

Risk Factors and Other Epidemiologic Considerations for Cervical Cancer Screening: A Narrative Review for the U.S. Preventive Services Task Force

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Despite the success of cervical cancer screening programs, questions remain about the appropriate time to begin and end screening. This review explores epidemiologic and contextual data on cervical cancer screening to inform decisions about when screening should begin and end.

Cervical cancer is rare among women younger than 20 years. Screening for cervical cancer in this age group is complicated by lower rates of detection and higher rates of false-positive results than in older women. Methods used to diagnose and treat cervical intraepithelial neoplasia have important potential adverse effects. High-risk human papillomavirus infections and abnormalities on cytologic and histologic examination have relatively high rates of regression. Accordingly, cervical cancer screening in women younger than 20 years may be harmful.

The incidence of, and mortality rates from, cervical cancer and the proportion of U.S. women aged 65 years or older who have had a Papanicolaou smear within 3 years have decreased since 2000. Available evidence supports discontinuation of cervical cancer screening among women aged 65 years or older who have had adequate screening and are not otherwise at high risk. Further reductions in the burden of cervical cancer in older women are probably best achieved by focusing on screening those who have not been adequately screened.

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Cervical cancer screening serves as a model for the success of a screening program: The age-adjusted incidence of and mortality rates from cervical cancer in the United States have decreased by more than 50% between 1975 and 2008 (1, 2). Nonetheless, U.S. data indicate that over 50% of women with cervical cancer were not screened within 3 to 5 years of diagnosis (3–7). Furthermore, the limited sensitivity of a single cytologic screening test, among other factors, has prompted exploration of new methods of cervical cancer screening.

To assist the U.S. Preventive Services Task Force (USPSTF) in updating its recommendation on cervical cancer screening, we performed a systematic review summarizing specific technological methods to improve screening test performance (8, 9). This concurrent narrative review uses the USPSTF's methods for assessing contextual questions (10) to explore and critique various epidemiologic and contextual data on cervical cancer screening. The review aims to inform decisions about when cervical cancer screening should begin and end. A companion modeling study that compares various lifetime cervical cancer screening strategies is forthcoming (11).

PATHOGENESIS OF CERVICAL CANCER

One reason why cytologic screening for cervical cancer has been so successful is that cervical cancer does not develop suddenly. Rather, it is preceded by precancerous changes of the cervix that are known as *cervical intraepithelial neoplasia* (CIN) (12). Cervical cytology results are not diagnostic of CIN or cancer; biopsy and histologic confirmation are required for diagnosis. The terminology for reporting the spectrum of cervical cytologic abnormalities is derived from the 2001 Bethesda System (13). Cervical intraepithelial neoplasia is categorized as increasing levels of severity: CIN1, CIN2, and CIN3. Newer data suggest that CIN1 does not predict any meaningful risk for CIN3 (14, 15). In addition, diagnoses of CIN1 and CIN2 are poorly reproduced (14–17). Progression of CIN to invasive cervical cancer (ICC) is slow, and the likelihood of CIN regression is high: Up to 43% of CIN2 lesions (18, 19) and 32% of CIN3 lesions may regress (18). A study of women in New Zealand with CIN3 found that 31% of those whose lesions were untreated or inadequately treated developed ICC within 30 years, compared with 0.7% in those who received adequate treatment (20).

ETIOLOGY OF CERVICAL CANCER

Infection with high-risk human papillomavirus (HPV) types is a necessary, although not sufficient, cause of almost all cases of cervical cancer (21). The progression from HPV infection to cervical cancer occurs over a series of 4 steps: HPV transmission, acute HPV infection, persistent HPV infection leading to precancerous changes, and ICC (14). More than 40 HPV types can infect the cervix, and researchers continue to refine the importance of various

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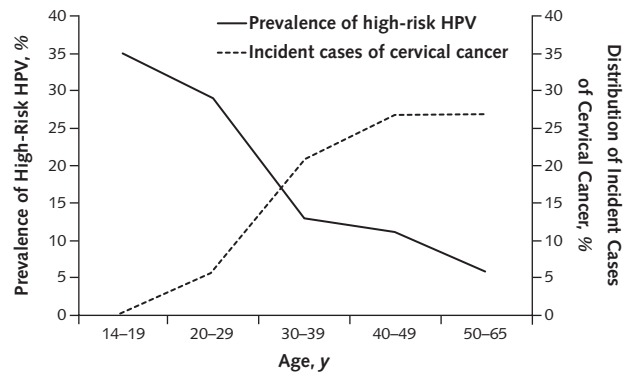
high-risk HPV types (22). Human papillomavirus types 16 and 18 are responsible for approximately 70% of cervical cancer cases (23, 24). As a result, tests have been developed to detect HPV in the clinical setting. The U.S. Food and Drug Administration has approved multiple HPV tests for specific uses in cervical cancer screening or follow-up, and additional tests are awaiting approval (9).

