

Screening for Cervical Cancer

Clinical Recommendations

The Women's Preventive Services Initiative recommends cervical cancer screening for average-risk women aged 21 to 65 years. For women aged 21 to 29 years, the Women's Preventive Services Initiative recommends cervical cancer screening using cervical cytology (Pap test) every 3 years. Co-testing with cytology and human papillomavirus testing is not recommended for women younger than 30 years. Women aged 30 to 65 years should be screened with cytology and human papillomavirus testing every 5 years or cytology alone every 3 years.

Implementation Considerations

The Women's Preventive Services Initiative recommends as a preventive service, cervical cancer screening for average-risk women aged 21 to 65 years. For average-risk women aged 30 to 65 years, informed shared decision-making between the patient and her clinician regarding the preferred screening strategy is recommended. Women who are at average risk should not be screened more than once every 3 years.

Women who have received the human papillomavirus vaccine should be screened according to the same guidelines as women who have not received the vaccine.

These recommendations are for routine screening in average-risk women and do not apply to women infected with human immunodeficiency virus, women who are immunocompromised because of another etiology (such as those who have received solid organ transplantation), women exposed to diethylstilbestrol in utero, or women treated for cervical intraepithelial neoplasia grade 2 or higher within the past 20 years. Screening strategies for high-risk women are outside the scope of these recommendations.

Cervical cancer screening is not recommended for women younger than 21 years or those older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. Adequate prior negative screening is defined as documentation (or a reliable patient report) of three consecutive negative cytology results or two consecutive negative co-test results within the previous 10 years with the most recent test within the past 5 years. Cervical cancer screening is also not recommended for women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesions (e.g., cervical intraepithelial neoplasia grade 2 or grade 3 or cervical cancer within the past 20 years).

EVIDENCE MAP

- Cervical cancer screening for average-risk women aged 21 to 65 years.
- For women aged 21 to 29 years, screening using cervical cytology (Pap test) every 3 years.
- Co-testing with cytology and human papillomavirus testing is not recommended for women younger than 30 years.

Systematic Reviews	Additional Studies	USPSTF ¹
<p>Cytology alone in younger women supported by:</p> <ul style="list-style-type: none"> • USPSTF review of epidemiologic and observational study data.¹ • USPSTF modeling study.² 	<p>Co-testing not recommended in younger women supported by:</p> <ul style="list-style-type: none"> • One diagnostic accuracy study.³ • One RCT.⁴ • USPSTF modeling study.² 	<p>USPSTF⁵: The USPSTF recommends screening for cervical cancer in women age 21-65 years with cytology (Pap smear) every 3 years or, for women age 30-65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years.</p>

Women aged 30 to 65 years should be screened with cytology and human papillomavirus testing every 5 years or cytology alone every 3 years.

Systematic Reviews	Additional Studies	USPSTF ¹
<p>Similar or greater detection of CIN2/3+ and cancer for co-testing versus cytology supported by:</p> <ul style="list-style-type: none"> • 2011 USPSTF review of 4 RCTs.^{1,6} Updated meta-analysis of 4 RCTs from • 2014 USPSTF review.⁷ 	<ul style="list-style-type: none"> • Similar or greater detection of CIN2/3+ and cancer for co-testing versus cytology supported by: USPSTF modeling study;² 4 RCTs updated from USPSTF review;⁸ 1 observational study.⁹ • Improved detection of adenocarcinoma using co-testing versus cytology demonstrated in 4 RCTs updated from USPSTF review.⁸ • Negative HPV test is more predictive of normal results in future screening rounds than negative cytology, supporting extended screening intervals with co-testing, supported by follow-up of 1 RCT¹⁰ and 1 observational study.^{9,11} 	<p>USPSTF: see above</p>

Evidence map continued on page 61.

Evidence Summary: Screening for Cervical Cancer

Cervical cancer screening is not recommended for women younger than 21 years or those older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.

