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We Have the Tools to Prevent Cervical Cancer—So Why Are Rates Increasing?

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The introduction of the Pap test in the 1940s has led to a significant decline in cervical cancer incidence and mortality in the United States.[1] More recent innovations, such as liquid-based cytology and human papillomavirus (HPV) testing, have further improved clinical performance in screening technology.[2] As a result, cervical cancer screening is often hailed as the most successful screening program ever implemented. Despite these past successes, cervical cancer incidence is no longer decreasing (Figure 1) and is *actually rising significantly* in younger women within the United States (Figure 2). In a country with a well-established screening program, effective screening tools, and HPV vaccination, it seems unfathomable that we are witnessing an increase in cervical cancers. This alarming trend should be cause for concern among all healthcare professionals.

There are approximately 14,100 new cases diagnosed and 4280 deaths due to cervical cancer each year in the United States.[3] These numbers may appear low, but it is important to remember that the aim of screening is to detect and treat precancerous lesions prior to ever developing cervical cancer, which means no one should get or die from cervical cancer. Furthermore, if a woman does develop cervical cancer, it is critical to detect it in the early, asymptomatic stages to ensure the best outcomes for the patient. While most cervical abnormalities are detected as precancerous lesions and 42% of cervical cancers are detected as Stage I, approximately 15% of cervical cancers are not diagnosed until Stage IV. This represents an increase in the rate of advanced-stage cancers diagnosed in recent years.[4,5] This is particularly concerning, given the difference in 5-year survival rates: 17% for Stage IV compared with 92% for Stage I cervical cancer.[5] It begs the question: What has happened to our cervical screening program?

Co-testing (Pap + HPV testing) is the most widely used screening paradigm in the United States with approximately 70% of women aged 30 to 65 receiving both tests.[6] This adoption has allowed many real-world evidence studies to identify the contribution of the Pap and HPV tests within the co-testing paradigm. As a result, it is well established that HPV primary testing alone is less sensitive than when it is combined with the Pap (co-testing) for the detection of precancerous lesions and cervical cancers. Approximately 9% of precancerous lesions and up to 31% of cancers were HPV negative in published literature from US populations.[7,8,9,10] While these studies have their limitations, they may be more representative of the United States population than the studies often used to develop screening and management guidelines, as studies in other populations tend to underrepresent cervical cancer risk and the contribution of the Pap test within underscreened populations. For example, data from the Centers for Disease Control and Prevention's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) found that for nearly every combination of HPV and cytology result, the risk of immediate CIN3+ was higher in the underscreened population compared with the women who were up-to-date with screening.[11] While the NBCCEDP was not able to assess the long-term cervical intraepithelial neoplasia (CIN)3+ risk in their patient population due to lack of compliance with follow-up, other studies have

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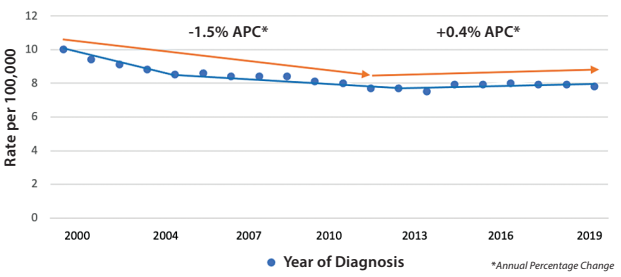
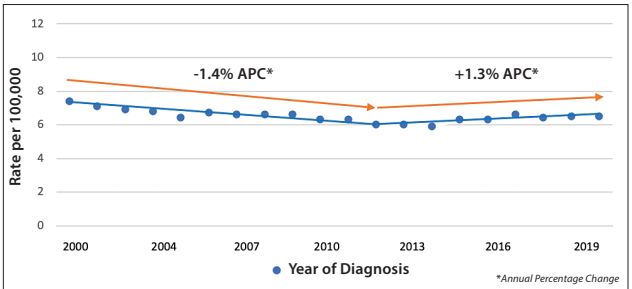
FIGURE 1 Cervical cancer rates in all women



Surveillance, Epidemiology, and End Results (SEER) Program Database: Incidence—SEER Research Data, 8 Registries, Nov 2021 Sub (2000-2019).

FIGURE 2 Cervical cancer is increasing in women <50



Surveillance, Epidemiology, and End Results (SEER) Program Database: Incidence—SEER Research Data, 8 Registries, Nov 2021 Sub (2000-2019).

demonstrated that a negative Pap + HPV (co-testing) reduces the long-term CIN3+ risk over a negative HPV primary test alone.[12]

Cervical screening guidelines have gone through many iterations over the past couple of decades, with the most notable change in 2012 when consensus guidelines were published.[13,14] The new guidelines recommended women aged 21 to 29 have a Pap test every 3 years, and women aged 30 to 65 receive Pap + HPV (co-testing) every 5 years.[15] The notable differences in these guidelines compared with previous versions were that Pap + HPV (co-testing) was the preferred screening option, and that the interval was extended to from 3 years to 5 years. At the time, Kinney et al wrote: *"At no point in the publications describing the new guidelines it is acknowledged that we are now recommending more cancer and more death from cancer than the previously recommended 3-year cotesting provides, and that we are doing so presumably for the purpose of avoiding a cervical treatment that is not associated with detectable increased mortality."*[16] This concern stems from the fact that risk of CIN3+ in women with negative screening results rises between 3 years and 5 years. Despite this, screening intervals have remained unchanged in subsequent guidelines, with the only substantive difference being the addition of HPV testing alone every 5 years as another option and the existing Pap + HPV (co-testing) every 5 years or a Pap test alone every 3 years.[17]

