precancer each year in the US to prevent cervical cancer. People with a cervix should be screened with HPV testing, and if HPV-positive, genotyping and cytology testing should be performed to assess the risk of cervical precancer and determine the need for colposcopy or treatment. HPV vaccination in adolescence will likely prevent more than 90% of cervical precancers and cancers.

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Author Affiliations: Boston University School of Medicine, Chobanian & Avedisian School of Medicine, Boston Medical Center, Massachusetts (Perkins); Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Wentzensen, Schiffman); Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania (Guido); UPMC Magee-Women's Hospital, Pittsburgh, Pennsylvania (Guido).

Corresponding Author: Rebecca B. Perkins, MD, MSc, Department of Obstetrics and Gynecology, Boston University School of Medicine, Boston Medical Center, 775 Albany St, Fourth Floor Dowling Building, Boston, MA 02118 (rbperkin@bu.edu).

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Each year in the US, approximately 100 000 people are treated for a cervical precancer. Precancers are abnormal cells that can progress to cancer unless treated and include histologic high-grade squamous intraepithelial lesions (HSIL), cervical intraepithelial neoplasia grade 3 (CIN3), and adenocarcinoma in situ (AIS). Because not all precancers are detected and treated, usually due to lack of screening, 14 000 people are diagnosed with cervical cancer and more than 4000 die from cervical cancer each year.[1] More than 90% of cervical cancers are caused by infection with human papillomavirus (HPV).[2] Although HPV vaccination has been associated with up to 90% reduction in cervical cancer for those vaccinated in adolescence,[3,4] the full benefits of vaccination will not occur until the population currently vaccinated in adolescence reaches mid to late life. Therefore, screening remains an important component of cervical cancer prevention. Currently, approximately half of cervical cancers occur in people with inadequate screening,[5,6] and up to 25% of individuals in the US are underscreened.[7] In addition, approximately 20% of the US population requires more frequent screening due to prior cervical cancer screening abnormalities or immunosuppression.[7]

Programs of repeated cytology (Papanicolaou test) screening, colposcopically guided biopsies, and excision of precancerous changes of the cervix have reduced population-level cervical cancer incidence and mortality by 60% to 80%.[8] Because cytological and histological classifications have intrinsic variability, however, including information related to HPV infection increases the accuracy of prevention strategies. Specifically, the risk of precancer can be accurately estimated by identifying the HPV genotype and using morphological and biochemical tests, such as cytology and p16/Ki67 dual stain, to understand whether the HPV infection is replicating (more likely benign) or abortive and transforming (more likely precancerous).[9,10] This review summarizes current evidence on HPV pathophysiology and cervical cancer prevention.

Methods

The International Agency for Research on Cancer (IARC) conducted a literature review of PubMed and Web of Science on February 17, 2020, for the IARC handbook on cervical cancer screening.[11] This publication summarized the state-of-the-art science of cervical cancer screening, HPV virology, pathophysiology, vaccination, diagnosis, and management and included relevant articles published through February 2020.[12] To update the evidence review, we conducted a PubMed search using the same search terms between January 2020 and March 2023 that identified 1848 articles. Of these, we included 30 articles: 1 clinical trial, 3 meta-analyses, 18 longitudinal observational studies, 1 cross-sectional study, and 7 guidelines publications.

Discussion

HPV and Cervical Cancer Pathophysiology

The squamocolumnar junction of the cervix (**Figure 1**) is particularly susceptible to HPV carcinogenesis; cellularchanges that are precursors to cervical cancer typically develop in this area. New evidence indicates "reserve cells" that are susceptible to malignant transformation and are also a reservoir for latent HPV infections. These cells are located above the basement membrane, scattered, and extend proximal to the visible squamocolumnar junction under the glandular epithelium of the endocervical canal.[13]

HPV Evolution and Carcinogenicity

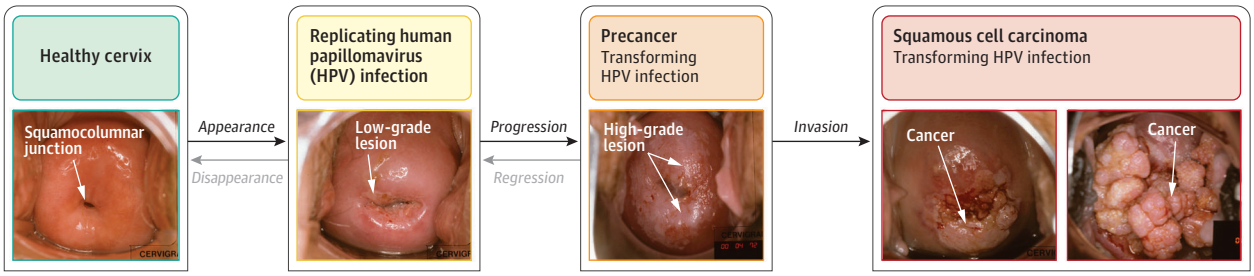
More than 450 genotypes of HPV have been identified and organized into genera and species and numbered in order of genetic identification. HPV is a stable double-stranded DNA virus that has evolved slowly into genotypes with potential to initiate cervical cancer. Among more than 40 000 cervical cancers tested worldwide, virtually all contained at least 1 of 13 carcinogenic HPV genotypes.[2]

Carcinogenic HPV genotypes are evolutionarily linked in a single branch of the alpha genus (**Figure 2**). Within this genus, the alpha-9, -7, -5, and -6 species contain the HPV genotypes that are carcinogenic, defined in laboratory testing as *high-risk* HPV. *Low-risk* HPV genotypes are not associated with increased cervical cancer risk and their detection plays no role in cancer prevention strategies. Virtually all high-risk HPV genotypes in the alpha-9 species group are carcinogenic (HPV-16, -31, -33, -35, -52, and -58).[14] HPV-16 is the most carcinogenic and is associated with more than 60% of cervical squamous cancers and adenocarcinomas and with oropharyngeal and other anogenital cancers.[2,11,15] Other alpha-9 HPV genotypes (HPV-31, -33, -35, -52, and -58) are *medium risk* and are each responsible for 2% to 4% of cancers.[2,11] Regional variation exists in the HPV genotypes associated with cervical cancer. For example, HPV-35 is associated with higher cancer risks among individuals of African descent than individuals of other racial backgrounds.[16] In the alpha-7 species group, HPV-18 and -45 are associated with both squamous cancers and adenocarcinomas, and together cause approximately 20% of cancers.[2,11] The less carcinogenic alpha-7 genotypes, HPV-39, -59, and -68 and the species alpha-5 (HPV-51) and alpha-6 (HPV-56) are *lower risk* carcinogenic genotypes, each responsible for less than 2% of cancers.[2,11] HPV genotype allows risk stratification and informs management, with colposcopy recommended when HPV-16 or -18 is detected.[10] When HPV results are positive for genotypes other than 16 or 18, additional information is important for determining the need for colposcopy.[10] Clinical guidelines for management based on additional genotypes (called extended genotyping) are in development.

Active and Latent Infections

A new HPV infection, regardless of genotype, is considered an active HPV infection that produces new copies of the virus. Active HPV infections may occur without microscopic or visible changes on the cervix or as equivocal or low-grade cellular abnormalities of the cervix (Figure 1), but precancerous changes are uncommon. Whether cellular abnormalities occur, such as low-grade squamous intraepithelial lesion (LSIL), most infections disappear within 12 to 24 months either due to lack of biological fitness or through suppression by the host cellular immune system. Although evidence of immunity against reinfection has been documented, immunity following natural infection is incomplete and poorly understood. However, immunity from HPV vaccination provides approximately 90% protection against HPV infection for at least 15 years.[17,18]

Figure 1. Stages of HPV-Mediated Carcinogenesis



This depicts the necessary, sequential stages of HPV-mediated carcinogenesis: HPV infection, intraepithelial precancer, and cancer. The images illustrate what a clinician might see on physical examination at each stage of carcinogensis. HPV genotype is a major influence on risks of progression to precancer and cancer compared with immune control and regression to negative results on HPV testing. Familiar and overlapping microscopic (cytologic and histologic) morphologic grading as well as visual classifications have been used to indicate the increasing severity of HPV-induced changes. However, morphologic and visual grading classifications have imperfect reproducibility and accuracy, and many diagnoses are equivocal. Molecular tests (eg, p16/Ki67 dual stain) are increasingly used to identify the likelihood of prevalent and incipient precancer.

