SUPPLEMENT TO
OBG MANAGEMENT
January 2022
AVAILABLE AT WWW.MDEDGE.COM/OBGYN
THIS PROMOTIONAL ARTICLE WAS DEVELOPED IN CONJUNCTION WITH AND SPONSORED BY HOLOGIC, INC.

ObGyns—Leaders, not followers, in cervical cancer screening

Optimize cervical cancer screening by initiating screening at 21 years of age, using cytology during the 20s, and co-testing (Pap+hrHPV) starting 30 years of age

Kameelah Phillips, MD, NCMP, IBCLC
Calla Women's Health, New York, New York

EXECUTIVE SUMMARY

Routine screening has substantially reduced cervical cancer incidence and mortality over the past few decades. As we reflect on the successes of cervical cancer screening, this article will highlight why it is important to assess the historical performance of screening and guidelines and determine where improvements can be made to continue driving toward the goal of cervical cancer elimination. It will also examine challenges physicians face when screening guidelines from professional societies differ. Given the impressive contributions that science and ObGyns have made in the last 80 years of cervical cancer screening in the United States, continued evaluation of society recommendations and consideration of tangible steps to move women's health forward will further strengthen cancer screening for the benefit of patients.

The author reports no financial relationships relevant to this article.

In the United States, routine screening has substantially reduced cervical cancer incidence and mortality over the past few decades, with new cases decreasing from 14.8 to 6.7 per 100,000 persons from 1975 to 2018.[1] Between 1975 and 2019, there was also a reduction in the mortality rate by more than half, from 5.55 to 2.16 per 100,000 persons.[1] One of the primary drivers for this progress has been more widespread implementation of cervical cancer screening, first with the conventional Pap smear, and then with improvements and additions including liquid-based cytology and human papillomavirus (HPV) testing in conjunction with cytologic screening.

Despite these significant advances, cervical cancer is still projected to cause approximately 4,300 deaths in 2021, ranking as the 15th most common cause of cancer death overall in the United States and the third most common gynecologic cancer.[1,2] As we celebrate the successes of cervical cancer screening during Cervical Health Awareness Month, it is key that we reflect upon the historical performance of screening and guidelines to assess where improvements can be made as we drive toward the goal of cervical cancer elimination.

Examining the 2012 consensus guidelines: Extended intervals increase rates of underscreening

In the years since the introduction of the Pap test, the United States has experienced several iterations of cervical

cancer screening guidelines. The most recent and broadly adopted of these were the 2012 consensus guidelines.[3] For nearly a decade, these have remained unchanged, with the exception of an option for HPV primary screening, which was added to the United States Preventive Services Task Force (USPSTF) screening guidelines in 2018.[4]

As we approach a decade since the consensus guidelines were released, we have begun to see some unintended consequences surface over time. First, it is now evident that patients are not seeing their ObGyn as often as they did in the years immediately preceding the 2012 consensus guidelines, a trend that has not been seen among primary care physicians.[5] While there is no way to be certain that the consensus guidelines caused this, it certainly seems plausible that patients have interpreted the less frequent need for cervical cancer screening to mean that they no longer require routine gynecologic care.

Second, it may be more difficult for patients to remember and keep track of when their cervical cancer screening is due, especially when they are not seeing their doctors regularly. Recently, a large study from the New Mexico Pap Registry demonstrated that in the years since the screening interval was increased to 5 years, the rate of underscreening increased significantly: for patients undergoing cytology screening, there was a greater than 4-fold increase in women being underscreened. There was also a statistically significant rise in the number of patients who were co-tested and waited longer than the recommended 5 years between screenings.[6] The authors of the study note that their data only go back 7 years, thus suggesting their calculations are underestimates of the true rate of underscreening. These statistics make it all the more concerning that we have seen a clear and significant increase in the rate of underscreening since the intervals were lengthened.

