Should Cervical Cancer Screening be Performed Before the Age of 25 Years?

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MODERATOR STATEMENT

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United States (US) guidelines for cervical cancer screening are currently being revised, and raising the age to begin screening is being considered. High levels of human papillomavirus (HPV) vaccine delivery in other countries have led to considerable declines in rates of high-grade cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3) among young adult women.[1,2] As ongoing vaccination efforts continue to reduce rates of infection due to oncogenic HPV types,[3] the number of high-grade lesions will decrease, and cytologic screening in young women will be more likely to detect low-grade abnormalities caused by transient infections, rather than true precancers. Although cervical cancer is rare before the age of 25 years, these women have high rates of transient HPV infections and associated abnormalities, leaving them vulnerable to overtreatment.

For older than 25 years, however, the risk of cervical precancer and cancer rise with broad agreement that the benefits of screening outweigh the harms underpinned by epidemiological evidence of effectiveness. In the US, vaccination rates remain below national goals, screening is largely opportunistic, health insurance coverage is highly variable, and a minority of young women follow screening guidelines.[4] In addition, screening rates seem to be falling precipitously in this age group.[5] Therefore, arguments can be made for continuing to advocate screening among women aged 21 to 24 years so that they make cervical screening part of their normal well woman care and facilitate prevention of cancers among women aged 25 to 29 years related to underscreening. In this forum, we address the question of when to begin screening in the US, considering both the epidemiology and natural history of disease and the practical limitations of the US healthcare setting.

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SIDE 1

Women Younger Than 25 Years in the US Should be Screened for Cervical Cancer

Discussant: Anna-Barbara Moscicki

Worldwide, cervical cancer remains the second most common cancer in women after breast cancer, and breast and cervical cancers make up most cancer cases and deaths among women aged 20 to 39 years in medium- and high-income countries.[6] Cervical cancer rates begin to increase at the ages of 25 of 29 years, emphasizing the importance of screening for precancers before this age.[6] Although other cancers occur in this age group, including leukemia, thyroid, and liver cancers, only cervical cancer is preventable through screening and treatment of precancers. Benard et al.[4] estimated the 1999 to 2008 US rate of cervical cancer in 20- to 24-year-old women to be 1.0 (1.33–1.48) per 100,000 and in 25- to 29-year-old women 6.0 (5.78–6.1). Most women with cervical cancer have not been screened, implying that many cancers among the ages of 25 to 29 years could have been prevented by earlier screening and treatment. Cervical cancer rates decreased among women aged 25 to 29 years between 1999 and 2008, when screening younger than 25 years was common, indicating that screening before the age of 25 years decreases cancer rates in the ages of 25 to 29 years. In contrast, the rate of cancer among the ages of 21 to 24 years is low and unaffected by screening; therefore, screening is not currently recommended for women younger than 21 years in the US.

The power of screening in the 21- to 24-year-old women to prevent cancers in 25- to 29-year-old women was recently demonstrated by reports of incident cervical cancer from England, Scotland, and Wales when the age to start screening changed from the ages of 20 to 25 years. After screening younger than 25 years ceased, the incidence of cervical cancer increased in women aged 25 to 29 years. This increase was most concerning in the youngest age cohorts, those aged 25 to 25.5 years and those aged 25.5 to 26 years.[7] The percent increase in incidence rate (per 100,000) was 43.7% (37.4–49.9) in the former group of women and 14% (9.9–18.1) in the latter.

Additional evidence supporting screening in women younger than 25 years comes from the ATHENA trial, a study of more than 47,000 women designed to examine the sensitivity and specificity of primary HPV testing for cervical cancer screening in the US.[8] As expected, detection of HPV was high in women aged 21 to 29 years—somewhat surprisingly, 38% of the CIN 3 was in women aged 21 to 29 years and 10% among women aged 21 to 24 years. Of the CIN 3 in women aged 25 to 29 years, almost 60% were cytology negative but HPV positive and were triaged to colposcopy and biopsy. This finding once again underscores the insensitivity of cytology to identify women at risk *if screened only once during this period.*

The HPV vaccine is expected to impact screening. However, HPV vaccination rates in the US continue to lag behind other countries, and less than 50% of age-eligible girls have received the full series.[9] In addition, the rates of vaccination vary greatly by state ranging from less than 49% to 70% or more. Modeling studies

suggest that vaccinating 75% to 80% of girls is critical to dramatically change HPV and CIN 3 rates.[10] In addition, national immunization registries do not exist in the US, making vaccine verification extremely difficult among young adult women.

