Screening With the Papanicolaou (Pap) Test: Benefits
Based on solid evidence, regular screening of appropriate women for cervical cancer with the Pap test reduces mortality from cervical cancer. The benefits of screening women younger than 21 years are small because of the low prevalence of lesions that will progress to invasive cancer. Screening is not beneficial in women older than 65 years if they have had a recent history of negative test results.[1-3]

**Magnitude of Effect:** Regular Pap screening decreases cervix cancer incidence and mortality by at least 80%.

- **Study Design:** Population-based and cohort studies.
- **Internal Validity:** Good.
- **Consistency:** Good.
- **External Validity:** Good.

Screening With the Pap Test: Harms
Based on solid evidence, regular screening with the Pap test leads to additional diagnostic procedures (e.g., colposcopy) and treatment for low-grade squamous intraepithelial lesions (LSILs), with long-term consequences for fertility and pregnancy. These harms are greatest for younger women, who have a higher prevalence of LSILs, lesions that often regress without treatment. Harms are also increased in younger women because they have a higher rate of false-positive results.

**Magnitude of Effect:** Additional diagnostic procedures were performed in 50% of women undergoing regular Pap testing. Approximately 5% were treated for LSILs. The number of women with impaired fertility and pregnancy complications is unknown.

- **Study Design:** Evidence obtained from cohort or case-control studies.
- **Internal Validity:** Good.
- **Consistency:** Good.
- **External Validity:** Good.

Screening With the Human Papillomavirus (HPV) DNA Test: Benefits
Based on solid evidence, screening with the HPV DNA or HPV RNA test detects high-grade cervical dysplasia, a precursor lesion for cervical cancer. Additional clinical trials show that HPV testing is superior to other cervical cancer screening strategies. In April 2014, the U.S. Food and Drug Administration approved an HPV DNA test that can be used alone for the primary screening of cervical cancer risk in women aged 25 years and older.[4]

**Magnitude of Effect:** In one prospective, clustered, randomized trial, HPV testing was superior to other strategies for preventing cervical cancer mortality.[5,6]

- **Study Design:** Clustered randomized controlled trial (RCT).
- **Internal Validity:** Good.
- **Consistency:** Good.
- **External Validity:** Good.
Screening With the HPV DNA Test: Harms

Based on solid evidence, HPV testing identifies numerous infections that will not lead to cervical dysplasia or cervical cancer. This is especially true in women younger than 30 years, in whom rates of HPV infection may be higher.

**Magnitude of Effect:** In one study, 86.7% of women with a positive HPV test did not develop cervical cancer or related premalignant disease after more than a decade of follow-up.[7]

- **Study Design:** Long-term observational trials.
- **Internal Validity:** Good.
- **Consistency:** Good.
- **External Validity:** Good.

Screening With the Pap Test and the HPV DNA Test (Cotesting): Benefits

Based on solid evidence, screening every 5 years with the Pap test and the HPV DNA test (cotesting) in women aged 30 years and older is more sensitive in detecting cervical abnormalities, compared with the Pap test alone. Screening with the Pap test and HPV DNA test reduces the incidence of cervical cancer.[3]

**Magnitude of Effect:** HPV-based screening provides 60% to 70% greater protection against invasive cervical carcinoma, compared with cytology.[8]

- **Study Design:** RCTs.
- **Internal Validity:** Good.
- **Consistency:** Good.
- **External Validity:** Good.

Screening With the Pap Test and the HPV DNA Test (Cotesting): Harms

Based on solid evidence, HPV and Pap cotesting is associated with more false-positives than is the Pap test alone. Abnormal test results can lead to more frequent testing and invasive diagnostic procedures.[3]

**Magnitude of Effect:** The percentage of U.S. women undergoing cotesting who will have a normal cytology test result and a positive HPV test result (and who will therefore require additional testing) ranges from 11% among women aged 30 to 34 years to 2.6% among women aged 60 to 65 years.[3]

- **Study Design:** RCTs.
- **Internal Validity:** Good.
- **Consistency:** Good.
- **External Validity:** Good.

Screening Women Without a Cervix

Based on solid evidence, screening is not helpful in women who do not have a cervix as a result of a hysterectomy for a benign condition.

**Magnitude of Effect:** Among women without cervices, fewer than 1 per 1,000 had abnormal Pap test results.

- **Study Design:** Evidence obtained from a single cohort study.
- **Internal Validity:** Good.
- **Consistency:** Good.
- **External Validity:** Good.

