A promising technology for predicting cervical dysplasia, cervical cancer outcomes and surgical technique, and updated USPSTF guidance on cervical cancer screening

Cervical cancer rates remain low in the United States, with the incidence having plateaued for decades. And yet, in 2019, more than 13,000 US women will be diagnosed with cervical cancer. Globally, in 2018 almost 600,000 women were diagnosed with cervical cancer; it is the fourth most frequent cancer in women. This is despite the fact that we have adequate primary and secondary prevention tools available to minimize—and almost eliminate—cervical cancer. We must continue to raise the bar for preventing, screening for, and managing this disease.

Human papillomavirus (HPV) vaccines provide a highly effective primary prevention strategy, but we need to improve our ability to identify and diagnose dysplastic lesions prior to the development of cervical cancer. Highly sensitive HPV testing and cytology is a powerful secondary prevention approach that enables us to assess a woman’s risk of having precancerous cells both now and in the near future. These modalities have been very successful in decreasing the incidence of cervical cancer in the United States and other areas with organized screening programs. In low- and middle-income countries, however, access to, availability of, and performance with these modalities is not optimal. Innovative strategies and new technologies are being evaluated to overcome these limitations.

Advances in radiation and surgical technology have enabled us to vastly improve cervical cancer treatment. Women with early-stage cervical cancer are candidates for surgical management, which frequently includes a radical hysterectomy and lymph node dissection. While these surgeries traditionally have been performed via an exploratory laparotomy, minimally invasive techniques (laparoscopic and robot-assisted surgical techniques) have decreased the morbidity with these surgeries. Notable new studies have shed light on the comparative effectiveness of minimally invasive technologies and have shown us that new is not always better.

The US Preventive Services Task Force (USPSTF) recently released its updated cervical cancer screening guidelines. The suggested approach to screening differs from previous recommendations. HPV testing as a primary...
When cervical screening tests like cytology and HPV testing show abnormal results, colposcopy often is recommended. The goal of colposcopy is to identify the areas that might harbor a high-grade precancerous lesion or worse. The gold standard in this case, however, is histology, not colposcopic impression, as many studies have shown that colposcopy without biopsies is limited and that performance is improved with more biopsies.3,4

Visual inspection with acetic acid (VIA) is an approach used often in low-resource settings where visual impression is the gold standard. However, as with colposcopy, a visual evaluation without histology does not perform well, and often women are overtreated. Many attempts have been made with new technologies to overcome the limitations of time, cost, and workforce required for cytology and histology services. New disruptive technologies may be able to surmount human limitations and improve on not only VIA but also the need for histology.

**New tech’s potential to identify high-grade cervical dysplasia may be a boon to low-resource settings**

In a recent observational study, Hu and colleagues used images that were collected during a large population study in Guanacaste, Costa Rica.5 More than 9,000 women were followed for up to 7 years, and cervical photographs (cervigrams) were obtained. Well-annotated histopathology results were obtained for women with abnormal screening, and 279 women had a high-grade dysplastic lesion or cancer.

Cervigrams from women with high-grade lesions and matched controls were collected, and a deep learning-based algorithm using artificial intelligence technology was developed using 70% of the images. The remaining 30% of images were used as a validation set to test the algorithm’s ability to “predict” high-grade dysplasia without knowing the final result.

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

Colposcopy remains the gold standard for evaluating abnormal cervical cancer screening tests in the United States. But can we do better for our patients using new technologies like AVE? If validated in large-scale trials, AVE has the potential to revolutionize cervical cancer screening in low-resource settings where follow-up and adequate histology services are limited or nonexistent. Future large studies are necessary to evaluate the role of AVE alone versus in combination with other diagnostic testing (such as HPV testing) to detect cervical lesions globally.
The better the “bend” of the knee of the curve, the better the performance of a given test. AVE was as accurate or more than all of the screening tests used in the cohort study. ROC curves of: A) AVE; B) cervicography; C) conventional Pap smear; D) liquid-based cytology; E) first-generation neural network-based cytology; and F) MY09-MY11 PCR-based HPV testing.

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; AUC, area under the curve; AVE, automated visual evaluation; HPV, human papillomavirus; hrHPV, high-risk HPV; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; PCR, polymerase chain reaction; ROC, receiver operating characteristic.
Data offer persuasive evidence to abandon minimally invasive surgery in management of early-stage cervical cancer


Over the past decade, gynecologic cancer surgery has shifted from what routinely were open procedures to the adoption of minimally invasive techniques. Recently, a large, well-designed prospective study and a large retrospective study both demonstrated worse outcomes with minimally invasive radical hysterectomy (MIRH) as compared with traditional open radical abdominal hysterectomy (RAH). These 2 landmark studies, initially presented at the Society of Gynecologic Oncology’s 2018 annual meeting and later published in the New England Journal of Medicine, have really affected the gynecologic oncology community.