HPV infections can persist in basal cells of the cervix and undergo slow replication, called *latent infection*. During latent infection, cervicovaginal tests for HPV are negative, no apparent cellular damage occurs, and cancer risk is minimal.[19] HPV infections can reappear throughout an individual's lifetime, with reappearance rates of up to 15% by 5 years.[20] Therefore, a newly positive HPV test result may be a newly acquired infection or the reappearance of an old infection. Currently available clinical tests do not distinguish between these alternatives. The risk of progression to precancer over 5 years is approximately 3% with either new or reappearing infections, suggesting that the distinction is not clinically relevant.[20]

Persistence and Progression to Precancer

When a carcinogenic HPV infection persists, infected cells may undergo neoplastic transformation.[14] The term *precancer* indicates the change from replicating infection to clonal growth of transformed cells. Replicating HPV infections undergo a complete viral lifecycle leading to virion production and release. In precancers, however, HPV viral oncoproteins activate the cell cycle and inhibit apoptosis, the process of programmed cell death that is essential for renewing the squamous epithelium and protecting against neoplasia. Precancers retain many normal cellular functions including contact inhibition, in which noncancerous cells stop proliferating when in contact with the basement membrane. Epithelia grow away from the basement membrane, which can allow earlier detection of abnormal growth. Precancerous cells sometimes regress and, when growing, usually enlarge circumferentially without invasion for years. This typically long period of intraepithelial growth accounts for the success of screening.

Several viral and host markers for precancers have been identified.[21] Methylation of viral and host DNA markers is observed at the transition from replicating HPV infection to oncogenic transformation, particularly the *L1* or *L2* genes that code for the viral capsid in active infections.[22,23] Methylation assays are promising for identifying molecular changes associated with cancer risk but are currently not available for clinical use in the US. The p16/Ki67 dual-stain test (CINtec Plus) is a new technology approved by the US Food and Drug Administration for detecting cell transformation. p16 indicates interruption of the retinoblastoma pathway by E7 oncoproteins and accumulates visibly in transformed cells. Ki67 is a marker of cellular proliferation. The combination of p16 and Ki67 suggests cellular transformation by HPV. Several studies of patients with positive HPV test results have shown improved performance of dual stain for distinguishing precancer from low-grade abnormalities over Papanicolaou-stain cytology.[24-26] p16/Ki67 dual-stain detection can be automated, which research suggests would further improve performance.[27]

Invasion: Squamous and Adenocarcinomas

HPV genotype determines the probability that an infection will progress to precancer and cancer. The genotype-specific variation in carcinogenicity is largely explained by differences in E6 and E7 protein structures and their subsequent ability to disrupt genomic integrity and the normal cell cycle leading to apoptosis. HPV-16 is associated with the highest risk of cancer.

Adenocarcinomas, cancers of the glandular cells of the endocervix, are caused almost exclusively by HPV-16, -18, and -45. Adenocarcinomas have a different pathophysiology than squamous cancers, which arise from the squamous cells of the exocervix. Adenocarcinoma precancers may be missed by screening and colposcopy, resulting in lower rates of precancer detection and treatment than squamous precancers. Consequently, screening programs have been less effective in preventing adenocarcinomas than squamous cancers.[28,29]

Epidemiology and Risk Factors

Most of the sexually active population is estimated to be infected with HPV during their lifetimes, although the exact percentage is unknown. Therefore, a positive HPV test result should simply be considered a marker of sexual activity. Cancers develop in people with persistence of an HPV infection that is not controlled by the immune system. The most important factors in determining risk of cervical cancer are HPV positivity, HPV genotype, and cytological changes associated with HPV-related cell transformation.[30] The precancer risks associated with abnormal HPV and cytology results are similar in diverse US settings.[31]

The age-adjusted and hysterectomy-corrected incidence rate of cervical cancer in the US is 11.5 per 100 000 women aged 15 to 75 years.[32] However, individuals with immunosuppression or diethylstilbestrol exposure have higher risks of cervical precancer and

Figure 2. Carcinogenic Human Papillomavirus Types

Carcinogenic human papillomavirus (HPV) type	Proportion of cervical cancers, %	9-Year risk of progression of incident HPV infection to cervical intraepithelial neoplasia grade 3 or worse (CIN3+)	HPV species	Risk group	Included in 9-valent vaccine
16	60.3	6.3	Alpha-9	Highest	Yes
18	10.5	3.0	Alpha-7	High	Yes
45	6.1	2.2	Alpha-7	High	Yes
33	3.7	4.5	Alpha-9	Medium	Yes
31	3.6	2.2	Alpha-9	Medium	Yes
52	2.7	2.2	Alpha-9	Medium	Yes
58	2.2	1.9	Alpha-9	Medium	Yes
35	2.0	2.8	Alpha-9	Medium	No
39	1.6	1.1	Alpha-7	Lower	No
51	1.2	1.1	Alpha-5	Lower	No
59	1.1	0.9	Alpha-7	Lower	No
56	0.9	0.8	Alpha-6	Lower	No
68	0.6	1.0	Alpha-7	Lower	No

This figure describes the carcinogenic HPV types ordered from highest (HPV 16) to lowest (HPV 68) and grouped by their risk of causing cervical cancers. All HPV types in the highest, high, and medium risk groups are included in the current 9-valent vaccines with the exception of HPV 35.

cancer.[33] Recent evidence may indicate decreased cervical cancer screening effectiveness in women with higher body mass index (BMI). Obese women had higher 5-year cancer risks (0.083% vs 0.056%) but lower 5-year precancer risks (0.51% vs 0.73%) than normal weight and underweight women even when screened similarly.[34] Those with a higher BMI may also have lower screening participation.[35] Cancer risks associated with higher BMI may therefore be due to both less screening and lower precancer detection among screened individuals.[34,35]

HPV Vaccination

HPV vaccination will likely prevent HPV infections, precancers, and cancers.[3,4,36,37] Guidelines recommend that vaccination be initiated for all children, regardless of sex, at age 9 years, with 2 doses of HPV vaccine given 6 to 12 months apart prior to the 13th birthday.[38,39] Vaccination is recommended for those aged 13 through 26 who were not vaccinated according to the recommended guidelines; 3 doses are recommended for those initiating vaccination at age 15 years or older. Vaccines are preventive, and effectiveness drops after first sexual intercourse. Most studies showed maximum benefits from vaccination administered prior to age 14 years, with decreasing effectiveness of vaccination with age.[40-42] Shared decision-making is recommended prior to vaccination of individuals aged 27 through 45 years because vaccination is not expected to be an effective or cost-effective form of cancer prevention on a population level.[38,41] National data from 2021 reported that only 62% of 13- through 17-year-olds had completed the HPV vaccine series.[43] Strategies are needed to promote vaccine uptake.

Vaccination status is not currently considered in cervical cancer screening guidelines because most individuals currently participating in screening were not vaccinated in early adolescence and requiring adolescent vaccination records to determine screening eligibility was considered a barrier to screening.

Cervical Cancer Screening Recommendations

Over a lifetime, cervical cancer develops in up to 5% of an unscreened population. Effective screening and treatment of cervical precancers can reduce the lifetime risk to less than 0.5%.[1] Regular screening of asymptomatic individuals is recommended to diagnose and treat precancers to prevent cervical cancer. However, screening applies only to asymptomatic individuals. People presenting with possible symptoms of cervical cancer, including irregular bleeding, pain, or vaginal discharge, require assessment including pelvic examination and cervical cytology.[44,45]

Screening Considerations

Effective cervical cancer screening consists of the following steps: (1) assess all patients for screening eligibility and screen when indicated (**Figure 3**); and (2) screen using HPV testing (with or without cytology). A negative HPV test result more accurately indicates the absence of cervical precancer than cytology alone. The sensitivity of cytology for detecting precancer is 50% to 70% compared with more than 90% for HPV testing.[10,46] Furthermore, cancer risk continues to decrease with subsequent rounds of negative HPV screening results.[47,48] Ninety-seven percent of precancers are HPV-positive, so performing concurrent cytology and HPV testing (cotesting) provides limited additional information compared with HPV testing alone.[47,49] Cervical cancer is most common in individuals who do not receive appropriate screening.[5,32]

Average-Risk Screening

The risk of cervical cancer begins to increase around age 30 years and remains elevated for the remainder of the lifespan.[50] Therefore, screening is recommended at least every 5 years for individuals aged 25 through 65 years who have a cervix (eg, women and transgender men who have not undergone hysterectomy). The US Preventive Services Task Force recommends screening average-risk individuals with cytology alone at ages 21 through 29 years and with HPV testing alone, HPV testing with cytology (cotesting), or cytology alone at ages 30 through 65 years.[46] Updated guidelines from the American Cancer Society,[51] noting a better balance of benefits and harms of HPV testing than cytology,[47] recommend HPV testing alone at 5-year intervals for those aged 25 though 65 years (see the red box in Figure 3).[51]

Surveillance or High-Risk Screening

Up to 20% of individuals in a general population have prior abnormal results, prior precancer or cancer, or immunosuppression and require screening at 1 or 3-year intervals (see the yellow box in Figure 3).[7] These patients are considered to be under surveillance or undergoing high-risk screening; management of their care is described in more detail below (**Table**).