References

Description of the Evidence

Natural History, Incidence, and Mortality

In the United States in 2019, it is estimated that 13,170 cases of invasive cervical cancer will be diagnosed and that 4,250 women will die of the disease.[1] These rates have been improving steadily. From 2006 to 2015, overall incidence rates stabilized. From 2007 to 2016, the death rate decreased by about 1% per year in women aged 50 years and older but was stable in women younger than 50 years.[1] This improvement has been attributed largely to screening with the Papanicolaou (Pap) test. When corrected for the prevalence of hysterectomy, the mortality rate for black women is nearly twice the mortality rate for white women.[2]

Invasive squamous carcinoma of the cervix results from the progression of preinvasive precursor lesions called cervical intraepithelial neoplasia (CIN), or dysplasia. CIN is histologically graded into mild dysplasia (CIN 1), moderate dysplasia (CIN 2), or severe dysplasia (CIN 3). Not all of these lesions progress to invasive cancer; many mild and moderate lesions regress. A further categorization, the Bethesda system, is based on cytologic findings: atypical squamous cells of undetermined significance (ASCUS) or cannot rule out low-grade squamous intraepithelial lesions (LSILs), LSILs (consisting of cytologic atypia and CIN 1), and high-grade squamous intraepithelial lesions (HSILs), primarily CIN 2–3 plus carcinoma in situ.[3]

The rate at which invasive cancer develops from CIN is usually slow, measured in years and perhaps decades.[4] This long natural history provides the opportunity for screening to effectively detect this process during the preinvasive phase, thus allowing early treatment and cure. Because many of these preinvasive lesions (especially LSILs) would have never progressed to invasive cancer,[5-7] screening also runs the risk of leading to treatment for women who do not need to be treated.

Human papillomavirus (HPV) is an oncogenic virus and the etiologic agent of cervical cancer and related premalignant disease. HPV is transmitted by sexual contact. Sexually inactive women rarely develop cervical cancer, while sexual activity at an early age with multiple sexual partners is a strong risk factor.[8] Nearly all women with invasive cervical cancer have evidence of HPV infection.[9-12] Most women with HPV infection, however, never develop cervical cancer; thus, this infection is necessary but not sufficient for the development of cancer.[13]

Although cervical cancer mortality increases with age,[14] the prevalence of CIN is highest among women in their 20s and 30s. Mortality is rare among women younger than 30 years; HSILs are rare among women older than 65 years who have been previously screened. About 70% of ASCUS and CIN 1 lesions regress within 6 years, while about 6% of CIN 1 lesions progress to CIN 3 or worse. In about 10% to 20% of women with CIN 3 lesions, the lesions progress to invasive cancer.[4,7,15]

Cervical cancer mortality is about 40% higher in black women younger than 65 years than in white women of the same age. Among women older than 65 years, cervical cancer mortality for black women is more than 150% higher than for white women.[14] In either case, mortality is rare among women of any age who have regular screenings.
The Pap Test

The Pap test has never been examined in a randomized controlled trial (RCT). A large body of consistent observational data, however, supports its effectiveness in reducing mortality from cervical cancer. Both incidence and mortality from cervical cancer have sharply decreased in a number of large populations after the introduction of well-run screening programs.[16-19] In Iceland, the mortality rate declined by 80% for more than 20 years, and in Finland and Sweden by 50% and 34%, respectively.[16,20] Similar reductions have been observed in large populations in the United States and Canada. Reductions in cervical cancer incidence and mortality were proportional to the intensity of screening.[16,20] Mortality in the Canadian provinces was reduced most remarkably in British Columbia, which had screening rates two to five times those of the other provinces.[21]

Case-control studies have found that the risk of developing invasive cervical cancer is three to ten times higher in women who have not been screened.[22-25] Risk also increases with long duration following the last normal Pap test, or similarly, with decreasing frequency of screening.[26,27] Screening every 2 to 3 years, however, has not been found to significantly increase the risk of finding invasive cervical cancer above the risk expected with annual screening.[27,28]

Accuracy of the Pap Test

Ideally, determining the sensitivity and specificity of a screening test would involve a study that applies a gold standard test (such as colposcopy with appropriate biopsy) to all participants (whether the screening test results are positive or negative). Sensitivity (the percentage of true-positive cases that are detected by the screening test) and specificity (the percentage of true-negative cases that are negative by the screening test) could be calculated. Such studies have rarely been done for any screening test for cervical cancer. Studies that compare the Pap test with repeat Pap testing have found that the sensitivity of any abnormality on a single test for detecting high-grade lesions is 55% to 80%.[29,30] Because of the usual slow-growing nature of cervical cancer, the sensitivity of a program of regular Pap testing is likely higher.