In addition to extending intervals and increasing the risk of missing additional cervical disease, there have been other potential unintended consequences—women have become less adherent to screening over time. One recent study found that only 65% of eligible women aged 30 to 65 and less than 50% of women aged 21 to 29 were up to date with screening.[18] Unfortunately, this study is not in isolation. Even higher rates have been observed in uninsured women, where only 40% were up to date with screening.[19,20,21] A recent study from the New Mexico Cancer Registry demonstrated that the rate of underscreening for cervical cancer has risen significantly since 2012. This led the authors to conclude that "*a new and alarming observation was the increasing percentage of women being screened at too long an interval.*"[10] This is a concerning trend, given that more than half of all new cervical cancers are in women who have never been screened or have not been screened in the previous 5 years.[22]

A recent study from the United States Preventive Services Task Force (USPSTF) examined cervical cancer screening behavior over time to assess, by sociodemographic factors, reasons why women do not receive up-to-date screening.[20] This study found that guideline-concordant screening behavior declined between 2005 and 2019, with lack of knowledge cited as the biggest barrier to being up to date with screening. While it is tempting to believe that guidelines should continue to evolve to thread the needle of harms and benefits of screening, the real focus should be on how to improve patient knowledge and adherence with current screening guidelines.

With the understanding that no woman should develop cervical cancer, it is concerning to see that screening efforts in the United States continue to be eroded amid decreases in screening participation and increases in cervical cancer. How can we improve the screening landscape in this country? We live in a diverse country with an imperfect healthcare system. Our screening guidelines should reflect that and allow us to make the best decisions for our patients. We need to advocate for our patients and educate about the importance of screening. We need to ensure that patients receive the best opportunity for disease detection and longer-term protection through screening with co-testing (Pap + HPV testing).

REFERENCES

1. American Cancer Society. The Pap (Papanicolaou) test. https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/screening-tests/pap-test.html
2. National Cancer Institute. Cervical cancer screening. https://www.cancer.gov/types/cervical/pap-hpv-testing-fact-sheet
3. American Cancer Society. Key statistics for cervical cancer. https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html
4. National Cancer Institute. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cervix uteri. Stage distribution of SEER incidence cases, 2010-2019. https://seer.cancer.gov/statistics-network/explorer/application.html?site=57&data_type=1&graph_type=4&compareBy=race&chk_race_1=1&hdn_sex=3&age_range=1&advopt_precision=1&hdn_view=0-graphArea
5. Francoeur AA, Liao C-I, Casear MA, et al The increasing incidence of stage IV cervical cancer in the USA: what factors are related? *Int J Gynecol Cancer*. 2022;ijgc-2022-003728.
6. 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.
7. Zhou, H, Mody, R.R, Luna E, et al. Clinical performance of the Food and Drug Administration-approved high-risk HPV test for the detection of high-grade cervicovaginal lesions. *Cancer Cytopathol*. 2016;124(5):317-323.
8. Austin RM, Onisko A, Zhao C. Enhanced detection of cervical cancer and precancer through use of imaged liquid-based cytology in routine cytology and HPV cotesting. *Am J Clin Pathol*. 2018;150(5):385-392.
9. Kaufman HW, Alagia DP, Chen Z, Onisko A, Austin RM. Contributions of liquid-based (Papanicolaou) cytology and human papillomavirus testing in cotesting for detection of cervical cancer and precancer in the United States. *Am J Clin Pathol*. 2020;154(4):510-516.
10. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol*. 2011;12(7):663-672.
11. Saraiya M, Cheung LC, Soman A, et al. Risk of cervical precancer and cancer among uninsured and underserved women from 2009 to 2017. *Am J Obstet Gynecol*. 2021;224(4):366.e1-366.e32.
12. Gage JC, Schiffman M, Katki HA, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J Natl Cancer Inst*. 2014;106(8):dju153.
13. Saslow D, Solomon D, Lawson HW, et al. 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.
14. Perkins RB, Guido RS, Castle PE, et al. 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.
15. Massad LS, Einstein MH, Huh WK, et al; 2012 ASCCP Consensus Guidelines Conference. 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2013;17(5 suppl 1):S1-S27.
16. Kinney WM, Poitras N, Fetterman B, Lorey T. Magnitude of increased lifetime risk of cervical cancer and death from cervical cancer with new screening recommendations. *Gynecologic Oncology*. 2014;133(Supp1): 38.
17. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(7):674-686.
18. MacLaughlin KL, Jacobson RM, Radecki Breitkopf CR, et al. Trends over time in Pap and Pap-HPV cotesting for cervical cancer screening. *J Womens Health (Larchmt)*. 2019;28(2):244-249.
19. 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;114(4)626-630.
20. Suk R, Hong Y-R, Rajan SS, Xie Z, Zhu Y, Spencer JC. Assessment of US Preventive Services Task Force guideline-concordant cervical cancer screening rates and reasons for underscreening by age, race and ethnicity, sexual orientation, rurality, and insurance, 2005 to 2019. *JAMA Netw Open*. 2022;5(1):e2143582.
21. Kiser LH, Butler J. Improving equitable access to cervical cancer screening and management. *Am J Nurs*. 2020;120(11):58-67.
22. Centers for Disease Control and Prevention. Millions of US women are not getting screened for cervical cancer. https://www.cdc.gov/media/releases/2014/p1105-vs-cervical-cancer.html