Finally, over the last several years since the consensus guidelines were published, it appears that extended intervals have contributed to an increase in cervical cancer for women under age 50.[1] While the guidelines demonstrate that extended interval testing is safe if followed perfectly, it seems that the unintended consequence has been decreased screening adherence and, potentially, a rise in cancer rates among younger women.

Looking to the future, we as leaders in women's health will need to do everything we can to encourage patients to continue regular screening, with a focus on systems that will remind patients and clinicians when cervical screening is due—a task that appears to be more difficult as we extend screening intervals. Building from this example, and as we consider the 2012 consensus guidelines, we see both successes and opportunities for improvement. We must now proactively anticipate the potential unintended consequences of new guidelines and their implementation.

American Cancer Society (ACS) 2020 guidelines: Anticipated challenges

As physicians, one challenge we face in medicine is when the guidelines of professional societies differ. This disconnect creates confusion over which guidelines to adopt for patients and doctors alike. ObGyns deal with this daily in terms of recommendations for breast cancer and colon cancer screening for our patients. Now, with the introduction of the ACS guidelines in 2020, we again are faced with conflicting recommendations for cervical cancer screening.

The 2020 ACS guidelines on cervical cancer screening propose a paradigm shift in terms of how we screen patients for cervical cancer in the United States. Historically, screening has been based on the Pap test, but the ACS has now advocated for gradual elimination of cytology as a screening test, and toward HPV screening alone in all patients.[7] Further, they recommend increasing the age at which screening starts from 21 to 25 years of age.[7] This has created increasing confusion for patients and controversy among ObGyns. At the bedside, each physician will have to now decide how to counsel their patients about screening in an area that has become increasingly complex in the past few decades.

Reflecting again on the unintended consequences of the 2012 consensus guidelines, it is only 10 years later that we note increased rates of cervical cancer in patients under 50, and a stark increase in rates of underscreening. We must consider the negative consequences we can anticipate if we broadly implement HPV primary screening at 25 years of age in our practices.

In fact, the other professional societies, led by the American College of Obstetricians and Gynecologists (ACOG), have issued a response to the ACS guidelines indicating that they have some concerns about their implementation. In the spring of 2021, ACOG released a Practice Advisory that was endorsed by the American Society for Colposcopy and Cervical Pathology (ASCCP) and the Society of Gynecologic Oncology (SGO), in which they recommend adhering to the 2018 United States Preventive Services Task Force guidelines over adoption of the 2020 ACS guidelines, for several reasons.[8]

Age at screening initiation

The first of these relates to age at screening initiation. The ACS guidelines suggest that screening not be started until age 25, moving away from age 21 as has been previously recommended. The ACS has pointed to the overall

low rates of invasive cancer in this age group, as well as a desire to minimize the risks of overdiagnosis of low-grade disease that would otherwise be destined to resolve in young patients. The consequence, however, is that if HPV primary screening were to be adopted in younger women, overdiagnosis of HPV would be a significant concern as 20-24 years is the age group in which HPV infections peak, and infection rates in 25- to 29-year-olds remain over 25%.[9]

Furthermore, while less common than in older age groups, severe dysplasia and even invasive cancer are seen in patients under 25. Approximately 1% of cervical cancers occur in patients under 25.[10,11] Are these women not worth 2 Pap tests between the ages of 21 and 25 if that can stop cervical cancer? While it is certainly important to avoid overtreatment of patients who have low-grade disease, the ASCCP guidelines have also moved toward a much more conservative approach in recent years, with the introduction of the 2019 ASCCP Risk-Based Management Guidelines. For example, patients are no longer treated for cervical intraepithelial neoplasia (CIN) 1, and conservative management is recommended prior to treating CIN 2 for young patients and those who desire future childbearing.[12] These changes significantly assuage concerns about the risk of overtreatment in these young age groups, as we may identify disease but will only treat severe dysplasia that represents a true threat to patient health.