Systematic Reviews	Additional Studies	USPSTF ¹
<p>Start and stop ages for cervical cancer screening:</p> <ul style="list-style-type: none"> • 2011 USPSTF review based on SEER and observational study data¹ supports starting age. • Stop age was not systematically reviewed in 2012 USPSTF review, but recommendation was based on 12 observational¹²⁻²² studies from 2002 USPSTF review²³ and epidemiologic and observational study data identified during the 2012 USPSTF review that supported prior findings. • Screening in women with a hysterectomy: USPSTF recommendation was based on 2 observational studies²⁴⁻²⁵ from the 2002 USPSTF review.²³ 	<ul style="list-style-type: none"> • USPSTF modeling study.² • 4 observational studies.^{11,26-28} 	<p>USPSTF: see page 70.</p>

Women who have received the HPV vaccine should be screened according to the same guidelines as women who have not been vaccinated.

Systematic Reviews	Additional Studies	USPSTF ¹
<p>None</p>	<p>None</p>	<p>USPSTF⁵: Clinical considerations note that current trials do not provide data on long-term efficacy; therefore, the possibility that vaccination might reduce the need for screening with cytology alone or in combination with HPV testing is not established. Given these uncertainties, women who have been vaccinated should continue to be screened.</p>

Abbreviations: ACA=Affordable Care Act, HPV=human papilloma virus, USPSTF=U.S. Preventive Services Task Force.

SUMMARY OF EVIDENCE

Introduction

Invasive cervical neoplasia is caused by persistent infection with high-risk strains of human papilloma virus (HPV) that lead to the development of squamous cell carcinoma and adenocarcinoma of the uterine cervix.^{29,30} HPV is the most common sexually transmitted infection in the United States with approximately 79 million currently infected individuals.³¹ Each year, an estimated 14 million individuals are newly infected.³¹ HPV infections are typically self-limited,³² asymptomatic, and not diagnosed.³³ The 10-year risk for development of cancer precursor lesions ranges from 13% to 17%,³⁴ while the risk of progression from precancerous lesions to invasive disease is 31% over 30 years.³⁵

Periodic screening of sexually active women with cytology-based techniques has long been the standard of care for early cancer detection. In recent years, the introduction of testing for high-risk HPV DNA has allowed the detection of viral strains most commonly associated with the development of cancer even when cytology results are negative.^{9,30,34,36,37}

Current Recommendations and Coverage of Service

The gap in services provided under the provisions of the Patient Protection and Affordable Health Care Act of 2010 (ACA) previously identified by the Institute of Medicine (IOM) Committee was the absence of coverage for co-testing with cytology and high-risk HPV DNA testing among women age 30 years and older (**Table 1**). In 2012, the U.S. Preventive Services Task Force (USPSTF) issued new recommendations for women age 30 to 65 years that included screening with a combination of cytology and HPV testing every 5 years. The USPSTF is currently updating this recommendation including an evaluation of the effectiveness and harms of HPV testing with or without cytology as a primary screening strategy.



Table 1. Summary of Recommendations Currently Covered by the Affordable Care Act

IOM Committee ³⁸	Addition of high-risk HPV DNA testing to cytology testing in women with normal cytology results. Screening should begin at 30 years of age and should occur no more frequently than every 3 years.
USPSTF ⁵	<p>Screening for cervical cancer in women age 21 to 65 years with cytology every 3 years or, for women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every 5 years (Level A 2012).</p> <p>Recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women age <30 years; screening women age <21 years; screening women age >65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer; screening women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer (Level D 2012).</p> <p>Clinical considerations: Current trials do not provide data on long-term efficacy; therefore, the possibility that vaccination might reduce the need for screening with cytology alone or in combination with HPV testing is not established. Given these uncertainties, women who have been vaccinated should continue to be screened</p>

Abbreviations: CIN=cervical intraepithelial neoplasia; HPV=human papilloma virus; IOM=Institute of Medicine; USPSTF=U.S. Preventive Services Task Force