To determine the sensitivity and specificity of the Pap smear, both a test threshold (i.e., the point at which the test will be considered to be positive) and a reference-standard threshold (i.e., the point at which the reference standard is considered to be positive) must be defined. In practice, ASCUS is often used as the test threshold, and CIN 1 is often used as the reference threshold. This combination gives a sensitivity of about 68% and a specificity of about 75%. A more appropriate test threshold may be LSIL, with a reference threshold of CIN 2-3. This combination gives a sensitivity of 70% to 80%, with a specificity of about 95%.[31]

One important factor in the accuracy of the Pap test is the adequacy of the specimen obtained. Adequate training and using techniques such as the cytobrush may improve sensitivity.[32]

New Screening Technologies

Newer techniques that employ liquid-based cytology (e.g., ThinPrep) have been developed to improve the sensitivity of screening. As with the Pap test, the optimal studies to determine the sensitivity and specificity of these technologies have not been conducted. Some less-than-optimal studies show that sensitivity is modestly higher for detecting any degree of CIN, with modestly lower specificity.[33,34] One careful study, however, showed that conventional Pap testing was slightly more sensitive and specific than liquid-based cytology.[35]

The evidence is also mixed about whether liquid-based techniques improve rates of test adequacy.[33,34] One advantage of liquid-based cytology is that HPV testing can be performed on the same preparation; one disadvantage is that liquid-based approaches are more expensive than conventional Pap testing. No study has examined whether liquid-based cytology actually reduces the number of women dying of cervical cancer compared with conventional Pap testing.

Screening Women Who Have Had a Hysterectomy

Women who have had a hysterectomy with removal of the cervix for benign disease rarely have important abnormalities found on Pap testing. Several studies have shown that the rate of high-grade vaginal lesions or vaginal cancer is less than 1 in 1,000 tests.[36,37] No study has shown that screening for vaginal cancer reduces mortality from this rare condition.

Screening Interval

Because cervical cancer is slow growing, considerable uncertainty surrounds the issue of the optimal screening interval. The most direct evidence about this issue comes from a prospective cohort analysis of an RCT.[38]
Among 2,561 women (mean age, 66.7 years) with normal Pap tests at baseline, 110 had an abnormal Pap test within the next 2 years. No woman was found to have CIN 2–3 or invasive cancer, and only one woman had CIN 1–2. Thus, the positive predictive value (PPV) of screening 1 year after a negative Pap test was 0%; after 2 years, the PPV was 0.9%. The authors concluded that Pap tests should not be repeated within 2 years of a negative test. A large (n = 332,000) prospective cohort study of cervical cytology and HPV DNA cotesting in U.S. women aged 30 years and older found that a negative Pap smear was associated with a low risk of developing CIN 3 or cancer (CIN 3+) for up to 5 years after the test (cumulative incidence of CIN 3+ at 3 and 5 years was 0.17% and 0.36%, respectively).[39]

A large study that included data from the National Breast and Cervical Cancer Early Detection Program together with modeling found little further mortality reduction from cervical cancer for screening every year as compared with screening every 3 years.[40] A similar modeling study from Australia found no differences between screening every 2 years and screening every 3 years.[41]

**HPV Testing**

Noninvasive cervical squamous cell abnormalities are graded histologically as CIN 1, CIN 2, or CIN 3, according to the severity of the cell changes and the percent of the epithelium replaced by abnormal cell growth. CIN 3 is a reasonably reproducible diagnosis and, if untreated, has an approximate 30% risk of developing into invasive cancer over many years.[42] CIN 2 has poor interobserver reproducibility,[43] and the biologic behavior is variable.[44] CIN 3 is therefore a more rigorous endpoint for clinical trials, while CIN 2 represents the threshold for treatment to provide an additional measure of safety.