Screening Cessation

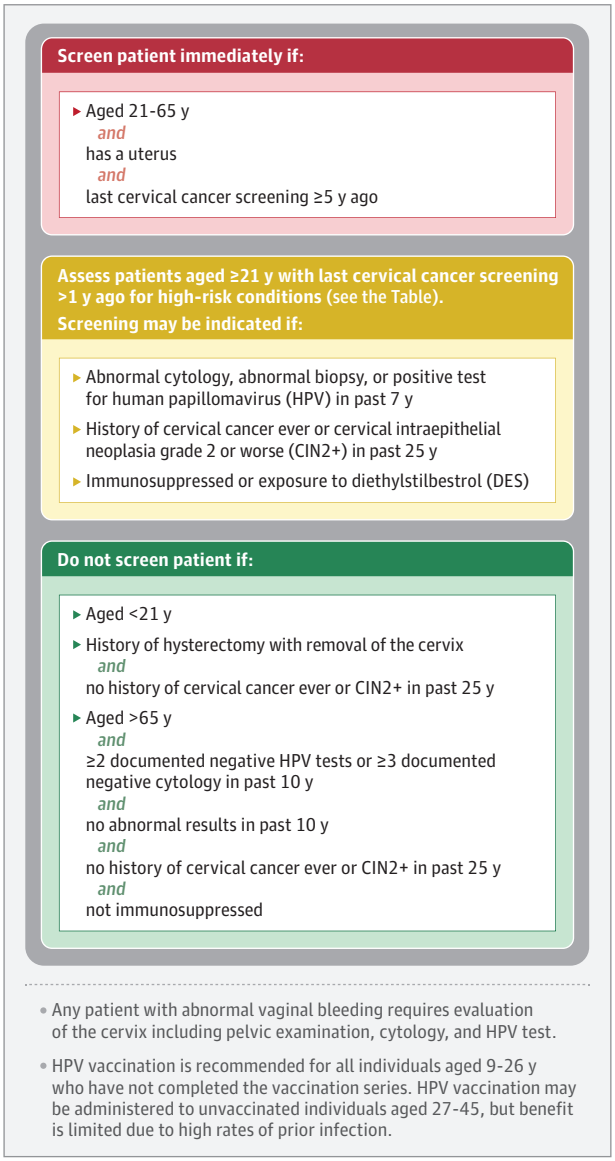
Screening is not recommended for asymptomatic individuals (1) younger than 21 years; (2) without a cervix (eg, after hysterectomy) unless previously diagnosed with cervical cancer or precancer; or (3) older than 65 years who fulfill screening cessation criteria: documentation of at least 3 consecutive negative cytology results or 2 consecutive negative HPV test results within the past 10 years with the most recent within the past 5 years, no abnormal results in the past 10 years, no history of cervical precancer in the past 25 years, no history of cervical cancer, and no immunosuppression (see the green box in Figure 3).[7,52,53]Adequate screening prior to cessation at age 65 years is critical. Undersreening is common between the ages of 45 and 65 years, and only one-third of women aged 64 through 66 years meet criteria to stop screening.[52] Approximately 25% of cervical cancers occur in women older than 65 years, their mortality is approximately twice as high as that of younger women,[54,55] and many individuals who developed cancer after age 65 years did not fulfill guideline criteria for screening cessation.[56,57]

Management of Abnormal Screening Test Results

Risk-Based Management: A New Framework

The risk of precancer is used to determine the next steps in management for patients whose current or past screening results were abnormal: HPV-positive or abnormal cytology or biopsy (Table).[10] Management in the US is guided by the 2019 ASCCP (formerly the American Society for Colposcopy and Cervical Pathology) Risk-Based Management Consensus Guidelines, which use the concept of *risk-based management*, defined as treating patients according to their estimated precancer risk.[10] This represents a paradigm shift from prior guidelines that focused primarily on test results. Precancer risks were precisely estimated using current and past cytology and HPV test and biopsy results from more than 1.5 million individuals who were followed up for up to 15 years at Kaiser Permanente Northern California.[49] Comprehensive risk tables are available at https://dceg.cancer.gov/research/cancer-types/cervix/enduring-guidelines. Results were validated in the Centers for Disease Control and Prevention (CDC) Breast and Cervical Cancer Early Detection Program to ensure that risk estimates were applicable to safety net settings.[31] The risk of precancer is used to determine the next steps in management following abnormal results.[10] This reduces testing in low-risk patients while increasing testing in high-risk patients, resulting in fewer procedures and better cancer prevention.[58] Reductions in overtesting mean that when clinicians implement risk-based guidelines, they will more frequently encounter abnormal results because (1) high-risk individuals screen more often than low-risk individuals; (2) colposcopy is deferred for some patients, but these individuals require follow-up in 1 year; and (3) a higher proportion of patients undergoing colposcopy will be diagnosed with precancer requiring treatment because colposcopy is deferred for lower-risk patients.

Figure 3. Assessing the Need for Screening



The red box applies to average-risk patients; the yellow box identifies patients requiring additional screening for surveillance or high-risk conditions; and the green box describes criteria for screening cessation.

Guidelines use the current (immediate) risk of CIN3, AIS, or cancer (defined collectively as *CIN3 or worse* [*CIN3+*]) to determine whether individuals require colposcopy or may be safely followed up with repeat HPV testing or cotesting in 1, 3, or 5 years (**Figure 4**). For results with immediate CIN3+ risks of less than 4%, the 3- or 5-year CIN3+ risks are examined to determine retesting intervals of 1, 3, or 5 years.[10,59] Specifically, patients should return in 5 years for screening if their risks of developing CIN3+ within 5 years are similar to the general screening population with a negative HPV test or cotest results (ie, <0.15%). Patients should return in 3 years for screening if their risks are

Table. Management Recommendations for Patients Aged 25 Years or Older (2019 ASCCP Risk-Based Management Consensus Guidelines)