Background

In 2012, cervical cancer was diagnosed in 12,042 women and caused 4,074 deaths in the United States.³⁹ Cervical cancer diagnosis was most frequent in women age 35 to 44 years (median 49 years) and deaths were most common among those age 45 to 54 years (median 57 years).⁴⁰ Although mortality from cervical cancer has generally declined since the introduction of screening programs in the 1950s, women with poor access to care and women of color continue to share a disproportionate burden of incidence and mortality. Among new cervical cancer cases in 2012, black and Hispanic³¹ women experienced incidence rates of 9.0 and 9.5 per 100,000, respectively, compared with 7.1 per 100,000 among white women;³⁹ death rates were 3.7 and 2.7 versus 2.1 per 100,000.³⁹

Although deaths from cervical cancer are less common than deaths from other types of cancer,⁴¹ they are mostly preventable through primary prevention, screening, and treatment.⁴² In 2010, the overall cervical cancer screening rate among American women was 83%,⁴³ although rates were lower among Asians (75%), American Indians/Alaska Natives (79%), and Hispanics (79%), as well as women without access to health care (64%). More than half of cervical cancer cases occur among women who had no cytology testing during the months preceding diagnosis, with the remainder attributed to failure of detection and follow-up.^{44,45} Healthy People 2020 contains objectives for increasing the proportion of women in the United States age 21 to 65 years who receive cervical cancer screening by 10% so that 93% of women are screened.⁴⁶

Traditionally, screening used cytology-based methods alone including either conventional dry slide or liquid-based platforms. In the United States, liquid-based cytology accounts for more than 90% of cytology testing,⁴⁷ offering improved sample quality compared with conventional cytology, though test characteristics are generally comparable.^{6,48-52} The most notable advantage of liquid-based cytology is that it allows both cytology and high-risk HPV testing on a single patient specimen. There are currently two U.S. Food and Drug Administration (FDA) approved liquid-based platforms for cervical cancer screening: the SurePath Pap and the ThinPrep Pap Test.

Co-testing for high-risk HPV types is an option for women between ages 30 and 65 years who wish to extend their screening interval from 3 to 5 years. FDA-approved HPV tests include the Digene HC2, the Cervista, the cobas 4800 HPV test,⁵³ and the APTIMA HPV Assay. In 2012, a survey by the College of American Pathologists found that 60% of U.S. laboratories were performing co-testing.⁵⁴ In 2014, the FDA approved the cobas HPV test to be used as a primary screening tool for cervical cancer in addition to its use in co-testing with cytology.^{55,56} This decision was based on findings from a large U.S. study⁵⁷ that found the HPV test to have equivalent or superior effectiveness compared with cytology for primary cervical cancer screening.⁵⁶

The HPV vaccine is an effective method for preventing infection with HPV. Two HPV vaccines are licensed in the United States.⁵³ HPV4 is a quadrivalent vaccine (HPV 16, 18, 6, 11) licensed for use in males and females and HPV2 (HPV 16, 18) is a bivalent vaccine licensed for use in females. These vaccines are composed of virus-like particles prepared from a capsid protein of targeted HPV strains. Vaccines are prophylactic and do not have any therapeutic effect on HPV-related disease or disease progression in those already infected with HPV. The HPV

vaccination is covered in the ACA under a separate recommendation for immunizations.⁵⁸ Currently, practice standards recommend screening women who have had an HPV vaccine under the same guidelines as women who have not been vaccinated.

Current practice recommendations from professional organizations are similar to the USPSTF and advise cytology alone or co-testing (**Table 2**).