One of the most compelling arguments for continuing to initiate screening starting at the age of 21 years in the US is the lack of organized screening programs for cervical cancer. Without organized reminder/recall, it is incumbent on young women to seek care and set up appointments for cancer screening. Young adults are one of the largest and growing populations without health insurance in the US. Without state and federal funding programs, this groups remains without preventive care services.[11] There are now disturbing data that cervical cancer screening has been decreasing among all women, but specifically young women.[5] Although screening is recommended at 3-year intervals (36 months), a recent study using Family Pact claims that data showed that the percent of women aged 21 to 29 years having at least a single screen within 42 months decreased from approximately 75% in 2012 to less than 50% in 2015,[5] indicating that increasing the screening interval from 1 to 3 years has resulted in high rates of underscreening in women younger than 30 years. In contrast, screening rates for chlamydia did not change in women aged 20 to 24 years, suggesting that women continue to have contact with the health care system but are not receiving the recommended cervical cancer screening. This may be due to the fact that young women rarely have pelvic examinations anymore with chlamydia and gonorrhea screening, because this is typically performed using self-collected vaginal swabs or urine. Young women and their providers seem to be delaying pelvic examinations, perhaps because these examinations are time-consuming and may be uncomfortable. Conversely, patients may believe that if a speculum examination was performed, cervical cancer screening was performed, which can lead to confusion around when the next screen is due.

In conclusion, women aged 25 to 29 years are at risk of cervical cancer, and screening before the age of 25 years seems to decrease cancer rates, supporting the utility of screening women aged 21 to 24 years in the US. With the absence of an organized screening call/recall program as it exists in other countries, many women may initiate screening later than the recommended ages, which could lead to screening initiation beyond the age of 25 years if the screening age is raised. In addition, many young women do not adhere to cervical cancer screening recommendations.[5] This elevates their risk of developing cervical cancer, because "underscreened" and "unscreened" women are at greatest risk of developing cervical cancer. The current low vaccination rates and lack of immunization registries for vaccine verification do not confer enough protection to support "not screening" in the 21 to 24 age group. Although some US states have achieved relatively high rates of complete HPV vaccine coverage, having varied recommendations for states based on uptake would be very confusing and unlikely to impact underscreening because state borders are easily crossed. Until HPV vaccine uptake rates achieve a goal high enough to reduce CIN 3 rates among all US women aged 21 to 24 years, screening will continue to prevent cancer in young women.

SIDE 2

Women Younger Than 25 Years in the US Should Not be Screened for Cervical Cancer

Discussants: Julia M. L. Brotherton and Marion Saville

Cervical screening is intended to prevent the development of cervical cancer, through the identification and treatment of lesions that may otherwise develop into cancer during a woman's lifetime. Since the implementation of cytology-based screening programs in developed countries in the 1960s, our understanding of the natural history of CIN has greatly improved. We now know that persistent infection with oncogenic types of HPV is the underlying cause of most cervical cancers. With this knowledge has come insight into why screening of women younger than 25 years, and treatment of identified lesions has not been found to be effective at preventing cervical cancer, in contrast to the clear effectiveness of cervical screening programs for older women.[12–14]

Human papillomavirus infection rates in women peak in the years after sexual debut.[15] Most HPV infections are apparently cleared within 1 to 2 years in young women.[16] It is now apparent that low-grade squamous intraepithelial lesions detected at cervical screening are associated with acute HPV infection and that these lesions do not inevitably progress to high-grade lesions and eventually cancer.[17] Low-grade squamous intraepithelial lesions are however a marker of HPV infection, which, if persistent, can result in viral integration and considerable disruption of the normal cellular growth regulation, usually associated with appearances consistent with a high-grade lesion. Although many high-grade lesions regress over time if left untreated,[18] some will progress to cancer, usually over many years, even decades. However, a longstanding difficulty for cervical screening has been an inability to distinguish from their cellular appearance, those lesions with truly malignant potential from those destined to regress. The treatment threshold of CIN 2, a likely hybrid diagnosis including a mix of disturbing appearing cases of CIN 1 (acute infection) and more bland-appearing cases of CIN 3 (true preneoplastic potential), which cannot be reliably distinguished, reflects this problem. Thus, relative overtreatment of lesions not likely to become a cancer in a woman's lifetime is an inherent part of current cervical screening programs. In young women, this issue is proportionally and manifestly more important because most HPV infections and their associated lesions are destined to regress.

