CME CREDIT **LEARNING OBJECTIVE:** Readers will routinely offer vaccination against human papillomavirus and screen women for cervical cancer

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Disparities in cervical cancer in African American women: What primary care physicians can do

ABSTRACT

African American women are disproportionately affected by cervical cancer, with higher rates of incidence and mortality than white women. Most of the difference would disappear with equal treatment. As usual, primary care providers are on the front lines.

KEY POINTS

Vaccination against human papillomavirus (HPV) is recommended for females ages 9 to 26 and males age 11 or 12. Three vaccines are available: a 2-valent, a 4-valent, and a newer 9-valent preparation.

HPV vaccination can now be given in a 2-dose series administered 6 to 12 months apart for patients who are ages 9 through 14 at the time of the first dose and are immunocompetent. Other patients should receive a 3-dose series, including patients who received 2 doses less than 5 months apart.

Cytologic screening (Papanicolaou testing) by itself is recommended every 3 years between the ages of 21 and 30. After age 30, combined screening with cytology and testing for HPV is recommended every 5 years.

Concomitant risk factors for cervical cancer such as human immunodeficiency virus infection and tobacco use should also be addressed during office visits.

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African American, Hispanic, American Indian, and Alaskan Native women continue to be disproportionately affected by cervical cancer compared with white women. From 2006 to 2010, the incidence of cervical cancer in African American women was 10.3 per 100,000; in white women it was 7.2.[1] The mortality rate from cervical cancer in African American women is twice that in white women.[1] Although cervical cancer rates have decreased nationwide, significant racial health disparities persist.

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As the first-line healthcare providers for many women, the primary care physician and the general obstetrician-gynecologist are optimally positioned to reduce these disparities.

Cervical cancer is the third most common gynecologic cancer, after uterine and ovarian cancer. Nearly 13,000 new cases are diagnosed each year in the United States, and more than 4,000 women die of it.[2] Fortunately, cervical cancer can be significantly prevented with adequate screening and vaccination against human papillomavirus (HPV).

WHY ARE BLACK WOMEN MORE LIKELY TO DIE OF CERVICAL CANCER?

Later stage at diagnosis. African American women are more likely to present with advanced cervical cancer than non-Hispanic white women.[3–6]

Less-aggressive treatment. African American women are more likely to receive no treatment after a cancer diagnosis.[6] Differences in treatment may be attributed to comorbid

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conditions, stage at cancer diagnosis, and patient refusal.[5,7]

Less access to care. A study from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute looked at 7,267 women (4,431 non-Hispanic white women, 1,830 Hispanic white women, and 1,006 non-Hispanic African American women) who were diagnosed with primary invasive cervical cancer from 1992 to 1996 and followed through 2000. African American women had a 19% higher mortality rate compared with non-Hispanic white women during follow-up despite adjusting for age, stage, histology, and time of first treatment.[8]

However, a later study from the same program found no such difference after 1995, when the data were adjusted for marital status, disease stage, age, treatment, grade, and histology.[6]

Equal access to healthcare may eliminate most of the disparity.[7] A study in women with cervical cancer who sought treatment within the United States military healthcare system found no difference in treatment or 5- and 10-year survival rates between African American and white women.[5] Equal access to comprehensive healthcare eliminated any disparity once cervical cancer was diagnosed.

CERVICAL CANCER SCREENING

The value of cervical cancer screening and prevention is well established. In 1941, Papanicolau reported that cervical cancer could be detected from vaginal smears.[9] Since the development and widespread implementation of the "Pap" smear, cervical cancer rates have decreased dramatically in the United States.

Another major advance was the discovery that persistent infection with HPV is necessary for the development of cervical cancer, precancerous lesions, and genital warts.[10]

With advancing research, guidelines for cervical cancer screening have changed considerably over the years. Today, combined cervical cytologic and HPV testing is the mainstay. (Isolated HPV testing is generally not available outside clinical trials.)

Who should be screened?