Table 2. Recommendations of Professional Organization

American College of Obstetricians and Gynecologists (ACOG) 2012, ⁵⁹ American Cancer Society (ACS) 2012, American Society for Clinical Pathology (ASCP) 2012, and American Society for Colposcopy and Cervical Pathology (ASCCP) 2012 ⁶⁰ , American College of Physicians (ACP), National Comprehensive Cancer Network (NCCN) ^{61,62}	
Start and Stop	Age 21 to 65 years of age*
Cytology	Age 21 to 65 years every 3 years
Cytology and HPV test together	Age 30 to 65 years every 5 years is preferred (ACP does not specify preference); HPV testing not recommended in women age < 30 years
Post-hysterectomy	Recommend against screening in women with a hysterectomy for benign disease that included removal of the cervix
HPV vaccinated women	Follow age-specific recommendations (same as unvaccinated women)

*Discontinuation of screening is based on an adequate screening history in women who are not otherwise at high risk for cervical cancer. Adequate screening history is defined as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years before cessation of screening, with the most recent test occurring within 5 years.

Abbreviations: HPV=human papilloma virus

Expert representatives from multiple advisory groups, including ACOG, ACS, ASCCP, and the ASCP recently convened to provide interim guidance on the use of HPV testing alone for cervical cancer screening. Based on a study that demonstrated equivalent or superior performance of primary HPV screening for detecting lesions compared with cytology alone, the interim advisory panel suggested that HPV alone could be considered as an alternative to current U.S.-based cervical cancer screening methods.⁶³ However, this option has not been incorporated into current recommendations.

UPDATE OF EVIDENCE

The 2012 USPSTF recommendation was based on a systematic review of the evidence of liquid-based cytology and high-risk HPV screening. This review included studies meeting criteria for fair and good-quality and focused on routine screening in populations in developed countries.¹⁶ In addition, the USPSTF commissioned a decision analysis modeling study to evaluate optimal ages at which to begin and end screening, optimal screening intervals, and benefits and harms of different screening strategies.

Ages to Start and Stop Screening; Screening Intervals

USPSTF systematic review and decision analysis

Data are lacking regarding the effectiveness of screening at specific ages and intervals. Indirect evidence includes data on the incidence, prevalence, and mortality of cervical cancer. Based on Surveillance, Epidemiology, and End Results Program (SEER) data from 2009 to 2013, 0.1% of all incident cervical cancer occurred in women younger than age 20 years⁴⁰ and there were no reported deaths in this age group. Five observational studies⁶⁴⁻⁶⁹ from the United Kingdom, United States, and Iceland suggested that high-risk HPV infections and cytological abnormalities were common and self-limited in women under age 20 years, whereas CIN3+ was less common in this group compared with women older than 25 years. Generally, in these studies, screening in younger women resulted in lower detection rates and higher false positive rates than screening in older women, and did not result in decreased incidence of cervical cancer.

Modeling studies demonstrated no advantage to screening prior to age 21 years,² with women in this age group experiencing the largest number of false positive test results (960 at age 20 years to 1003 at age 15 years with annual screening), and the lowest number of expected cancer cases (<3 per 1000 women). With each successive year that screening was delayed beyond age 21 years, the number of false positive test results declined and expected cancer cases increased. In modeling studies, screening every 5 years from age 21 years was associated with a difference in cancer mortality of 2.4 per 1000 women and cancer incidence of 10.2 per 1000 women compared with screening every year. Screening each year was associated with almost four times the number of colposcopies compared with screening every 5 years. Strategies that screen women every 3 to 5 years starting in their 20s were more efficient than annual screening during the teen years. A strategy of screening beginning at age 21 and repeated every 3 years was identified as particularly efficient.²

The age to stop screening was not systematically addressed by the 2012 USPSTF review because a prior review undertaken in 2002 found limited evidence based on 12 observational studies¹²⁻²² regarding the benefits of screening women older than age 65 years.²³ In particular, the 2002 systematic review noted that the incidence and prevalence of CIN tends to decrease with age, cervical cancer in older women is not more aggressive or progressive than in younger women, and that rates of high-grade intraepithelial lesions (HSIL) are low among older women who have been screened. Though not systematically addressed, evidence from the 2012 USPSTF systematic review confirmed reduced rates of abnormal cytology and detection of CIN3+ cases as women age and with subsequent screening.^{65,66,70,71}