The ACOG Practice Advisory shares these concerns related to delaying the screening age to 25. In their response, they recommend maintaining the current screening strategy of cytology alone in 21- to 29-year-olds and preservation of screening starting at age 21.[8] They point to the already suboptimal screening rates in patients under 30, below-target HPV vaccination rates in the United States, and the potential for the ACS changes to worsen existing health inequities in cervical cancer screening, incidence, morbidity, and mortality.[8]

In sum, with patient adherence already a growing concern since the lengthening of screening intervals almost a decade ago, the new ACS guidelines that advocate for HPV-alone testing and delaying screening initiation for women until age 25 could reasonably be anticipated to further worsen screening adherence, especially among women under 30 years of age who may be confused by the changes or assume they no longer require regular screening.

Potential unintended consequences of moving to HPV primary screening

Although the ACS guidelines advocate for a transition to HPV primary screening, there are several concerns and potential unintended consequences that must be considered in this area as well. First, as previously noted, HPV infections tend to peak in the under-30 age group and are often transient and self-limited. Thus, one concern relating to HPV screening in patients under 30 is that there will be high rates of HPV diagnosis, the need for cytology triage testing, and ultimately higher colposcopy rates in this population of patients.[7] The model utilized by the ACS does predict an increase in colposcopies if we move to an HPV primary strategy.[7] Until HPV vaccination rates are much higher in the population, this disadvantage will remain and expose patients to increased anxiety and testing.

Second, studies have shown a significant rate of HPV-negative disease in the population.[13-15] Although most cervical cancers are *caused* by HPV, as dysplasia progresses and the underlying cytologic abnormalities worsen, patients can actually test negative for HPV. In this setting, the combination of cytology plus HPV in patients over 30 provides a needed safety net, to ensure that HPV-negative disease is accounted for. While HPV primary screening will identify most pre-cancers and cancers, studies have consistently shown that HPV-negative disease is a persistent concern, demonstrating that 9%-10% of invasive cancers will test negative with commercially available tests.[13-15] We have also seen that patients with dysplasia can test negative for HPV, with the largest study demonstrating a 2.4% rate of HPV-negative CIN3/adenocarcinoma in situ (AIS).[16] If these patients do not have a Pap done along with their HPV test, they will likely be told to have their next screen in 5 years, at which time they will be at risk of already having invasive disease.

In acknowledgement of these findings, ACOG continues to recommend maintaining cytology every 3 years in patients 21-29 years old, and has recommended maintaining the current screening strategy that allows for patient and clinician choice between cytology alone, HPV alone, and co-testing in patients 30 and over.[8] Given that co-testing provides the most sensitive screening strategy for patients, it's understandable that HPV primary has not taken hold despite the ACS recommendations, with the most recent data showing an annual test use of <0.5% across all age groups.[17]

Debate about screening women >65 years of age

Looking to future guideline updates, one area of significant interest recently relates to the age at screening cessation. While we are now accustomed to the recommendation to allow patients to exit screening at age 65, recently epidemiologists and experts in the field have begun to question the appropriateness of this recommendation.

There are several reasons for this: first and foremost, life expectancy has risen, and patients are living on average another 20 years beyond age 65, making ongoing screening a more reasonable consideration. Additionally, we know that approximately 20% of cervical cancers occur in patients over 65, and that Black patients are disproportionately impacted in this age group.[18] Further, while the current recommendations do specify strict criteria to qualify for screening cessation, approximately two-thirds of patients in this age group do not meet criteria for screening cessation.[19] Thus, it may be reasonable to simplify and extend screening recommendations in the future to ensure that we are truly, accurately assessing risk and missing the fewest number of patients possible. For this reason, some have recently called for a re-examination of the data to assess whether it might better serve public health to extend routine screening beyond age 65.

Choosing guidelines wisely

Based on all these considerations, ObGyns have a clear responsibility to help ensure that patient care and cervical cancer screening guidelines optimize the diagnosis of true disease, while minimizing unnecessary intervention and patient burden wherever possible. We must do so with an awareness of the unintended consequences that we have seen come to pass as a result of prior screening recommendations and attempt to predict and mitigate potential unintended consequences of future recommendations.