Approximately 15 cancer-associated (high-risk or carcinogenic) HPV genotypes cause virtually all cases of cervical cancer and precursor lesions of CIN 2 and CIN 3. However, carcinogenic HPV infections are very common, particularly in young women, and the majority clear on their own within 1 to 2 years. Therefore, the challenge of incorporating HPV testing in cervical screening programs is to balance sensitivity for detection of CIN 2 or CIN 2+ and to minimize the over-referral of women with transient HPV infections and cervical changes that are destined to regress.

The U.S. Food and Drug Administration (FDA) has approved several HPV tests. Most of these tests are based on the detection of DNA from one or more oncogenic types of HPV. One test detects HPV RNA. HPV testing is approved for use in two contexts: (1) as a second (i.e., triage) test after an equivocal cytology result of ASCUS; and (2) for primary screening in conjunction with cervical cytology for women aged 30 years and older.[45] Testing for low-risk HPV types does not identify women at risk of developing CIN 2 or 3.[46,47]

**Triage**

A large randomized clinical trial, the ASCUS/LSIL Triage Study (ALTS), demonstrated the cost-effectiveness of using HPV testing to clarify the risk of an ASCUS Pap result.[48] ALTS randomly assigned women with ASCUS to one of three management strategies: immediate colposcopy regardless of enrollment test results, referral to colposcopy if HPV test results were positive or if the enrollment cytology was HSIL, and referral to colposcopy only if the cytology was HSIL. The HPV triage strategy was as sensitive for detection of CIN 2+ as immediate colposcopy, while referring only about half of the women for the procedure. Repeat cytology with referral to colposcopy at the threshold of HSIL was less sensitive for CIN 3+ (60%) compared with HPV triage (92%); however, using a cytologic threshold of ASCUS for referral increased sensitivity but resulted in 72% of women with ASCUS undergoing colposcopy.[49] HPV testing is not recommended for adolescent women with ASCUS because most of these women are HPV positive.[50,51]

HPV DNA testing is generally not appropriate or clinically useful following cytology results of LSIL, which is more severe than ASCUS, and most of these women (84%–96%) are carcinogenic HPV DNA positive.[52] One exception may be to clarify the risk for postmenopausal women with cytologic LSIL, which is an interpretation that can be falsely positive, presumably due to atrophic changes.[53]

**Primary screening**

Testing for HPV DNA as a primary screening test has been FDA approved only in conjunction with cervical cytology and only in women aged 30 years and older. Women who are negative by cytology and HPV testing are at extremely low risk of CIN 3+ and therefore may be screened less frequently. A prospective cohort study of nearly 332,000 U.S. women aged 30 years and older undergoing HPV DNA and cervical cytology cotesting every 3 years found that the cumulative incidence of CIN 3+ in women with negative results for both tests at baseline was 0.047% at 3 years and 0.16% at 5 years.[39] A second study of more than 43,000 women aged 29 to 61 years, one-half of whom underwent three rounds of HPV DNA and cervical cytology cotesting every 5 years, found that
the cumulative incidence of CIN 3+ in women with negative results for both tests at baseline was 0.01% (95% confidence interval [CI], 0.00%–0.05%) at 9 years and 0.07% (95% CI, 0.03%–0.17%) after 14 years of follow-up.[54] Screening more frequently than every 3 years would not improve sensitivity significantly but would increase costs and overtreatment.[55,56]

Numerous studies have demonstrated that, compared with cytology, HPV DNA testing is more sensitive for identifying women who have CIN 2+ (range of sensitivities, 84%–97%).[33,57-62] In one randomized trial using both Pap and HPV testing in random order among women aged 30 to 69 years, sensitivity of HPV was 95% compared with 55% for Pap cytology. The combination of HPV and cytology had 100% sensitivity and a referral rate of 7.9%.[58]

The lower specificity of HPV DNA testing compared with cytology is a consideration. Among women older than 30 years, cytology had a specificity of 97% compared with 94% for HPV testing.[58] The specificity of HPV DNA testing would likely be even lower among women younger than 30 years, who have more transient HPV infection that is of little consequence. Thus, detecting such women would potentially increase the number of follow-up diagnostic workups. Potential approaches to minimize over-referral with HPV DNA testing and improve specificity include: (1) triage HPV-positive results with cytology[62] or another more specific molecular assay;[63] and (2) trigger further workup only after two sequential positive HPV test results because it is the persistence of carcinogenic HPV that confers the greatest risk of CIN 2–3.[64,65]