In addition, the recommended age to stop screening was supported by epidemiological data and modeling studies. SEER data from 2009 to 2013 indicate that the median age at diagnosis of cervical cancer was 49 years⁴⁰ and incidence declined during the fourth decade. Modeling studies showed that in women with adequate screening histories, changing the age at which to end screening from 65 to 95 years by 5-year intervals resulted in less than 1 life-year improvement after age 65 years, but substantially increased harms related to false positive tests and increased number of colposcopies and cervical biopsies.² An adequate screening history was defined as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years prior to stopping screening, with the most recent test being within 5 years. However, in women who have never

been screened or have had inadequate screening, screening past age 65 years was shown to have a mortality advantage. In modeling studies, strategies that involved screening women who had never been screened every 2 to 5 years starting at age 65 years and ending at age 70 to 75 years demonstrated a balanced tradeoff between benefits and harms.²

Overall, the USPSTF-commissioned modeling study found that a strategy of screening with cytology every 3 years prior to age 30 and then co-testing every 5 years was associated with fewer colposcopies (575 vs. 1083 per 1000), cancers (7.44 vs. 8.50 per 1000), and cancer deaths (1.35 vs. 1.55 per 1000) compared with cytology screening every 3 years from age 21 years.² In this model, data were limited to HPV DNA testing using one HPV testing platform (HC2) and the effect of vaccination was not accounted for.

Relevant studies published since the USPSTF systematic review

A large U.S. cohort study of health plan enrollees (Kaiser Permanente Northern California cohort) that estimated the 5-year risk of CIN₃⁺ results in women age 21 to 24 years found very low risks of cervical cancer.⁷² In addition, a positive cytology test result predicted low CIN₃⁺ risk except in 0.6% of results that were high grade.⁷² The more common HPV positive/ASC-US and low-grade squamous intraepithelial lesion (LSIL) results in women age 21 to 24 years in this study predicted CIN₃⁺ risks similar to ASC-US in women age 30 to 64 years, for which a 6- to 12-month return visit is recommended. Further, the 5-year risk (4.4%) of these women did not reach the 5.2% implicit threshold for colposcopy, supporting repeat testing. In those with HPV-negative/ASC-US and Pap-negative results, CIN₃⁺ risks were similar to cytology alone in women age 30 to 64 years, for which a 3-year return visit is recommended.

Similarly, an observational study used national screening data from England and Wales to compare 3-yearly screening in 100,000 women starting at age 20 versus 25 years. Results indicated that starting at age 20 would lead to an estimated excess of 119,000 screens, 20,000 non-negative test results, over 8,000 referrals to colposcopy, and nearly 3,000 women treated with potentially 1.3 additional cancers detected per 100,000 women.²⁶ Based on these data, between 12,500 and 40,000 additional women would be screened, and between 300 and 900 treated for CIN to prevent one invasive cancer.

Studies of screening older women are based on observational studies of screened versus unscreened or inadequately screened women. A review of screening histories of Kaiser Permanente Northern California enrollees aged 65 years and older who were diagnosed with cervical cancer found few cancers in this age group, and most cancers were diagnosed in women who were inadequately screened previously (i.e., not meeting criteria of 3 consecutive negative cytology tests or a single co-test).²⁷ In a case-control study conducted in the United Kingdom, women with adequate negative screening at age 65 years had the lowest risk of cervical cancer (8 cancers per 10,000 women 20-year risk) compared with those not screened at age 50 to 64 years (49 cancers per 10 000 women 20-year risk).²⁸ Screening at least every 5.5 years between the ages of 50 to 64 years was associated with a 75% lower risk of cervical cancer between ages 65 to 79 years compared with not screening. In this study, adequate screening was defined as at least three tests at age 50 to 64 years with at least one between ages 60 to 64 years, the last three of which were negative, and no HSIL or worse since age of 50 years. Regular

screening was associated with low risk of cervical cancer until age 75 years, and by age 80 years, the risk in adequately screened women was half that of unscreened women.