Current HPV test result	Current cytology (Papanicolaou test) or biopsy result	Prior results	Management recommendation	Risk of CIN3+[10,49]
Recommendation for 5-y follow-up				
Negative	NILM or no cytology	Unknown or HPV-negative	HPV test or HPV/cytology cotest in 5 y	≤0.14% at 5 y
Negative	NILM	ASCUS HPV-negative	HPV or HPV/cytology cotest in 5 y	0.14% at 5 y
Negative	NILM	3 consecutive negative HPV tests after colposcopy confirming low-grade abnormality (eg, 7-y normal follow-up)	HPV or HPV/cytology cotest in 5 y	0.03% at 5 y
Recommendation for 3-y follow-up				
Negative	ASC-US	Unknown	HPV test or HPV/cytology cotest in 3 y	0.40% at 5 y
Negative	NILM	Low-grade abnormal cytology (ASC-US, LSIL) and colposcopy with no CIN2+ (HSIL) found	HPV test or HPV/cytology cotest in 3 y for 3 consecutive negative results before returning to a 5-y screening interval	0.18% at 5 y
Negative	NILM	HIV+ or immunosuppressed	HIV+ and immunosuppressed: screen at 3-y intervals	Special situation: opportunistic infection guidelines[33]
Negative	NILM or no cytology	Treatment of CIN2+ followed by 3 consecutive negative HPV tests or HPV/cytology cotests	Following initial surveillance after CIN2+ treatment: screen every 3 y for at least 25 y through 65 y; may continue at 3-y intervals while patient is in good health	0.35% at 5 y for HPV-negative NILM; 0.44% at 5 y for HPV-negative only
Recommendation for 1-y follow-up				
Negative	LSIL	Unknown or HPV-negative[a]	HPV test or HPV/cytology cotest in 1 y	0.44%-1.1% current risk; 0.79%-2.0% at 5 y
Positive	NILM	Unknown or HPV-negative[a]	HPV test or HPV/cytology cotest in 1 y	0.74%-2.1% current risk; 2.3-4.8% risk at 5 y
Positive	ASC-US or LSIL	Negative screening results with HPV testing or negative HPV/cytology cotesting within past 5 y[b]	HPV test or HPV/cytology cotest in 1 y	2.0%-2.1% current risk; 3.8% at 5 y
Positive	ASC-US or LSIL	Colposcopy within the past year with no CIN2+ (HSIL) found and preceded by NILM, ASC-US, or LSIL cytology	HPV test or HPV/cytology cotest in 1 y	2.1%-3.1% current risk; 6.0% at 5 y
Positive	p16/Ki-67 dual-stain negative[c]	Noncontributory	HPV test in 1 y	0.75% current risk, 1.5% at 3y
	Colposcopy with normal or CIN1 (LSIL) biopsy results	NILM, ASCUS, or LSIL cytology	HPV test or HPV/cytology cotest in 1 y (Note observation is preferred to treatment for persistent results of CIN1 [LSIL])	0.53% current risk; 2.6% at 5 y
	Colposcopy with normal or CIN1 (LSIL) biopsy results	HSIL cytology	Colposcopy plus either HPV test or HPV/cytology cotest at year 1, HPV test or HPV/cytology cotest at year 2, then HPV test or HPV/cytology cotest at 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Special situation[10,d]
	Colposcopy with normal or CIN1 (LSIL) biopsy results	ASC-H cytology	HPV test or HPV/cytology cotest at 1 and 2 y, then HPV test or HPV/cytology cotest at 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Special situation[10,d]
	Colposcopy with normal or CIN1 (LSIL) biopsy results	AGC cytology	Repeat HPV/cytology cotest at years 1 and 2, then HPV/cytology cotest in 3 y, then HPV test or HPV/cytology cotest at 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Special situation[10,d]
Recommendation for repeat testing				
Unsatisfactory cytology			Repeat cytology as soon as convenient and no later than 4 mo; If both Papanicolaou and HPV test were performed, repeat both; A negative HPV result is not considered valid in the setting of an unsatisfactory cytology result Note: absent transformation zone is not unsatisfactory and should be managed as a NILM result	Special situation[10,d]

(continued)

Table. Management Recommendations for Patients Aged 25 Years or Older (2019 ASCCP Risk-Based Management Consensus Guidelines) (continued)

Current HPV test result	Current cytology (Papanicolaou test) or biopsy result	Prior results	Management recommendation	Risk of CIN3+[10,49]
Recommendation for 6-mo follow-up				
	CIN2: observation[e]		If observation is elected for CIN2, colposcopy plus either HPV test or HPV/cytology cotest is recommended at 6-mo intervals for up to 2 y Treatment is recommended if CIN3 develops at any time or CIN2 persists for 2 y If CIN2 regresses at 6 and 12 mo visits, repeat HPV test or HPV/cytology cotest in 1 y If negative, repeat HPV test or HPV/cytology cotest at 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Special situation[10,d]
	CIN2+ (HSIL): after treatment		Repeat HPV test or HPV/cytology cotest at 6 mo, 18 mo, 30 mo (until 3 consecutive negative results obtained) then move to 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Multiple-risk estimates[49]
	AIS: after treatment		HPV test, cytology, and ECC at 6-mo intervals for 3 y, then annually for 2 y, then HPV testing or HPV/cytology cotesting at 3 y intervals for at least 25 y or while in good health Hysterectomy preferred when childbearing complete	Special situation[10,d]
Recommendation for colposcopy				
Negative or no HPV test	ASC-H	Noncontributory	Colposcopy	Special situation[10,d]
Noncontributory	AGC	Noncontributory	Colposcopy with ECC and perform endometrial biopsy if age ≥35 y or age <35 y with obesity or anovulation	Special situation[10,d]
Noncontributory	Atypical endometrial cells	Noncontributory	Endometrial and endocervical biopsy; if both negative, colposcopy	Special situation[10,d]
Positive	Noncontributory	HPV positive[f]	Colposcopy recommended for HPV-positive results occurring twice consecutively due to elevated CIN3+ risk associated with persistent HPV infection	Risk varies by situation[10]
Positive for genotype HPV-16 and/or HPV-18	Noncontributory	Noncontributory	Colposcopy for all HPV-16 or HPV-18 results	Risk varies by situation[10]
Positive	ASC-US or LSIL	Unknown or HPV-positive	Colposcopy	4.4% current risk
No HPV test	LSIL[g]	Noncontributory	Colposcopy	Special situation[10,d]
Positive	p16/Ki-67 dual-stain positive[c]	Noncontributory	Colposcopy	12% current risk
Recommendation for colposcopy or expedited treatment[h]				
Positive	ASC-H	Noncontributory	Colposcopy or expedited treatment	26% current risk
Positive: untyped Positive: genotype other than HPV-16 negative No HPV test	HSIL	Noncontributory	Colposcopy or expedited treatment	49% current risk for HPV-positive untyped
Recommendation for expedited treatment[i]				
Positive: genotype HPV-16	HSIL	Noncontributory	Expedited treatment	60% current risk
Positive	HSIL	No screening in >5 y	Expedited treatment	64% current risk

Abbreviations: AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells cannot exlude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; ECC, endocervical curettage; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.

[a] Colposcopy may be warranted for patients with a history of high-grade lesions. These include: AIS, CIN3, histologic HSIL, CIN2, cytologic HSIL, ASC-H, AGC.

[b] Negative HPV test or HPV/cytology cotest results only reduce risk sufficiently to defer colposcopy if performed for screening purposes within the last 5 years. Colposcopy is still warranted if negative HPV test or cotest results occurred in the context of surveillance for a prior abnormal result.

[c] World Health Organization guidelines support dual stain for triage of HPV-positive screening test results; US guidelines were pending at the time of this review.

[d] Special situation refers to scenarios for which CIN3+ risk estimates were not available or when other criteria were used for guidelines.

[e] Patients should be counseled on their preference for treatment vs serial colposcopy. Considerations include but are not limited to age, future pregnancy considerations, ability and desire to undergo repeated colposcopy vs treatment.

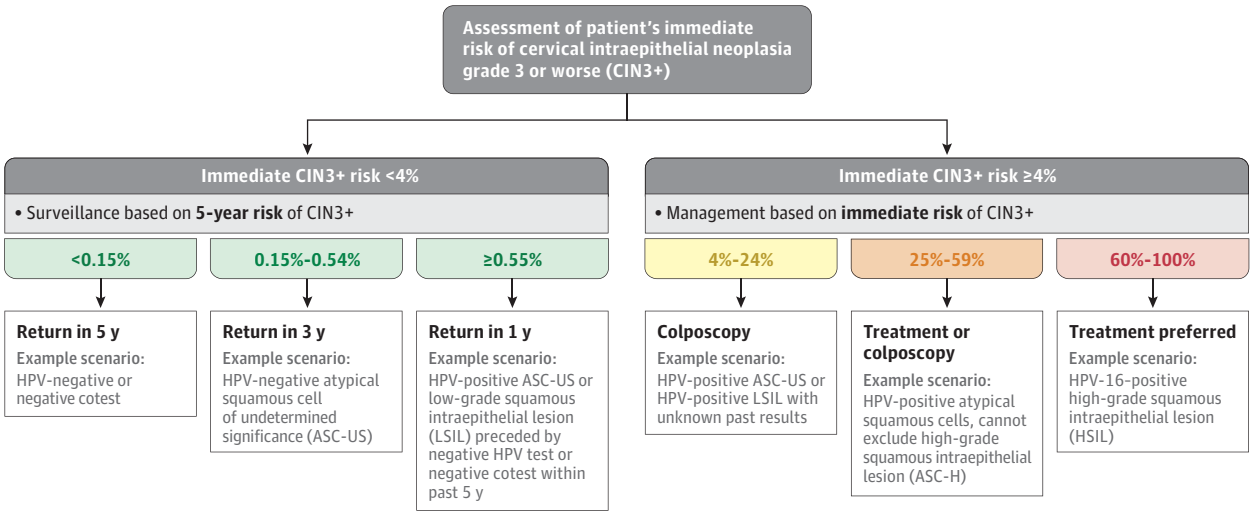
[f] Prior cytology results do not modify the recommendation; colposcopy is always recommended for 2 consecutive HPV-positive tests (note if colposcopy is performed between the 2 HPV tests, they are not considered consecutive).