An Italian population-based, randomized trial of HPV DNA testing versus cervical cytology performed at 3-year intervals in approximately 94,000 women aged 25 to 60 years found a statistically significant decrease in the number of invasive cervical cancer cases diagnosed in the HPV DNA arm at the second round of screening (0 cases vs. 9 cases; P = .004). However, about 48% of individuals in the HPV DNA arm also received conventional cytology testing at the first screening round, making it impossible to discern whether the observed difference resulted from the use of a combined testing strategy or HPV DNA testing alone. Of note, many more women in the HPV DNA arm than in the cytology-alone arm were referred to colposcopy for abnormal findings (4,436 women vs. 1,416 women), prompting the authors to conclude that if the HPV DNA test is used as a primary screening strategy, women with positive test results should be triaged by cytology before referral.[66]

A study using data from a population-based randomized trial of cervical screening among women aged 32 to 38 years compared 11 different screening strategies using HPV DNA testing and cytology. The strategy of initial screening with an HPV DNA test and a triage of HPV-positive results with cytology, and subsequent repeat HPV DNA testing after 1 year for women who were HPV positive but cytology negative, increased the sensitivity for detection of CIN 3+ by 30% compared with cytology alone, and increased the total number of screening tests performed by only 12%.[67] In a review of data from a large integrated health system, the added benefit of cotesting versus HPV testing alone would improve detection of CIN 3 or early-stage cervical cancer in very few women. Only 5.1% of locally advanced invasive cancers and 3.6% of CIN 3 were cytology positive and HPV negative, representing a very small fraction of all screened women.[68]

**Screening Benefit According to Age**

Cervical cancer mortality, usually occurring among unscreened women, increases with age, with the maximum mortality for white women between the ages of 45 years and 70 years, and for black women in their 70s.[55,69] (Also available online.) Mortality among women with negative Pap screening is low at all ages.

Screening by Pap testing with associated diagnostic testing and treatment is effective in reducing the incidence of all histologies and stages of invasive cervical cancer.[70] The benefit increases with age. Whereas the odds ratio (OR) is 0.79 (95% CI, 0.57–1.1) among women screened at age 30 to 31 years for developing cancer at age 35 to 39 years, it improves to 0.26 (95% CI, 0.19–0.36) among women screened at age 52 to 54 years for developing cancer at age 55 to 59 years.

Women aged 20 years and younger are more likely to have Pap abnormalities leading to further testing and treatment (refer to the Evidence of Harm section of this summary for more information), so forgoing Pap testing in these women may improve the benefit-risk balance for this intervention. Women in this age group have a very low risk of cervical cancer and a high likelihood that cervical cell abnormalities will go away on their own.[71]

HSILs are rare among women older than 65 years who have been previously screened. For women with a negative Pap test at age 60 years and older, the likelihood of having a new diagnosis of CIN 3+ on repeat screening is less than 1 in 1,000 (in some studies, as few as 2–6 in 10,000).[38]

**Alternative Screening and Treatment Strategies Including Low-Resource Settings**
Choice in methods of screening for cervical cancer in resource-limited countries or underserved populations has prompted the evaluation of one-time screen-and-treat approaches.

A clustered, randomized, controlled trial in rural India evaluated the impact of one-time visual inspection of the cervix with acetic acid (VIA) and immediate colposcopy, directed biopsy, and cryotherapy (where indicated) on cervical cancer incidence and mortality in healthy women aged 30 to 59 years. Fifty-seven clusters (n = 31,343 women) received the intervention, while 56 control clusters (n = 30,958 women) received counseling and education about cervical cancer screening. After 7 years of follow-up, with adjustments for age, education, marital status, parity, and cluster design, there was a 25% relative reduction in cervical cancer incidence in the intervention arm compared with the control group (hazard ratio [HR], 0.75; 95% CI, 0.55–0.95). Using the same adjustments, cervical cancer mortality rates demonstrated a 35% relative reduction in the intervention arm compared with the control group (HR, 0.65; 95% CI, 0.47–0.89); the age-standardized rate of death due to cervical cancer was 39.6 per 100,000 person-years for the intervention group versus 56.7 per 100,000 person-years for the control group. However, using the same cohort, the same authors subsequently reported that HPV testing is superior at reducing cervical cancer mortality. This population was essentially screen naive at entry into the study and demonstrated a much higher overall risk of cervical cancer death (11% of the controls) than that observed in the U.S. population; therefore, these findings are not applicable to U.S. and similar Western health care. Histological diagnosis of cervical lesions happened after treatment had already taken place, and approximately 27% of patients in this trial received cryotherapy for lesions later determined to be nonmalignant.