A case-control study from two U.S. health plans that investigated the screening histories of women age 55 to 79 years who had died from cervical cancer found that cytology screening 5 to 7 years prior to diagnosis was associated with a 74% reduction in cervical cancer death (odds ratio 0.26; 95% CI, 0.10 to 0.63) after adjustment for covariates (smoking, marital status, race/ethnicity).⁷³ This study estimated that 630 deaths would be averted annually by screening all women age 55 to 79 years in the United States, though estimates were based on small numbers of cases. A second study of the same two U.S. health plans that included women age 55 to 79 years who were diagnosed with invasive cervical cancer found that cytological screening approximately 1 year prior to the occult invasive phase of cervical cancer was associated with a 75% to 77% reduction in the risk of invasive cervical cancer.⁷⁴ In this study, incidence remained low for several years following a negative screen, returning to the incidence of unscreened women after 5 to 7 years.

HPV Testing in Combination with Cytology

USPSTF systematic review and decision analysis

Four fair-quality randomized controlled trials comparing combination HPV (co-testing) versus cytology alone were included in the USPSTF review.^{1,6} Trials included women from national screening programs in Italy (NTCC Phase 1),⁴ the United Kingdom (ARTISTIC),⁷⁵ Sweden (Swedescreen),⁷⁶ and the Netherlands (POBASCAM)⁷⁷ enrolling more than 127, 000 women age 20 to 64 years. Colposcopy referral thresholds, follow-up duration, and completeness varied between trials, limiting data on harms and complete ascertainment of outcomes.

Among women age 30 years or older, round-specific screening resulted in relatively more CIN₂₊ lesions detected with co-testing compared with cytology alone after round 1, less CIN₃₊ detected after round 2, and fewer cancer cases in the co-testing compared with the cytology group. Cumulative CIN₃₊ detection was similar between co-testing and cytology alone after two screening rounds in all trials. Cumulative invasive cancer detection was similar, or just slightly higher, for cytology alone versus co-testing in three of four trials.^{4,76,77} Only the NTCC trial found a relative increase in any cumulative CIN measure after co-testing, with increased CIN₂₊ and CIN₃₊ detection after one screening round and cumulative detection of CIN₂₊ overall.⁴ However, this trial used a lower threshold for colposcopy referral, increasing sensitivity of the primary test.

An observational study of the Kaiser Permanente Northern California cohort compared co-testing to cytology alone among 330,000 women and found that cumulative 5-year incidence of cervical cancer was lower in the HPV-negative and cytology-negative group versus the cytology-negative group alone (3.2 per 100,000 vs. 7.5 per 100,000).⁹ Detection of CIN₃₊ was also higher in earlier screening rounds with co-testing versus cytology alone in this study.

Modeling studies supported similar benefits of co-testing every 5 years or cytology every 3 years (7.44 vs. 8.50

cancer cases and 1.35 vs. 1.55 deaths, respectively), though the preferred strategy would incorporate 3-yearly cytology screening under age 30 and then co-testing after age 30 to limit the number of colposcopies.²

In a trial of co-testing (NTCC Phase 1)⁴ that included younger women, CIN₂₊ detection was increased in a substantial number of women under the age of 35 years during the first round and cumulatively. However, younger women who tested positive in this study were not referred to immediate colposcopy like their older counterparts and were instead retested. This difference in testing protocol led to differential loss to follow-up between the study arms. Also, no cumulative data on colposcopy were provided by the study.