Previous recommendations called for women to undergo Pap testing when they first became sexually active and then every year. However, cervical lesions are likely to regress in young women.[11] One study found that 28% of cervical intimal neoplasia (CIN) grade 2 and 3 lesions spontaneously regressed by 15 weeks, although lesions associated with HPV 16 infection were less likely to regress than with other HPV types.[12] A study of college women found that HPV infection persisted in only 9% of women after 24 months.[13]

To minimize unnecessary treatment of young women with dysplasia, the American Society for Colposcopy and Cervical Pathology in 2012 recommended cytologic screening for all women 21 years or older, regardless of age at first sexual encounter.[14] Screening intervals were changed from every year to every 3 years until age 30, at which time cotesting with cytology and HPV testing is performed every 5 years. Routine cotesting is not recommended for women younger than 30, who have a high likelihood of HPV infection and spontaneous regression.

In 2014, the US Food and Drug Administration approved primary HPV screening (ie, testing for HPV first, and then performing cytology in samples that test positive) for women age 25 and older.[15]

Patients who need further evaluation and testing should be referred for colposcopy. The current guidelines for patients who have abnormal results on cervical cancer screening[16] can be reviewed at www.asccp.org/asccp-guidelines.

As screening guidelines continue to evolve, primary care physicians will need to stay current and also help educate their patients. For example, many of our patients have undergone annual Pap screening for most of their lives and may not yet know about the new testing intervals.

Equal access to healthcare may eliminate most of the disparity

Are there disparities in screening and follow-up?

Disparities in screening and follow-up may exist, but the evidence is not clear-cut.

In a 2013 National Health Interview Survey report, the rates of cervical cancer screening with Pap tests did not differ between African American and white women.[17] However, the information on Pap testing was based on a single question asking participants if they had had a Pap test in the last 3 years. In our experience, patients may confuse Pap tests with

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TABLE 1

HPV vaccines available in the United States

Vaccine	HPV types covered
2-valent (Cervarix)	16,18
4-valent (Gardasil)	6, 11, 16, 18
9-valent (Gardasil-9)	6, 11, 16, 18, 31, 33, 45, 52, 58

speculum examinations.

Once women are screened, adequate and timely follow-up of abnormal results is key.

In a study from the National Breast and Cervical Cancer Early Detection Program,[18] women who had cytology findings of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions were to undergo repeat Pap testing every 4 to 6 months for 2 years. African American women were the least likely to have a follow-up Pap smear compared with other racial groups.

HPV vaccination rates lag behind those of other routine vaccines such as Tdap and meningococcal conjugate

On the other hand, there was no difference related to race in follow-up rates of abnormal Pap tests in women ages 47 to 64 in the South Carolina Breast and Cervical Cancer Early Detection Program.[19]

In a study in an urban population (predominantly African African), the overall follow-up rate was only 26% at 12 months from an initial abnormal Pap smear. This study did not find any differences in follow-up according to race or ethnicity; however, it had insufficient power to detect a difference because only 15% of the study participants were white.[20]

What is in a genotype?

HPV is implicated in progression to both squamous cell carcinoma and adenocarcinoma of the cervix. Worldwide, HPV genotypes 16 and 18 are associated with 73% of cases of invasive cervical cancer; most of the remainder are associated with, in order of decreasing prevalence, genotypes 58, 33, 45, 31, 52, 35, 59, 39, 51, and 56.[21]

High-grade cervical lesions in African American women may less often be positive for HPV 16 and 18 than in white women.[22,23] On the other hand, the proportion of non-Hispanic black women infected with HPV 35 and 58 was significantly higher than in non-Hispanic white women.[22] Regardless, HPV screening is recommended for women of all races and ethnicities.

The 2-valent and 4-valent HPV vaccines do not cover HPV 35 or 58. The newer 9-valent vaccine covers HPV 58 (but not 35) and so may in theory decrease any potential disparity related to infection with a specific oncogenic subtype.