A second cluster-randomized trial of VIA screening in low socioeconomic areas of urban Mumbai, India, similarly demonstrated its efficacy in reducing cervical cancer mortality. In this trial, primary community health workers (as opposed to medical personnel) were trained to provide biennial VIA screening to 75,360 women aged 35 to 64 years. Women with positive screening results were referred to a central hospital for free diagnostic confirmation (including Pap smear, colposcopy, and biopsy, if indicated) and treatment—where warranted—according to hospital protocol. A control group (n = 76,178) received general cancer education. After 12 years, the relative risk (RR) of dying from cervical cancer was reduced by 31% in the screening arm (rate ratio, 0.69; 95% CI, 0.54–0.88), corresponding to about 5 fewer deaths per 100,000 woman-years. Compliance with treatment was about 15% lower for those in the control arm, which may have inflated the observed mortality benefit somewhat.

A demonstration project in Kolkata, India, enrolled 39,740 women aged 30 to 60 years who underwent screening with VIA and Hybrid Capture II HPV DNA testing with colposcopy referral for a positive test, followed by biopsy and treatment if indicated. Estimated test performance for detection of CIN 3+, corrected for verification bias, demonstrated that VIA achieved a sensitivity of 59.9% (95% CI, 49.9%–69.1%) and a specificity of 93.2% (95% CI, 92.9%–93.4%) compared with HPV testing, which resulted in a sensitivity of 91.2% (95% CI, 85.4%–95.7%) and a specificity of 96.9% (95% CI, 96.7%–97.0%). HPV testing identified an additional 32 CIN 3+ cases and 7 invasive cancer cases missed by VIA.

A study of the feasibility of single-visit management of high-grade cervical lesions was conducted among a predominantly Latina population in California. Women were randomly assigned to a single-visit group (n = 1,716) in which the Pap test was evaluated immediately and treatment administered the same day for women with HSILs or atypical glandular cells of undetermined significance (AGUS); or to usual care (n = 1,805), with results of the Pap test provided within 2 to 4 weeks and referrals for treatment based on results. The program was feasible, with a high degree of acceptability and results in 14 of 16 women (88%) with abnormal test results completing treatment by 6 months versus 10 of 19 women (53%) in the usual care arm completing treatment by 6 months. Follow-up at 12 months was also higher among women in the single-visit group with HSILs/AGUS than among those in the usual-care arm; among all women, only 36% in each group had a follow-up Pap test at 1 year.

Self-collected HPV testing may be an alternative method for cervical screening in communities with limited access to health care providers. A population-based cluster-randomized trial in Argentina, comparing screening uptake using self-collection of samples for HPV DNA testing with that of clinic-based cervical sample collection with cytology and HPV triage, found that self-collection was associated with increased screening (RR, 4.02; 95% CI, 3.44–4.71), which translated into higher detection of CIN 2+ and treatment. A Dutch study among women who participated in the national cervical cancer screening program found that vaginal self-sampling was highly concordant (96.8%; 95% CI, 96.0%–97.5%) with high-risk HPV prevalence in physician-collected samples and was both convenient and user friendly. Vaginal self-sampling will be offered in the Dutch national screening program for those who do not participate in their routine screening. A pooled analysis of cervical screening studies conducted in China compared sensitivity and specificity of self-collection of cervical specimens for HPV DNA...
testing, physician-collected specimens for HPV testing, liquid-based cytology (LBC) and visual inspection of the VIA. The study included 13,004 participants in the analysis. Women had all three sampling methods; in one study included in the pooled analysis, all women had colposcopy and biopsies. Of note, the women were instructed in the self-collection methodology by physicians, which likely affected the quality of specimen collection and thus the accuracy of the test in these studies. Physician-collected specimen HPV DNA testing had the highest sensitivity, 97% for CIN 2+ (95% CI, 95.2%–98.3%) and 97.8 for CIN 3+ (95% CI, 95.3%–99.2%). Self-collected specimen HPV testing had moderate agreement with physician-collected specimen testing (κ = 0.67). Pooled sensitivity for self-collected HPV testing was 86.2% for CIN 2+ (95% CI, 82.9%–89.1%) and 86.1% for CIN 3+ (95% CI, 81.4%–90.0%). Pooled specificity for self-collected HPV DNA testing was 80.7% (95% CI, 75.6%–85.8%) for CIN 2+ and 79.5% (95% CI, 74.1%–84.8%) for CIN 3+. The specificity of HPV testing was lowest of all screening modalities. Whereas pooled sensitivity was highest for physician-based HPV testing, it was lowest for the VIA screening methods—50.3% for CIN 2+ and 55.7% for CIN 3+. Pooled specificity was highest for LBC—94.0% for CIN 2+ and 92.8% for CIN 3+.[80]