Harms of co-testing were difficult to assess because of incomplete reporting of outcomes and varying approaches to abnormal results in studies. However, approaches to management of abnormal screening results in these studies generally differed from U.S. recommendations, limiting their clinical applicability. In four diagnostic accuracy studies,^{3,7,8-80} co-testing was generally more sensitive, but less specific than cytology alone, though these data were limited by different thresholds for positivity across studies.

In study of test performance for co-testing in younger women,³ co-testing (64.0%) was less sensitive for CIN₃₊ than HPV (92.5%) but not cytology (65.4%) testing alone. Specificity was higher with co-testing (87.6%) than with cytology (81.5%) and HPV testing alone (70.1%).

Relevant studies published since the USPSTF systematic review

A meta-analysis of four European randomized controlled trials included in the USPSTF review that compared co-testing with cytology alone for the detection of high grade CIN lesions and cancer (ARTISTIC, NTCC Phase 1, POBASCAM, Swedescreen) found that co-testing at baseline was associated with significantly higher detection of CIN₂₊ (RR 1.41, 95% confidence interval [CI] 1.12 to 1.76) and non-significantly higher detection of CIN₃₊ (RR 1.15, 95% CI 0.99 to 1.33).⁷ At the second round, co-testing was associated with significantly lower detection rates of both CIN₂₊ and CIN₃₊ (RR 0.77, 95% CI 0.63 to 0.96; RR 0.68, 95% CI 0.55 to 0.85; respectively). Overall detection rates did not differ between testing strategies for CIN₂₊ or CIN₃₊.

A follow-up study of the four European trials that followed more than 176,000 women age 20 to 64 years over a median of 6.5 years indicated reduced invasive cancer (rate ratio 0.60, 95% CI 0.40 to 0.89).⁸ Detection was similar between screening strategies for the first 2.5 years, but was lower among women who had subsequent co-testing (RR 0.45, 95% CI 0.25 to 0.81). Also, the cumulative incidence of invasive cervical cancer was lower with negative entry tests among those who were co-tested compared with cytology alone (4.6 per 100,000 vs. 7.9 at 3.5 years; 8.7 per 100,000 vs. 36.0 at 5.5 years). Rate ratios were generally lower for adenocarcinoma than squamous-cell carcinoma and lowest among women age 30 to 34 years.

An extended follow-up study of the ARTISTIC trial found that a negative HPV test was significantly more predictive of normal results than a negative cytology result over 3 rounds, adding support to extended screening intervals with co-testing.¹⁰ The Kaiser Northern California cohort study reported similar results that indicated the 5-year CIN₃₊ risk for women with HPV-negative/cytology-negative results was 0.08% (95% CI 0.07% to 0.09%), which is less than the 3-year CIN₃₊ risk for cytology-negative results of 0.16% in this population.¹¹

HPV Testing Compared with Cytology

USPSTF Systematic Review and Decision Analysis

The USPSTF review^{1,6} included six^{3,78-82} fair- and good-quality diagnostic accuracy studies that found 1-time HPV testing was more sensitive, but less specific than cytology, with HPV testing sensitivity ranging from 86% to 97% for CIN₃+ outcomes and 63% to 98% for CIN₂+ outcomes versus 46% to 50% and 38% to 65%, respectively for cytology. Specificity for these outcomes was 3 to 5 percentage points less using HPV testing compared with cytology. One large fair-quality Italian randomized controlled trial (NTCC Phase 2)⁸³ that compared first round screening with HPV to cytology found increased detection of CIN₃+ cancer in women screened with HPV alone compared with cytology, and equivalent numbers of invasive cancers detected in both arms. When invasive cancer cases from HPV testing alone were combined with cases from HPV co-testing strategies from an earlier trial, the cumulative incidence of invasive cancer was lower compared with cytology in women age 35 years and older. However, this finding is based on pooling non-comparable screening strategies.