[g] Patients aged 24 y or younger are managed differently: after ASC-US or LSIL results, repeat cytology is recommended at 1 y and 2 y with colposcopy if ASC-US or LSIL persists at 2 y. Colposcopy is recommended for cytology results of AGC, ASC-H, HSIL

[h] Expedited treatment is defined as proceeding to excisional treatment without first performing colposcopy with biopsy. See footnote *e* for considerations related to shared decision-making.

[i] Expedited treatment is preferred for nonpregnant patients aged 25 y or older. Colposcopy with biopsy is an acceptable option if desired by patient after shared decision-making. Considerations are described in footnote *e*. Note that if referring for treatment would delay diagnosis, colposcopy should be performed because up to 8% of patients with these results will have invasive cancer.

Figure 4. Risk Thresholds, Clinical Actions, and Example Patient Scenarios



This summarizes the principles of risk-based management of abnormal cervical cancer screening test results. Patients whose risk of currently having precancer is less than 4% do not require immediate intervention, whereas those whose risk is 4% or greater require immediate intervention with either colposcopy or treatment. Treatment in this case refers to proceeding directly to surgical excision of the lesion and transformation zone without first performing colposcopy with biopsy.

similar to the general screening population with a normal (negative for intraepithelial lesion or malignancy [NILM]) result on cytology-only screening (5-year CIN3+ risk, 0.15%-0.54). Patients should return in 1 year if their risks are between someone who qualifies for returning in 3 years and someone who requires colposcopy. Colposcopy is recommended for those whose immediate CIN3+ risk is 4% to 24%, which is approximately that of the general screening population with HPV-positive, low-grade cytological abnormalities (eg, HPV-positive atypical squamous cells of undetermined significance [ASC-US] or HPV-positive LSIL of unknown duration). Colposcopy or treatment with excision is recommended for those whose immediate CIN3+ risk is 25% to 59%, similar to that of the general screening population with HPV-positive high-grade cytology results (eg, HSIL or ASC cannot exclude HSIL [ASC-H]). For those with CIN3+ risks of 60% or higher (eg, HPV-16–positive HSIL), proceeding directly to treatment with excision (expedited treatment) is preferred over first performing colposcopy with biopsy, although performing colposcopy is an acceptable option. If treatment is not readily available, colposcopy should be performed to prevent diagnostic delay. Both current results and past history affect risk. Risks are 50% lower for HPV-positive low-grade cytological abnormalities when preceded by an HPV-negative test result or by a cytology and colposcopy confirming low-grade abnormalities compared with when prior screening results are not known.[49] Clinical decision support is available via the ASCCP Management Guidelines app or website (https://www.asccp.org/mobile-app), the Cervical Cancer Risk Assessor (cervicalrisk.com), and in the Table.

Colposcopic Examination

For patients with abnormal screening test results, colposcopy with biopsy is used to detect precancer, which is then treated to prevent the development of cancer. Colposcopy involves evaluation of the cervix by a trained clinician using magnification after application of 3% to 5% acetic acid. Transformed cells that become precancerous clones often form laterally spreading high-grade lesions that can be visible as acetowhite plaques on colposcopy (Figure 1). To reduce unnecessary procedures, new management guidelines recommend follow-up rather than colposcopy for lower-risk patients.[10] Therefore, a higher proportion of patients undergoing colposcopy will be diagnosed with precancer. Identification of abnormal cervical epithelium and ensuring targeted biopsies of all acetowhite areas at the time of colposcopy is important to avoid missing precancerous lesions.

Colposcopy Standards consensus guidelines were published in 2017 to improve the reliability and reproducibility of colposcopy in the US.[60] Guidelines include requirements for a comprehensive examination and describe risk-based biopsy recommendations.[61] In nonpregnant patients, biopsies should be performed in all acetowhite areas, typically 2 to 4 biopsies per patient. A greater number of biopsies is associated with improved CIN3+ detection, from approximately 60% for 1 biopsy to more than 80% for 2 to 4 biopsies.[62,63] However, biopsy may be deferred for low-risk patients, defined as cytology of NILM, ASC-US, or LSIL, no evidence of HPV-16 or -18 infection, and no visible abnormalities. In addition to biopsies of all acetowhite areas, sampling of the endocervical canal with endocervical curettage is recommended for high-grade cytology (ASC-H, HSIL, or AGC), HPV-16 or -18 infection, positive results on dual stain, following precancer treatment, during observation of CIN2, and when the squamocolumnar junction is not fully visualized; endocervical curettage is preferred for those aged 40 years or older.[64] During pregnancy, biopsies should be deferred unless there is concern for cancer, and endocervical curettage is contraindicated.[10]

Management of Biopsy Results

Colposcopic biopsy results are typically reported using the Bethesda system as CIN1, 2, 3 or using the Lower Anogenital

Squamous Terminology system as histologic LSIL or HSIL.[65,66] Histologic LSIL approximately corresponds to CIN1, and histologic HSIL to CIN2 and CIN3. Recent guidelines recommend specifying HSIL as CIN2 or CIN3 to improve risk prediction.[10] CIN3 is a more reproducible diagnosis than CIN2, with more than 80% agreement between expert pathologists on CIN3 diagnoses compared with less than 30% agreement on CIN2 diagnoses.[67] CIN3 is also more likely to be a histological correlate of cellular transformation with a substantial risk of progression to cancer and is often associated with highly carcinogenic HPV genotypes (Figure 2).[9,68] Treatment is recommended for all nonpregnant individuals with a diagnosis of CIN3, histologic HSIL, or AIS.[10]

Treatment is also recommended for nonpregnant patients with CIN2, although observation is an option for those concerned about future pregnancies because the effects of treatment on future pregnancy is unclear.[69,70] A meta-analysis indicated an 8.6% risk of preterm labor (<37 weeks' gestation) following excisional treatment compared with 4.6% in those with normal results. However, preterm labor rates were similar when treated women were compared with women with prior abnormal results without treatment, indicating that HPV infection, rather than treatment, may cause preterm delivery.[71] Compared with CIN3, CIN2 is more heterogenous, more often associated with lower-risk HPV genotypes, and may resolve spontaneously, especially among those younger than 30 years.[72] Prognosis varies by genotype. Among women younger than 30 years followed up for 2 years, HPV-16–associated CIN2 progressed to CIN3 in half of patients, compared with less than 20% progression for CIN2 associated with other HPV genotypes.[73] Shared decision-making discussions for patients considering observation should include pregnancy considerations, risk of progression, and need to undergo serial colposcopies with biopsies at 6-month intervals for up to 2 years.

Importantly, CIN1 (histologic LSIL), is a not an immediate cancer precursor, so observation is preferred to treatment.[10] The microscopic classification of CIN1 is neither a reliable nor an important modifier of the course of active HPV infection. In the past, treatment of persistent CIN1 was believed to prevent progression to CIN2 and CIN3. However, subsequent research showed that CIN1 can be caused by many genotypes of HPV, that repeated CIN1 is not necessarily indicative of viral persistence, and that only 8% progress to CIN3 over 2 years, making treatment unnecessary in most patients.[74,75]

Treatment and Prognosis

Treatment of precancer involves excision or destruction of the entire squamocolumnar junction in addition to destruction of lesions detected on colposcopy. Treatment aims to eliminate the majority of HPV-infected cells that have undergone precancerous transformation to reduce the risk of developing cervical cancer.[76] Most excisional treatments in the US are performed using electrocautery (eg, loop electrical excision procedure or large loop excision of the transformation zone), although cold knife cone may be used in some circumstances. Excisional procedures are preferred but ablation therapies are acceptable in current US guidelines.[10] However, ablation techniques including cryotherapy and thermal ablation are frequently used elsewhere and should follow the World Health Organization guidelines.[77]

The short-term risks of CIN3 recurrence following excision and ablation, respectively, are approximately 1.6% and 2.9% at 6 months, rising to 3.2% and 7.2% at 12 months.[76,78] The risk of invasive cancer remains elevated for decades following treatment for precancer[79,80] and particularly for those older than 50 years.[81] Therefore, guidelines recommend continued screening at 3-year intervals through age 65 years and for a minimum of 25 years after treatment with the option to continue for as long as the individual remains in good health.[10]