THE ROLE OF PREVENTION

HPV vaccination

Currently, 3 vaccines against HPV are available in the United States, a 2-valent, a 4-valent, and since 2015, a 9-valent preparation (**Table 1**).

The Females United to Unilaterally Reduce Endo/Ectocervical Disease study demonstrated that the 4-valent vaccine was highly effective against cervical intraepithelial neoplasia due to HPV 16 and 18.[24] In another study, the 2-valent vaccine reduced the incidence of CIN 3 or higher by 87% in women who received all 3 doses and who had no evidence of HPV infection at baseline.[25]

HPV vaccination is expensive. Each shot costs about $130, plus the cost of administering it. Although the Vaccines for Children program covers the HPV vaccine for uninsured and underinsured children and adolescents under age 19, Medicaid coverage varies from state to state for adults over age 21.

The Advisory Committee on Immunization Practices (ACIP)[26] recommends routine vaccination for:

- Males 11 or 12 years old
- Females ages 9 to 26.

In October 2016, the ACIP approved a 2-dose series given 6 to 12 months apart for patients starting vaccination at ages 9 through 14 years who are not immunocompromised. Others should receive a 3-dose series, with the second dose given 1 to 2 months after the first dose and the third dose given 6 months after the first dose.[27] Previously, 3 doses were recommended for everyone.

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Disparities in HPV vaccination rates

HPV vaccination rates among adolescents in the United States increased from 33.6% in 2013 to 41.7% in 2014.[28] However, HPV vaccination rates continue to lag behind those of other routine vaccines, such as Tdap and meningococcal conjugate.

Reagan-Steiner et al[28] reported that more black than white girls age 13 through 17 received at least 1 dose of a 3-dose HPV vaccination series, but more white girls received all 3 doses (70.6% vs 61.6%). In contrast, a meta-analysis by Fisher et al[29] found African American and uninsured women generally less likely to initiate the HPV vaccination series. Kessels et al[30] reported similar findings.

Barriers to HPV vaccination

Barriers to HPV vaccination can be provider-dependent, parental, or institutional.

Malo et al[31] surveyed Florida Medicaid providers and found that those who participated in the Vaccines for Children program were less likely to cite lack of reimbursement as a barrier to vaccination.

Meites et al[32] surveyed sexually transmitted disease clinics and found that common reasons for not offering HPV vaccine were cost, staff time, and difficulty coordinating follow-up visits to complete the series.

Providers report lack of urgency or lack of perception of cervical cancer as a true public health threat, safety concerns regarding the vaccine, and the inability to coadminister vaccines as barriers.[33]

Studies have shown that relatively few parents (up to 18%) of parents are concerned about the effect of the vaccine on sexual activity.[34] Rather, they are most likely to cite lack of information regarding the vaccine, lack of physician recommendation, and not knowing where to receive the vaccine as barriers.[35,36]

Guerry et al[37] determined that the single most important factor in vaccine initiation was physician recommendation, a finding reiterated in other studies.[35,38] A study in North Carolina identified failure of physician recommendation as one of the missed opportunities for vaccination of young women.[39]

Therefore, the primary care physician, as the initial contact with the child or young adult, holds a responsibility to narrow this gap. In simply discussing and recommending the vaccine, physicians could increase vaccination rates.

REPRODUCTIVE HEALTH

Although 80% of women will be infected with HPV in their lifetime, only a small proportion will develop cervical cancer, suggesting there are other cofactors in the progression to cervical cancer.[40]

Given the infectious etiology of cervical cancer, other contributing reproductive health factors have been described. As expected, the number of sexual partners correlates with HPV infection.[41,42] Younger age at first intercourse has been linked to development of cervical neoplasia, consistent with persistent infection leading to neoplasia.[41,42]

Primary care physicians should provide timely and comprehensive sexual education, including information on safe sexual practices and pregnancy prevention.