Based on the best current available evidence, we need to encourage our patients to start cervical cancer screening and well-woman exams at age 21. To optimize protection as well as minimize need for reflex testing and colposcopies, we should be doing so with cytology alone in the 20s, with co-testing beginning at age 30. Having identified opportunities to improve screening adherence in the last decade, we must continue to update, educate, and remind patients of when their next screenings are due and provide opportunistic screening whenever possible. Finally, with an eye to the future, we must reconsider the potential role of screening in patients over 65, and until guidelines potentially re-examine this age group, we must be proactive to ensure we have reviewed each patient's screening history prior to exiting her from surveillance. As we reflect on the impressive contribution science and ObGyns have made in the last 80 years of cervical cancer screening in the United States, we encourage continued evaluation of society recommendations and consideration of tangible steps we can make to move women's health forward and strengthen this critical cancer screening for the benefit of our patients.

REFERENCES

1. Cancer Stat Facts: Cervical Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/cervix.html
2. Cervical Cancer: Statistics. January 2021. https://www.cancer.net/cancer-types/cervical-cancer/statistics
3. Saslow D, Solomon D, Lawson HW, et al; American Cancer Society, American Society for Colposcopy and Cervical Pathology, American Society for Clinical Pathology. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol.* 2012;137(4):516-542.
4. US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA.* 2018;320(7):674-686.
5. Polcari AM, Hecht E. Trends in cervical cancer screening versus national guidelines. *Obstet Gynecol.* 2017(5);129:108S-109S.
6. Castle PE, Kinney WK, Chen L, et al; for the New Mexico HPV Pap Registry Steering Committee. Adherence to national guidelines on cervical screening: a population-based evaluation from a statewide registry. *J Natl Cancer Inst.* 2021 Aug 31;djab173. doi: 10.1093/jnci/djab173. Online ahead of print.
7. 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.
8. Updated Cervical Cancer Screening Guidelines. April 2021. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines
9. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA.* 2007;297(8):813-819.
10. Kong Y, Zong L, Yang J, et al. Cervical cancer in women aged 25 years or younger: a retrospective study. *Cancer Manag Res.* 2019;11:2051-2058.
11. Teixeira JC, Santos DZ, Campos CS, et al. Cervical cancer in women under 25 years of age and outside the screening age: diagnosis profile and long-term outcomes. *Int J Gynecol Obstet.* 2020;154(1):150-156.
12. Perkins RB, Guido RS, Castle PE, et al; for the 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.
13. Zhao C, Li Z, Nayar R, et al. Prior high-risk human papillomavirus testing and Papanicolaou test results of 70 invasive cervical carcinomas diagnosed in 2012: results of a retrospective multicenter study. *Arch Pathol Lab Med.* 2015;139(2):184-188.
14. Blatt AJ, Kennedy R, Luff R, Austin RM, Rabin DS. Comparison of cervical screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol.* 2015;123(5):282-288.
15. Zheng B, Li Z, Griffith CC, et al. Prior high-risk HPV testing and Pap test results for 427 invasive cervical cancers in China's largest CAP-certified laboratory. *Cancer Cytopathol.* 2015;123(7):428-434.
16. Kaufman HW, Alagia DP, Chen Z, et al. Contributions of liquid-based (Papanicolaou) cytology and human papillomavirus testing in co-testing for detection of cervical cancer and precancer in the United States. *Am J Clin Pathol.* 2020;154(4):510-516.
17. Qin J, Shahangian S, Saraiya M, et al. Trends in the use of cervical cancer screening tests in a large medical claims database, United States, 2013-2019. *Gynecol Oncol.* 2021;163(2):378-384.
18. Dilley S, Huh W, Blechter B, et al. It's time to re-evaluate cervical cancer screening after 65. *Gynecol Oncol.* 2021;162(1):200-202.
19. 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.