Cervical Cancer Disparities

In the US, hysterectomy-corrected cancer incidence is higher in Black women (16.8 per 100 000) and Hispanic women (15.8 per 100 000) than in White women (6.8 per 100 000),[32] and 5-year survival is lower for Black women (55.8%) than for White women (63.0%). More late-stage diagnoses have led to decreased survival over the past 20 years.[82] Disparities in access to screening, diagnostic, and treatment services exist related to race and ethnicity, socioeconomic status, insurance status, education, and rurality; these disparities contribute to higher cancer rates, later stages of diagnosis, and higher mortality.[83] Universal HPV vaccination and access to screening and treatment could eliminate disparities.[84,85] In the US, clinician-focused multilevel interventions that involved strong consistent recommendations prior to age 11 years increased HPV vaccination rates by more than 20 percentage points in safety net settings of care.[86-91] Mechanisms to address disparities in screening participation and management of abnormal results were outlined in the President's Cancer Panel report and included improved communication, facilitating equitable access to screening using community outreach, promoting alternative screening techniques like HPV self-sampling when available, supporting team-based care to support cancer screening and risk assessment, and effectively using clinical decision support to ensure that each patient receives appropriate care.[92] Specific programs with demonstrated effectiveness in at-risk populations include community-based outreach and patient navigation.[83] Adequate health insurance coverage is also critical—higher screening rates were noted following implementation of the Affordable Care Act and Medicaid expansion.[93]

Limitations

This review has several limitations. First, not all topics related to cervical cancer prevention were covered, such as 1-dose vaccination schedules. Second, quality of the included literature was not evaluated using a formal and systematic approach. Third, some new technologies in development were outside the scope of this review, including self-collected HPV testing. Fourth, the discussion of disparities was not comprehensive. Fifth, some relevant articles may have been missed.

Conclusions

Approximately 100 000 people are treated for cervical precancer each year in the US to prevent cervical cancer. People with a cervix should be screened with HPV testing, and if HPV-positive, genotyping and cytology testing should be performed to evaluate the risk of cervical precancer and determine the need for colposcopy or treatment. HPV vaccination in adolescence will likely prevent more than 90% of cervical precancers and cancers.

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REFERENCES

1. Cervix. Cancer Statistics Center. American Cancer Society. Accessed July 31, 2023. https://cancerstatisticscenter.cancer.org/?_ga=2.20975355.1746569515.1533055502-552426982.1496697483#!/cancer-site/Cervix

2. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *Int J Cancer*. 2012;131(10):2349-2359. doi:10.1002/ijc.27485

3. Mix JM, Van Dyne EA, Saraiya M, Hallowell BD, Thomas CC. Assessing impact of HPV vaccination on cervical cancer incidence among women aged 15-29 years in the United States, 1999-2017: an ecologic study. *Cancer Epidemiol Biomarkers Prev*. 2021;30(1):30-37. doi:10.1158/1055-9965.EPI-20-0846

4. Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med*. 2020;383(14):1340-1348. doi:10.1056/NEJMoa1917338

5. Benard VB, Jackson JE, Greek A, et al. A population study of screening history and diagnostic outcomes of women with invasive cervical cancer. *Cancer Med*. 2021;10(12):4127-4137. doi:10.1002/cam4.3951

6. Kirschner B, Poll S, Rygaard C, Wåhlin A, Junge J. Screening history in women with cervical cancer in a Danish population-based screening program. *Gynecol Oncol*. 2011;120(1):68-72. doi:10.1016/j.ygyno.2010.09.021

7. Lee YW, Morgan JR, Fiascone S, Perkins RB. Underscreening, overscreening, and guideline-adherent cervical cancer screening in a national cohort. *Gynecol Oncol*. 2022;162(2):181-188. doi:10.1016/j.ygyno.2022.09.012

8. Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. *Syst Rev*. 2013;2:35. doi:10.1186/2046-4053-2-35

9. Demarco M, Hyun N, Carter-Pokras O, et al. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. *EClinicalMedicine*. 2020;22:100293. doi:10.1016/j.eclinm.2020.100293

10. 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(2):102-131. doi:10.1097/LGT.0000000000000525

11. *Cervical Cancer Screening: IARC Handbooks of Cancer Prevention*. Vol 18. IARC Publications; 2022. Accessed December 23, 2022. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Cervical-Cancer-Screening-2022

12. Bouvard V, Wentzensen N, Mackie A, et al. The IARC perspective on cervical cancer screening. *N Engl J Med*. 2021;385(20):1908-1918. doi:10.1056/NEJMsr2030640

13. Reich O, Regauer S. Elimination of reserve cells for prevention of HPV-associated cervical cancer. *Virus Res*. 2023;329:199068. doi:10.1016/j.virusres.2023.199068

14. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007;370(9590):890-907. doi:10.1016/S0140-6736(07)61416-0

15. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 2017;141(4):664-670. doi:10.1002/ijc.30716

16. Mendoza RP, Haidary T, Gabutan E, et al. Mixed and nonvaccine high risk HPV types are associated with higher mortality in Black women with cervical cancer. *Sci Rep*. 2021;11(1):14064. doi:10.1038/s41598-021-93485-1

17. Porras C, Tsang SH, Herrero R, et al; Costa Rica Vaccine Trial Group. Efficacy of the bivalent HPV vaccine against HPV 16/18-associated precancer: long-term follow-up results from the Costa Rica Vaccine Trial. *Lancet Oncol*. 2020;21(12):1643-1652. doi:10.1016/S1470-2045(20)30524-6

18. Kjaer SK, Nygård M, Dillner J, et al. A 12-Year follow-up on the long-term effectiveness of the quadrivalent human papillomavirus vaccine in 4 Nordic countries. *Clin Infect Dis*. 2018;66(3):339-345. doi:10.1093/cid/cix797

19. Hammer A, Demarco M, Campos N, et al. A study of the risks of CIN3+ detection after multiple rounds of HPV testing: results of the 15-year cervical cancer screening experience at Kaiser Permanente Northern California. *Int J Cancer*. 2020;147(6):1612-1620. doi:10.1002/ijc.32950

20. Malagón T, Trottier H, El-Zein M, Villa LL, Franco EL; Ludwig-McGill Cohort Study. Human papillomavirus intermittence and risk factors associated with first detections and redetections in the Ludwig-McGill cohort study of adult women. *J Infect Dis*. 2023;jiad043. Published online February 15, 2023. doi:10.1093/infdis/jiad043

21. Sahasrabuddhe VV, Luhn P, Wentzensen N. Human papillomavirus and cervical cancer: biomarkers for improved prevention efforts. *Future Microbiol*. 2011;6(9):1083-1098. doi:10.2217/fmb.11.87

22. Clarke MA, Gradissimo A, Schiffman M, et al. Human papillomavirus DNA methylation as a biomarker for cervical precancer: consistency across 12 genotypes and potential impact on management of HPV-positive women. *Clin Cancer Res*. 2018;24(9):2194-2202. doi:10.1158/1078-0432.CCR-17-3251

23. Clarke MA, Wentzensen N, Mirabello L, et al. Human papillomavirus DNA methylation as a potential biomarker for cervical cancer. *Cancer Epidemiol Biomarkers Prev*. 2012;21(12):2125-2137. doi:10.1158/1055-9965.EPI-12-0905

24. Clarke MA, Cheung LC, Castle PE, et al. Five-year risk of cervical precancer following p16/Ki-67 dual-stain triage of HPV-positive women. *JAMA Oncol*. 2019;5(2):181-186. doi:10.1001/jamaoncol.2018.4270

25. Wentzensen N, Clarke MA, Bremer R, et al. Clinical evaluation of human papillomavirus screening with p16/Ki-67 dual stain triage in a large organized cervical cancer screening program. *JAMA Intern Med*. 2019;179(7):881-888. doi:10.1001/jamainternmed.2019.0306

26. Wright TC Jr, Stoler MH, Ranger-Moore J, et al. Clinical validation of p16/Ki-67 dual-stained cytology triage of HPV-positive women: results from the IMPACT trial. *Int J Cancer*. 2022;150(3):461-471. doi:10.1002/ijc.33812