Human immunodeficiency virus

In 2010, the estimated rate of new human immunodeficiency virus (HIV) infections in African American women was nearly 20 times greater than in white women.[43] Previous studies have shown a clear relationship between HIV and HPV-associated cancers, including cervical neoplasia and invasive cervical cancer.[44,45]

The estimated rate of new HIV infections in African American women was nearly 20 times greater than in white women

Women with HIV should receive screening for cervical cancer at the time of diagnosis, 6 months after the initial diagnosis, and annually thereafter.[46]

Conflicting evidence exists regarding the effect of highly active antiretroviral therapy on the incidence of HPV-related disease, so aggressive screening and management of cervical neoplasia is recommended for women with HIV, regardless of CD4+ levels or viral load.[47–49]

Additional infectious culprits

Coinfection with other sexually transmitted infections, specifically *Chlamydia*, herpes, and HIV, has been associated with cervical neoplasia and invasive cervical cancer. A positive linear association exists between the number of sexually transmitted infections and cervical neoplasia.[50]

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TABLE 2

Cervical cancer prevention: Tips for the primary care physician

Have the conversation. Educate women about cancers related to human papillomavirus (HPV), including cervical cancer.

Screen all women for cervical cancer and ensure adequate follow-up of abnormal tests by implementing patient reminders and interactive telephone counseling.

Routinely offer HPV vaccination with other required vaccinations. Introduce the HPV vaccine as a vaccine for cancer prevention, as opposed to a vaccine related to sexually transmitted disease.

Vaccinate all children equally. Do not offer the vaccine based on perceived risk factors. In other words, do not assume certain children are not at risk.

Educate patients about risk factors for cervical cancer.

C *trachomatis* is the most common sexually transmitted infection in the United States, with a 6-times higher rate in African American women.[51] Women who are seropositive for C *trachomatis* are at twofold higher risk of developing squamous cell cervical cancer.[52,53] Women who are seropositive for *Chlamydia* infection, herpes virus 2, or HPV are at markedly increased risk of invasive cervical cancer.[50]

Women who are seropositive for *Chlamydia*, herpes virus 2, or HPV are at markedly higher risk of invasive cervical cancer

Tobacco use

The negative impact of smoking on numerous other cancers resulted in investigation of its role in cervical cancer.

Early case-control studies found an association between cervical cancer and smoking,[54] but because these studies did not account for HPV infection status, they could not establish causality. Subsequently, several studies did control for HPV infection; the risk of squamous cervical cancer was twice as high in women who had ever smoked.[55] Furthermore, the more cigarettes smoked per day, the higher the risk of cervical neoplasia.[41,56]

According to the US Centers for Disease Control and Prevention in 2014, the highest prevalence of smoking was among American Indian and Alaskan Native women, 32.5% of whom said they smoked every day, compared with 17.2% of white women and 13.7% of African American women.[57]

HOW CAN PRIMARY CARE PHYSICIANS CLOSE THE GAP?

Primary care physicians are the first point of contact for patients of all ages and so can help minimize such disparities. They can tackle 2 important cervical cancer prevention interventions first-hand: vaccination and screening (**Table 2**), including follow-up of abnormal screening results.

By promoting HPV vaccination to children and young adults, primary care physicians can help prevent cervical cancer. Moreover, primary care physicians will see most adolescents for a nonpreventive health visit, an optimal opportunity to discuss sexual activity practices and HPV vaccination.[58] Including the HPV vaccine as routine with other vaccinations can close the gap.[38]

Screening and treatment of sexually transmitted infection during these visits can affect the risk that future HPV infection will progress to neoplasia or cancer. Persistent lifestyle modification counseling, especially smoking cessation through motivational interviewing, can lessen the risk of cervical cancer neoplasia progression.

Additionally, in light of recent changes in cervical cancer screening guidelines, the primary care physician's role as educator is of utmost importance. In one study, although 99% of women had received a Pap test, 87% could not identify the purpose of the Pap test.[59] The primary care physician's role is perhaps the most influential in preventing disease and, as such, has the greatest impact on a patient's disease process.

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