Assessment of harms from trial data was limited because women with positive HPV results or ASC-US on cytology were immediately referred to colposcopy, resulting in more colposcopies among women screened with the more sensitive HPV test compared with cytology (5.8% vs. 2.5%). This strategy would not be applicable to U.S. women who would have been referred for repeat testing prior to colposcopy. Also, determination of harms was generally limited by incomplete reporting, use of different screening strategies in different rounds of the trial (cytology alone was done in both arms of round 2), and differing referral criteria. Four fair-quality observational studies⁸⁴⁻⁸⁷ found that women who tested positive for HPV had increased immediate anxiety and distress compared with women who tested negative, but this difference had resolved by 6 months.

In women younger than 30 or 35 years, results were similar to those in older women, but they had higher rates of colposcopy referrals after HPV testing.^{4,75,83,88-99} One study that provided test characteristics of HPV and cytology testing in younger women showed that HPV test sensitivity for CIN₃+ and CIN₂+ was 23% to 27% higher than cytology, but specificity of HPV testing was reduced to a much greater degree in younger women compared with older women (about 11%).³

Relevant studies published since the USPSTF systematic review

In April 2014, the FDA approved the cobas HPV test for primary cervical cancer screening on the basis of findings from a large U.S. study (ATHENA)⁵⁷ that found it to have equivalent or superior performance for detecting lesions compared with cytology alone. The ATHENA study enrolled 42,000 women age 25 years and older who had cytology and HPV testing. Women without CIN₂+ findings were entered into a 3-year follow-up phase to compare three screening strategies: cytology with HPV testing only for ASC-US (cytology); cytology in women under age 30 years followed by co-testing in women 30 years and older (hybrid); and HPV testing in women 25 years and older (HPV primary).

At follow-up, the 3-year cumulative incidence rate of CIN₃+ cases in cytology negative women was 0.8% (95% CI, 0.5% to 1.1%) compared with 0.3% (95% CI, 0.1% to 0.7%) in HPV-negative women, and 0.3% (95% CI, 0.1% to 0.6%) in women who were negative for both tests. Cytology was less sensitive (47.8%) for the detection

of CIN₃+ cases versus HPV primary testing (76.1%) and the hybrid strategy (61.7%), but was more specific (specificity of 97.1%, 94.6%, and 93.5% for cytology, hybrid strategy, and HPV primary testing, respectively). Overall, the HPV primary screening strategy resulted in increased detection of CIN₃+ cases compared with other strategies, but also resulted in more colposcopies, though the number of colposcopies needed to detect a single case of CIN₃+ was similar to that for the hybrid strategy.

A follow-up study from the Kaiser cohort⁹ evaluated the effectiveness of primary HPV testing every 3 years compared with primary Pap testing every 3 years or concurrent Pap and HPV testing (co-testing) every 5 years.¹⁰⁰ This study included data from 1,037,021 women age 30 to 64 who underwent screening at approximately 3-year intervals using co-testing with Pap and high risk HPV testing. Estimation of 3-year risks of cancer and CIN₃+ or worse following a negative HPV result were lower than 3-year risks following a negative Pap result (CIN₃+ = 0.069% vs 0.19%, $P < 0.0001$; cancer = 0.011% vs 0.020%, $P < 0.0001$) and 5-year risks following an HPV negative/Pap negative co-test (CIN₃+ = 0.069% vs 0.11%, $P < 0.0001$; cancer = 0.011% vs 0.014%, $P = 0.21$).

CONCLUSIONS

Pap tests are effective in identifying abnormal cervical cytology for women age 21 to 29 years, and co-testing with HPV DNA tests in conjunction with cervical cytology are effective for women age 30 to 65. Research supports preferred screening intervals of 3 years for women age 21 to 65 years using cytology alone (Pap test); and every 5 years for women age 30 to 65 years using cytology and HPV DNA testing (co-testing). Data are lacking on the effectiveness of primary HPV testing. Further research is needed to clearly define the optimal screening interval and most effective combination of tests for screening for cervical cancer, as well as the effectiveness of screening using high risk HPV testing alone.



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