27. Wentzensen N, Lahrmann B, Clarke MA, et al. Accuracy and efficiency of deep-learning-based automation of dual stain cytology in cervical cancer screening. *J Natl Cancer Inst*. 2021;113(1):72-79. doi:10.1093/jnci/djaa066

28. Nogueira-Rodrigues A, Ferreira CG, Bergmann A, de Aguiar SS, Thuler LCS. Comparison of adenocarcinoma (ACA) and squamous cell carcinoma (SCC) of the uterine cervix in a sub-optimally screened cohort: a population-based epidemiologic study of 51,842 women in Brazil. *Gynecol Oncol*. 2014;135(2):292-296. doi:10.1016/j.ygyno.2014.08.014

29. Castle PE, Kinney WK, Cheung LC, et al. Why does cervical cancer occur in a state-of-the-art screening program? *Gynecol Oncol*. 2017;146(3):546-553. doi:10.1016/j.ygyno.2017.06.003

30. Demarco M, Egemen D, Hyun N, et al. Contribution of etiologic cofactors to CIN3+ risk among women with human papillomavirus-positive screening test results. *J Low Genit Tract Dis*. 2022;26(2):127-134. doi:10.1097/LGT.0000000000000667

31. Saraiya M, Cheung LC, Soman A, et al. Risk of cervical precancer and cancer among uninsured and underserved women from 2009 to 2017. *Am J Obstet Gynecol*. 2021;224(4):366.e1-366.e32. doi:10.1016/j.ajog.2020.10.001

32. Cohen CM, Wentzensen N, Castle PE, et al. Racial and ethnic disparities in cervical cancer incidence, survival, and mortality by histologic subtype. *J Clin Oncol*. 2023;41(5):1059-1068. doi:10.1200/JCO.22.01424

33. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Centers for Disease Control and Prevention. Accessed October 10, 2022. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/human-0?view=full

34. Clarke MA, Fetterman B, Cheung LC, et al. Epidemiologic evidence that excess body weight increases risk of cervical cancer by decreased detection of precancer. *J Clin Oncol*. 2018;36(12):1184-1191. doi:10.1200/JCO.2017.75.3442

35. Wee CC, McCarthy EP, Davis RB, Phillips RS. Screening for cervical and breast cancer: is obesity an unrecognized barrier to preventive care? *Ann*

Intern Med. 2000;132(9):697-704. doi:10.7326/0003-4819-132-9-200005020-00003

36. Oliver SE, Unger ER, Lewis R, et al. Prevalence of human papillomavirus among females after vaccine introduction-national health and nutrition examination survey, United States, 2003-2014. *J Infect Dis*. 2017;216(5):594-603. doi:10.1093/infdis/jix244

37. McClung NM, Gargano JW, Park IU, et al; HPV-IMPACT Working Group. Estimated number of cases of high-grade cervical lesions diagnosed among women—United States, 2008 and 2016. *MMWR Morb Mortal Wkly Rep*. 2019;68(15):337-343. doi:10.15585/mmwr.mm6815a1

38. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee On Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68(32):698-702. doi:10.15585/mmwr.mm6832a3

39. Markowitz LE, Dunne EF, Saraiya M, et al; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63(RR-05):1-30.

40. Leval A, Herweijer E, Ploner A, et al. Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. *J Natl Cancer Inst*. 2013;105(7):469-474. doi:10.1093/jnci/djt032

41. Laprise JF, Chesson HW, Markowitz LE, et al. Effectiveness and cost-effectiveness of human papillomavirus vaccination through age 45 years in the United States. *Ann Intern Med*. 2020;172(1):22-29. doi:10.7326/M19-1182

42. Herweijer E, Sundström K, Ploner A, Uhnoo I, Sparén P, Arnheim-Dahlström L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: a population-based study. *Int J Cancer*. 2016;138(12):2867-2874. doi:10.1002/ijc.30035

43. Pingali C, Yankey D, Elam-Evans LD, et al. National vaccination coverage among adolescents aged 13-17 years—National Immunization Survey-Teen, United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(35):1101-1108. doi:10.15585/mmwr.mm7135a1

44. ACOG committee opinion no. 557: management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. *Obstet Gynecol*. 2013;121(4):891-896. doi:10.1097/01.AOG.0000428646.67925.9a

45. ASCCP clinical practice statement: evaluation of the cervix in patients with abnormal vaginal bleeding. Published online February 2017. Accessed July 20, 2023. https://www.asccp.org/Assets/9d92e617-858f-43f3-af62-44adf76cfc67/636220616039000000/vaginal-bleeding-statement-final-02-06-17-pdf

46. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;320(7):674-686. doi:10.1001/jama.2018.10897

47. Schiffman M, Kinney WK, Cheung LC, et al. Relative performance of HPV and cytology components of cotesting in cervical screening. *J Natl Cancer Inst*. 2018;110(5):501-508. doi:10.1093/jnci/djx225

48. Castle PE, Kinney WK, Xue X, et al. Effect of several negative rounds of human papillomavirus and cytology co-testing on safety against cervical cancer: an observational cohort study. *Ann Intern Med*. 2018;168(1):20-29. doi:10.7326/M17-1609

49. Egemen D, Cheung LC, Chen X, et al. Risk estimates supporting the 2019 ASCCP risk-based management consensus guidelines. *J Low Genit Tract Dis*. 2020;24(2):132-143. doi:10.1097/LGT.0000000000000529

50. Islami F, Fedewa SA, Jemal A. Trends in cervical cancer incidence rates by age, race/ethnicity, histological subtype, and stage at diagnosis in the United States. *Prev Med*. 2019;123:316-323. doi:10.1016/j.ypmed.2019.04.010

51. Fontham ETH, Wolf AMD, 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(5):321-346. doi:10.3322/caac.21628

52. Mills JM, Morgan JR, Dhaliwal A, Perkins RB. Eligibility for cervical cancer screening exit: comparison of a national and safety net cohort. *Gynecol Oncol*. 2021;162(2):308-314. doi:10.1016/j.ygyno.2021.05.035

53. Harper DM, Plegue M, Harmes KM, Jimbo M, SheinfeldGorin S. Three large scale surveys highlight the complexity of cervical cancer under-screening among women 45-65 years of age in the United States. *Prev Med*. 2020;130:105880. doi:10.1016/j.ypmed.2019.105880

54. Feldman S, Cook E, Davis M, et al. Cervical cancer incidence among elderly women in Massachusetts compared with younger women. *J Low Genit Tract Dis*. 2018;22(4):314-317. doi:10.1097/LGT.0000000000000435

55. Gravitt PE, Landy R, Schiffman M. How confident can we be in the current guidelines for exiting cervical screening? *Prev Med*. 2018;114:188-192. doi:10.1016/j.ypmed.2018.07.005

56. Castanon A, Green LI, Sasieni P. Impact of screening between the ages of 60 and 64 on cumulative rates of cervical cancer to age 84y by screening history at ages 50 to 59: a population-based case-control study. *Prev Med*. 2021;149:106625. doi:10.1016/j.ypmed.2021.106625

57. Dinkelspiel H, Fetterman B, Poitras N, et al. Screening history preceding a diagnosis of cervical cancer in women age 65 and older. *Gynecol Oncol*. 2012;126(2):203-206. doi:10.1016/j.ygyno.2012.04.037

58. Munshi VN, Perkins RB, Sy S, Kim JJ. Cost-effectiveness analysis of the 2019 American Society for Colposcopy and Cervical Pathology risk-based management consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Am J Obstet Gynecol*. 2022;226(2):228.e1-228.-e9. doi:10.1016/j.ajog.2021.09.012

59. Egemen D, Perkins RB, Clarke MA, et al; Enduring Consensus Cervical Cancer Screening and Management Committee. Risk-based cervical consensus guidelines: methods to determine management if less than 5 years of data are available. *J Low Genit Tract Dis*. 2022;26(3):195-201. doi:10.1097/LGT.0000000000000685

60. Wentzensen N, Schiffman M, Silver MI, et al. ASCCP colposcopy standards: risk-based colposcopy practice. *J Low Genit Tract Dis*. 2017;21(4):230-234. doi:10.1097/LGT.0000000000000334

61. Wentzensen N, Massad LS, Mayeaux EJ Jr, et al. Evidence-based consensus recommendations for colposcopy practice for cervical cancer prevention in the United States. *J Low Genit Tract Dis*. 2017;21(4):216-222. doi:10.1097/LGT.0000000000000322