Prospective trial showed MIRH was associated with lower survival rates

From 2008 to 2017, Ramirez and colleagues conducted a phase 3, multicenter, randomized controlled trial to prospectively establish the noninferiority of MIRH compared with RAH. The study included 631 women from 33 centers. The prespecified expected disease-free survival rate was 90% at 4.5 years.

To be included as a site, centers were required to submit details from 10 minimally invasive cases as well as 2 unedited videos for review by the trial management committee. In contrast to Melamed and colleagues’ retrospective study, of the 319 procedures that were classified as minimally invasive, only 15.6% were robotically assisted. Similarly, most women had stage IB1 tumors (91.9%), and most were squamous cell carcinomas (67%). There were also no differences in the postoperative pathology findings or the need for adjuvant therapy administered between...
FAST TRACK

Large trials of cotesting in 25- to 65-year-olds consistently showed that primary hrHPV screening led to a statistically significant increased detection of CIN 3+ in the initial screening round.

USPSTF updated guidance on cervical cancer screening

Past guidelines for cervical cancer screening have included testing for high-risk HPV (hrHPV) as a cotest with cytology or for triage of atypical squamous cells of undetermined significance (ASCUS) in women aged 30 to 65 years. The American Society for Colposcopy and Cervical Pathology and the Society of Gynecologic Oncology, with other stakeholder organizations, issued interim guidance for primary HPV testing—that is, HPV test first and, in the case of non-16/18 hrHPV types, cytology as a triage. The most recent evidence report and systematic review by Melnikow and colleagues for the USPSTF offers an in-depth analysis of risks, benefits, harms, and value of cotesting and other management strategies.

Focus on screening effectiveness

Large trials of cotesting were conducted in women aged 25 to 65. These studies all consistently showed that primary hrHPV screening led to a statistically significant increased detection of cervical intraepithelial neoplasia (CIN) 3+ in the initial round of screening, with a relative risk of detecting CIN 3+ ranging from 1.61 to 7.46 compared with cytology alone.

Four additional studies compared cotesting with conventional cytology for the
### TABLE USPSTF recommendations for cervical cancer screening

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<tr>
<th>Population age</th>
<th>Screening recommendation</th>
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<tr>
<td>21–29 years</td>
<td>Every 3 years with cytology alone</td>
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| 30–65 years    | Every 3 years with cytology alone  
|                | Every 5 years with hrHPV testing alone, or  
|                | Every 5 years with cotesting |
| <21 years, >65 years with adequate prior screening, and women who have had a hysterectomy | Do not screen |

**Clinical summary**

**Risk assessment**
- All women 21–65 years are at risk for cervical cancer because of potential exposure to high-risk HPV types (hrHPV) through sexual intercourse and should be screened
- Certain risk factors increase risk for cervical cancer: HIV infection, compromised immune system, in utero exposure to diethylstilbestrol, previous treatment of a high-grade precancerous lesion
- Women with the above risk factors should receive individualized follow-up

**Screening tests**
- Screening with cervical cytology alone, primary testing for hrHPV alone, or both at the same time (cotesting) can detect high-grade precancerous cervical lesions and cervical cancer
- Clinicians should focus on ensuring that women receive adequate screening, appropriate evaluation of abnormal results, and indicated treatment, regardless of the screening strategy used

**Treatments and interventions**
- High-grade cervical lesions may be treated with excisional and ablative therapies
- Early-stage cervical cancer may be treated with surgery (hysterectomy) or chemotherapy

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**Risks of screening**

In the same studies reviewed for screening effectiveness, the investigators found that overall, screening with hrHPV primary or cotesting was associated with more false-positive results and higher colposcopy rates. Women screened with hrHPV alone had a 7.9% referral rate to colposcopy, while those screened with cytology had a 2.8% referral rate to colposcopy. Similarly, the rate of biopsy was higher in the hrHPV-only group (3.2% vs 1.3%).

Overall, while cotesting might have some improvement in performance compared with hrHPV as a single modality, there might be risks of overreferral to colposcopy and overtreatment with additional cytology over hrHPV testing alone.

This evidence review also included an analysis of more potential harms. Very limited evidence suggests that positive hrHPV test results may be associated with greater psychological harm, including decreased sexual satisfaction, increased anxiety and distress, and worse feelings about sexual partners, than abnormal cytology results. These were assessed, however, 1 to 2 weeks after the test results were provided to the patients, and long-term assessment was not done.

**New recommendations from the USPSTF**

Based on these data, the USPSTF issued new recommendations regarding screening (TABLE). For women aged 21 to 29, cytology alone should be used for screening every...
Primary screening with hrHPV is more effective in diagnosing a CIN 3+ than cytology alone. Cotesting with cytology and hrHPV testing appears to have limited performance improvement, with potential harm, compared with hrHPV testing alone in diagnosing CIN 3+.

The Task Force recommendation is hrHPV testing alone or cotesting every 5 years.

References