This is also of course the reason that primary HPV-based screening is not feasible in women younger than 25 years (and likely 30 in the absence of high coverage HPV vaccination)—because the presence of even the most oncogenic HPV types 16 and 18 has very limited predictive value in a population where acute generally transient HPV infection rates are high. Australia has recently transitioned from cytology screening every 2 years between the ages of 20 and 69 years to primary HPV-based screening every 5 years between the ages of 25 and 74 years, a change predicted to reduce cervical cancer incidence and mortality in Australia by a further 20% to 30%.[19] Commencing HPV-based screening from the age of 25 years, when HPV infection is still quite prevalent, was only possible because of the high HPV vaccine coverage achieved and subsequent dramatic declines in HPV 16/18 infection rates in young women documented in Australia.[20]

As with all population based screening programs, screening should only be implemented when the benefits outweigh the harms. There is an absence of apparent benefit in terms of effectiveness in screening women younger than 25 years but also clear evidence of harm.[21] Beside the financial, time, and psychosocial costs of cervical screening in young women, which requires a speculum examination, there is high-quality evidence that treatment of the cervix to remove lesions detected at screening is associated with adverse obstetric outcomes including preterm birth.[21] Because the rate of HPV infection and underlying lesions peaks in women younger than 25 years, who are at an age whereby most have not completed childbearing (and many not yet commenced), screening women younger than 25 years is likely to have the greatest adverse population level impacts through future obstetric harm from cervical treatments.

It can be enormously challenging to reduce expectations of heath care provision, and this is true for cervical screening programs in some countries that have traditionally offered screening

to women younger than 25 years. Many women, clinicians, and pathologists have personal stories and perceptions of perceived benefit to women from identifying and treating cervical lesions younger than 25 years. However, we now have clear evidence that cervical cancers are rare younger than 25 years, and most of those that do occur are identified through investigation of symptoms, rather than screening.[22] Therefore, cervical screening does not seem to prevent cancer in this age group but does have the potential to cause reproductive harm. We are however fortunate that routine HPV vaccination of preadolescents now offers a highly effective way of preventing the oncogenic HPV infections that cause most of the rare cervical cancers presenting in women younger than 25 years, which are more likely than in older women to be caused by the most oncogenic, but vaccine preventable types, HPV 16 and 18.[23] Until a reliable screening test is available that can distinguish the persistent HPV infections and/or their associated lesions with true malignant potential from the many acute infections destined to regress, cervical screening of women younger than 25 years should not be recommended.

Rebuttal by Dr. Moscicki

The article by Drs. Brotherton and Saville reminds us that treatment is associated with harms such as preterm labor. On the other hand, screening should not be associated with overtreatment in the US because atypical squamous cells of undetermined significance, HPV positive/atypical squamous cells of undetermined significance, and low-grade squamous intraepithelial lesions are not immediate referrals to colposcopy in women aged 21 to 24 years. Watchful waiting is recommended with repeated cytology annually until the abnormality is cleared or persists for 2 years. Guidelines also recommended that a CIN 2,3 diagnosis on histopathology in this age group be observed with colposcopy and cytology for up to 2 years. Consequently, young women can be saved treatment and yet be followed to ensure that persistent infections/lesions are identified and treated when persistence is documented. We should also be reminded that cervical cancer cases actually increased in Scotland, England, and Wales once the screening age was raised from 21 to 25 years of age—as pointed out in the article by Castanon et al.[7] Thus, there is an argument that it is not effective, which I do not believe to be true. Most importantly, the US does not have an organized screening program. Data from the CDC show that most women aged 21 to 29 years have not been screened in the past 3 years, and rates are declining rapidly.[24,25] One reason for the decline may be that young women no longer have routine pelvic examinations for sexually transmitted infection testing, which in the past was performed in conjunction with cervical cancer screening. Lack of screening is believed to underlie racial/ethnic disparities in cervical cancer incidence and mortality, which is noted even among young women. Failing to ensure that young adults are screened for cervical cancer is a disservice to women younger than 25 years.