A randomized trial in South Africa evaluated the impact on diagnosis of CIN 2+ at 6 months with a screen-and-treat approach with VIA and HPV versus delayed evaluation.[81] Women underwent HPV DNA testing and VIA testing (n = 6,555) and then returned in 2 to 6 days and were randomly assigned to one of three groups to receive (1) cryotherapy if the HPV DNA test result was positive (n = 2,163; 473 HPV+ and 467 treated); (2) cryotherapy if the VIA test result was positive (n = 2,227; 492 VIA+ and 482 treated); or (3) delayed evaluation (n = 2,165). At 6 months, CIN 2+ was diagnosed in 0.80% of women in the HPV+/cryotherapy group, in 2.23% of the VIA+/cryotherapy group, and in 3.55% of the delayed evaluation group. Differences in the prevalence of CIN 2+ persisted among the subset of women evaluated at 12 months. For the secondary outcome of CIN 3+, prevalence of CIN 3+ lesions was low among the three groups but followed the same pattern (two cases in the HPV DNA group, three cases in the VIA group, and eight cases in the delayed evaluation group).

References


Evidence of Harm

Annually in the United States, an estimated 65 million women undergo cervical cancer screening,[1] about 3.9 million (6%) will be referred for further evaluation.[2] About 11,000 cases of invasive cervical cancer were diagnosed in 2008. Thus, Papanicolaou (Pap) test screening results in a large number of colposcopies for benign conditions.

The major potential harm of screening for cervical cancer lies in the screening detection of many cytologic abnormalities such as atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL), the majority of which would never progress to cervical cancer. Women with human papillomavirus (HPV)-positive ASCUS or LSIL on Pap testing are usually referred for colposcopy. Histological CIN 2+ is treated with cryotherapy or loop electrosurgical excision procedure. These procedures permanently alter the cervix and have consequences on fertility and pregnancy.[3] Younger women are more likely to acquire HPV infections and be referred for diagnostic workup, and they are more likely to suffer harms from interventions for a condition that often resolves spontaneously.

On the basis of an analysis of screening records from nearly 350,000 women in Bristol, England, investigators projected that 1,000 women would need to be screened for cervical cancer for 35 years to prevent one death from the disease. For each death prevented, the authors estimated that more than 150 women have an abnormal result, more than 80 women are referred for investigation, and more than 50 women have treatment.[4]

References


Changes to This Summary (03/08/2019)

Description of the Evidence

Updated statistics with estimated new cases and deaths for 2019 (cited American Cancer Society as reference 1). Also revised text to state that from 2006 to 2015, overall incidence rates stabilized; and from 2007 to 2016, the death rate decreased by about 1% per year in women aged 50 years and older but was stable in women younger than 50 years.
About This PDQ Summary

Purpose of This Summary
This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about cervical cancer screening. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates
This summary is reviewed regularly and updated as necessary by the PDQ Screening and Prevention Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

Any comments or questions about the summary content should be submitted to Cancer.gov through the NCI website’s Email Us. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

Levels of Evidence
Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Screening and Prevention Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

Permission to Use This Summary
PDQ is a registered trademark. Although the content of PDQ documents can be used freely as text, it cannot be identified as an NCI PDQ cancer information summary unless it is presented in its entirety and is regularly updated. However, an author would be permitted to write a sentence such as “NCI’s PDQ cancer information summary about breast cancer prevention states the risks succinctly: [include excerpt from the summary].”

The preferred citation for this PDQ summary is:


Images in this summary are used with permission of the author(s), artist, and/or publisher for use within the PDQ summaries only. Permission to use images outside the context of PDQ information must be obtained from the owner(s) and cannot be granted by the National Cancer Institute. Information about using the illustrations in this summary, along with many other cancer-related images, is available in Visuals Online, a collection of over 2,000 scientific images.