62. Gage JC, Hanson VW, Abbey K, et al; ASCUS LSIL Triage Study (ALTS) Group. Number of cervical biopsies and sensitivity of colposcopy. *Obstet Gynecol*. 2006;108(2):264-272. doi:10.1097/01.AOG.0000220505.18525.85

63. Wentzensen N, Walker JL, Gold MA, et al. Multiple biopsies and detection of cervical cancer precursors at colposcopy. *J Clin Oncol*. 2015;33(1):83-89. doi:10.1200/JCO.2014.55.9948

64. Massad LS, Perkins RB, Naresh A, et al. Colposcopy standards: guidelines for endocervical curettage at colposcopy. *J Low Genit Tract Dis*. 2023;27(1):97-101. doi:10.1097/LGT.0000000000000710

65. Davey DD, Neal MH, Wilbur DC, Colgan TJ, Styer PE, Mody DR. Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med*. 2004;128(11):1224-1229. doi:10.5858/2004-128-1224-BIARRP

66. Darragh TM, Colgan TJ, Cox JT, et al; Members of LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis*. 2012;16(3):205-242. doi:10.1097/LGT.0b013e31825c31dd

67. Carreon JD, Sherman ME, Guillén D, et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3: results from a histological review of population-based cervical samples. *Int J Gynecol Pathol*. 2007;26(4):441-446. doi:10.1097/pgp.0b013e31805152ab

68. Demarco M, Egemen D, Raine-Bennett TR, et al. A study of partial human papillomavirus genotyping in support of the 2019 ASCCP risk-based management consensus guidelines. *J Low Genit Tract Dis*. 2020;24(2):144-147. doi:10.1097/LGT.0000000000000530

69. Werner CL, Lo JY, Heffernan T, Griffith WF, McIntire DD, Leveno KJ. Loop electrosurgical excision procedure and risk of preterm birth. *Obstet Gynecol*. 2010;115(3):605-608. doi:10.1097/AOG.0b013e3181d068a3

70. Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. *BJOG*. 2011;118(9):1031-1041. doi:10.1111/j.1471-0528.2011.02944.x

71. Conner SN, Frey HA, Cahill AG, Macones GA, Colditz GA, Tuuli MG. Loop electrosurgical excision procedure and risk of preterm birth: a systematic review and meta-analysis. *Obstet Gynecol*. 2014;123(4):752-761. doi:10.1097/AOG.0000000000000174

72. Tainio K, Athanasiou A, Tikkinen KAO, et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ*. 2018; 360:k499. doi:10.1136/bmj.k499

73. Kylebäck K, Ekeryd-Andalen A, Greppe C, Björkenfeldt Havel C, Zhang C, Strander B. Active expectancy as alternative to treatment for cervical intraepithelial neoplasia grade 2 in women aged 25 to 30 years: ExCIN2-a prospective clinical multicenter cohort study. *Am J Obstet Gynecol*. 2022;227(5):742.e1-742e11. doi:10.1016/j.ajog.2022.06.051

74. Loopik DL, Bentley HA, Eijgenraam MN, IntHout J, Bekkers RLM, Bentley JR. The natural history of cervical intraepithelial neoplasia grades 1, 2, and 3: a systematic review and meta-analysis. *J Low Genit Tract Dis*. 2021;25(3):221-231. doi:10.1097/LGT.0000000000000604

75. Greenberg MD, Reid R, Schiffman M, et al. A prospective study of biopsy-confirmed cervical intraepithelial neoplasia grade 1: colposcopic, cytological, and virological risk factors for progression. *J Low Genit Tract Dis*. 1999;3(2):104-110. doi:10.1097/00128360-199904000-00005

76. D'Alessandro P, Arduino B, Borgo M, et al. Loop electrosurgical excision procedure versus cryotherapy in the treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis of randomized controlled trials. *Gynecol Minim Invasive Ther*. 2018;7(4):145-151. doi:10.4103/GMIT.GMIT_56_18

77. WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia; 2011. Accessed December 2, 2019. World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/44776/9789241502856_eng.pdf;jsessionid=4E43B299F3AEAD2DA5FD62809C40F101?sequence=1

78. Papalia N, Rohla A, Tang S, Nation J, Nelson G. Defining the short-term disease recurrence after loop electrosurgical excision procedure (LEEP). *BMC Womens Health*. 2020;20(1):34. doi:10.1186/s12905-020-00901-1

79. Sand FL, Frederiksen K, Munk C, Jensen SM, Kjaer SK. Long-term risk of cervical cancer following conization of cervical intraepithelial neoplasia grade 3—a Danish nationwide cohort study. *Int J Cancer*. 2018;142(9):1759-1766. doi:10.1002/ijc.31202

80. Kalliala I, Anttila A, Pukkala E, Nieminen P. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. *BMJ*. 2005;331(7526):1183-1185. doi:10.1136/bmj.38663.459039.7C

81. Strander B, Hällgren J, Sparén P. Effect of ageing on cervical or vaginal cancer in Swedish women previously treated for cervical intraepithelial neoplasia grade 3: population based cohort study of long term incidence and mortality. *BMJ*. 2014;348:f7361. doi:10.1136/bmj.f7361

82. Matz M, Weir HK, Alkhalawi E, Coleman MP, Allemani C; US CONCORD Working Group. Disparities in cervical cancer survival in the United States by race and stage at diagnosis: an analysis of 138,883 women diagnosed between 2001 and 2014 (CONCORD-3). *Gynecol Oncol*. 2021;163(2):305-311. doi:10.1016/j.ygyno.2021.08.015

83. Perkins R, Mitchell E. Cervical cancer disparities. *J Natl Med Assoc*. 2023;115(2S):S19-S25.

84. Garland SM, Giuliano A, Brotherton J, et al; IPVS. IPVS statement moving towards elimination of cervical cancer as a public health problem. *Papillomavirus Res*. 2018;5:87-88. doi:10.1016/j.pvr.2018.02.003

85. Gultekin M, Ramirez PT, Broutet N, Hutubessy R. World Health Organization call for action to eliminate cervical cancer globally. *Int J Gynecol Cancer*. 2020;30(4):426-427. doi:10.1136/ijgc-2020-001285

86. Perkins RB, Foley S, Hassan A, et al. Impact of a multilevel quality improvement intervention using national partnerships on human papillomavirus vaccination rates. *Acad Pediatr*. 2021;21(7):1134-1141. doi:10.1016/j.acap.2021.05.018

87. Fisher-Borne M, Preiss AJ, Black M, Roberts K, Saslow D. Early outcomes of a multilevel human papillomavirus vaccination pilot intervention in federally qualified health centers. *Acad Pediatr*. 2018;18(2S):S79-S84. doi:10.1016/j.acap.2017.11.001

88. Casey SM, Jansen E, Drainoni ML, Schuch TJ, Leschly KS, Perkins RB. Long-term multilevel intervention impact on human papillomavirus vaccination rates spanning the COVID-19 pandemic. *J Low Genit Tract Dis*. 2022;26(1):13-19. doi:10.1097/LGT.0000000000000648

89. Perkins RB, Legler A, Jansen E, et al. Improving HPV vaccination rates: a stepped-wedge randomized trial. *Pediatrics*. 2020;146(1):e20192737. doi:10.1542/peds.2019-2737

90. Brewer NT, Hall ME, Malo TL, Gilkey MB, Quinn B, Lathren C. Announcements versus conversations to improve HPV vaccination coverage: a randomized trial. *Pediatrics*. 2017;139(1):e20161764. doi:10.1542/peds.2016-1764

91. Efua Sackey M, Markey K, Grealish A. Healthcare professional's promotional strategies in improving human papillomavirus (HPV) vaccination uptake in adolescents: A systematic review. *Vaccine*. 2022;40(19):2656-2666. doi:10.1016/j.vaccine.2022.03.054

92. Closing gaps in cancer screening: connecting people, communities, and systems to improve equity and access. cervical cancer companion brief. Presidents Cancer Panel. February 2022. Accessed April 15, 2022. https://prescancerpanel.cancer.gov/report/cancerscreening/pdf/PresCancerPanel_CancerScreening_CB_Cervical_Feb2022.pdf

93. Huguet N, Angier H, Rdesinski R, et al. Cervical and colorectal cancer screening prevalence before and after Affordable Care Act Medicaid expansion. *Prev Med*. 2019;124:91-97. doi:10.1016/j.ypmed.2019.05.003