Rebuttal by Drs. Brotherton and Saville

We certainly agree that young American women deserve to be protected against cervical cancer, as do all young women globally. However, we disagree that providing cervical screening to women younger than 25 years is an effective way to do this. Working within the constraints of the US health care system, we believe that there is definitely room for improving HPV vaccination coverage and increasing screening participation among women aged 25 to 29 years, and those 30 years and older, by incorporating current evidence for highly effective strategies to prevent cervical cancer.[26] There is good evidence that even at the coverage rates achieved in the US to date that the vaccine is preventing high-grade CIN in young women,[27] as predicted by models indicating substantial herd protection even at limited coverage rates,[28] and emerging data suggest that cervical cancer rates may have already started falling among young American women.[29]

We disagree that the data from the United Kingdom suggest that initiating screening at the age of 25 years is unsafe.[7] Only England ceased screening younger than 25 years in the period examined in the study, whereas Wales and Scotland *continued screening women younger than 25 years*. All 3 countries observed similar increases in cervical cancer in 25- to 29-year-old women. This strongly suggests that underlying changes, likely in sexual behavior, underlie these increases rather than cessation of screening in younger than 25 years.

We appreciate that the US model of care and ethos is based on the individual, meaning that there is no organized cervical screening program or associated program infrastructure. In our view, this makes it even more vital that young women are informed that cervical screening younger than 25 years has not been demonstrated to prevent cervical cancer even in countries with robust programs, has substantial associated obstetric harms, and may have adverse psychosocial effects. We believe that there are many things a young woman can do to improve her sexual and reproductive health and prevent cancer, such as chlamydia screening and quitting smoking, but early cervical screening is not one of them.

Summary

Rebecca B. Perkins, MD, MS

When should young women begin cervical cancer screening? Dr. Moscicki states that we should continue to initiate screening before the age of 25 years in the US. The reasons include a lower rate of HPV vaccination among the current generation of young adult women and increases in invasive cervical cancer cases in countries that have raised the screening age to 25 years. She further cites specific shortcomings of the US healthcare system that can contribute to underscreening among young women, including fragmented healthcare, lack of health insurance, and a rapidly declining rate of pelvic examinations for cervical cancer screening among this age group, despite current guidelines that continue to recommend screening. She posits that although cervical cancer is rare among women aged 21 to 24 years, promoting screening in this age group acts as a safety net to prevent cancers among women aged 25 to 29 years.

Drs. Brotherton and Saville argue that screening before the age of 25 years has not been shown to decrease cervical cancers. They further argue that screening before the age of 25 years does more harm than good, because many young women will undergo colposcopy with biopsy for transient HPV infections, and a substantial minority may receive treatment for CIN 2 lesions that are destined to regress. As HPV vaccination reduces precancers in this age group, the relative harms of screening women younger than 25 years will further increase.

The ideal recommendation is difficult to determine, because the issues are as much logistical as scientific. High-quality screening of the entire population beginning at the age of 25 years would probably achieve nearly all the benefits accrued from initiating screening earlier, even in an unvaccinated population. Furthermore, the aging of vaccinated girls into the young adult population will further skew the risk-benefit ratio toward later screening. However, the reality of the US healthcare system means that initiating screening is incumbent on a woman and her provider. Unless coupled with an expansive, targeted, public education campaign aimed at both patients and providers around the need to screen every 25-year-old woman, raising the screening the age of 25 years will likely mean that a substantial minority of women do not initiate screening until several years later. Continuing to recommend screening beginning at the age of 21 years would provide an additional safety net

for patients who do not present frequently for care. However, doing so incurs the cost of additional screening, diagnostic procedures, and perhaps treatment that are unlikely to benefit most patients. As a society, we must determine the level of overscreening and treatment we are willing to tolerate to prevent cancers in women who might otherwise fall through the cracks of our fragmented healthcare system.

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