INFECTION WITH AND REGRESSION AND PERSISTENCE OF HPV

An important consideration for HPV testing in the clinical setting is that the prevalence of infection is highest among teens and women in their early 20s and decreases as age increases (25–27). In a study of 9657 U.S. women, the prevalence of high-risk HPV decreased from 35% among women aged 14 to 19 years to 6% among women aged 50 to 65 years (Figure 1) (27). Although the prevalence of high-risk HPV peaked among teens, a study of 49 655 women in the United Kingdom demonstrated that prevalent cases of CIN3 or worse peaked among women aged 35 to 39 years, and incident cases of CIN3 or worse peaked among women aged 25 to 29 years (Figure 2) (25). The incidence of CIN3 or worse in women aged 65 to 69 years was similar to that in women aged 15 to 19 years (25). No prevalent cases of cancer were identified among women younger than 20 years. The prevalence of positivity for high-risk HPV was lower for women with normal smears than for those with abnormal smears (25). Among women aged 15 to 19 years, 17% with normal smears and 74% with abnormal smears tested positive for high-risk HPV; among women aged 50 to 54, the respective proportions were about 2% and 41% (25).

Infection with HPV is very likely to regress among women with both normal and abnormal cytology results, and among women with the HPV subtypes most likely to be associated with CIN3 or cancer (types 16 and 18) (28–30). A 4-year prospective study of 1203 women aged 16 to 23 years with no history of abnormal cytology found that about 93% of incident infections with HPV 16 and 18 had cleared by 36 months (31). In a prospective study of 4504 women aged 18 years or older with a cytologic diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion, 91% of prevalent HPV infections detected at enrollment cleared within 24 months (28). Cytologic abnormalities in young women are also likely to regress. A cohort of 1075 women in the United Kingdom aged 15 to 19 years with normal cytology and negative high-risk HPV tests at baseline was followed prospectively with serial smears and HPV tests (31). During a median follow-up of 29 months, 26% of women became positive for 6 high-risk HPV types. The median duration of the first HPV-positive episode was 13.7 months for any HPV type, 10.3 months for HPV 16, and 7.8 months for HPV 18. The cumulative 3-year risk for any cytologic abnormality was 28% (95% CI, 25% to

Figure 1. Prevalence of high-risk HPV and incident cases of cervical cancer in the United States, 2003–2005.



Surveillance Epidemiology and End Results (SEER) data for incident cases among females aged 15 to 19 years and 50 to 64 years. Data are from references 27 and 45. HPV = human papillomavirus.

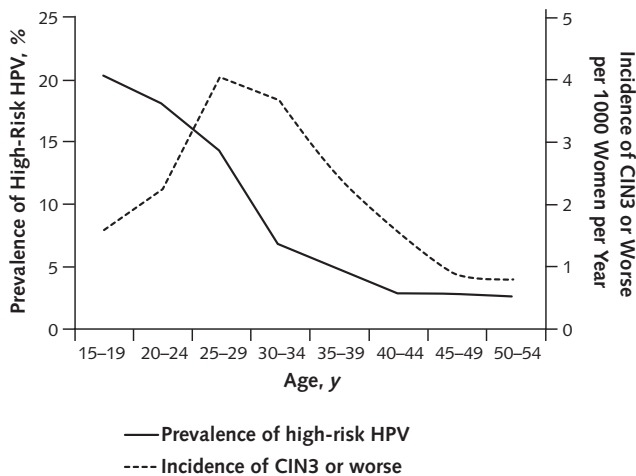
32%). The median duration of the first episode of cytologic abnormality was 8.7 months. In this cohort, 28 women (2.6%) developed CIN2 (1.3%) or CIN3 (1.3%) during a median of 36 months of follow-up.

One rationale for using HPV testing in older women is that the prevalence of HPV decreases with age, but the risk for HPV persistence increases (28). Therefore, HPV testing among women aged 30 years or older may identify more clinically significant persistent infections (22). Among 4504 women aged 18 years or older with a cytologic diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion who were followed prospectively for 24 months, the odds of persistent high-risk HPV infections were highest among women aged 50 years or older, compared with those aged 20 years or younger (odds ratio, 1.47 [CI, 1.11 to 1.94]) (28). The probability of persistent infection increased with duration of infection, so that about two thirds of infections that persisted at 18 months were still present at 24 months (28).

RISK FACTORS FOR HPV ACQUISITION AND CERVICAL CANCER

Infection with, and persistence of, HPV are not only associated with age. The risk for HPV acquisition markedly increases with the number of lifetime sexual partners (32, 33). Co-infection with other sexually transmitted agents, such as *Chlamydia trachomatis* and herpes simplex virus, may be associated with risk for HPV infection (21, 34–36). Co-infection with HIV may impair the ability of the immune system to control HPV infections (22). Additional risk factors for cervical cancer include history of smoking, younger age at first intercourse and at first pregnancy, high parity, and long-term use of oral contraceptives (14, 33, 34, 37–41). Women previously treated for

Figure 2. Prevalence of high-risk HPV and incidence of CIN3 or worse.



High-risk HPV types are 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68. Data are from reference 25. Reproduced with permission from Macmillan Publishers, *British Journal of Cancer*, copyright 2004. CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus.

any CIN (42) or for CIN3 (43) have a 2- to 3-fold increased risk for future cervical cancer, but may not have an increased risk for death from cervical cancer (44).

INCIDENCE OF CIN AND ICC

Whereas HPV infection and cytologic abnormalities are common among women younger than 20 years, ICC is rare. Between 2000 and 2008, the age-adjusted incidence rate of cervical cancer among women younger than 20 years in the United States was 0.05 case per 100 000 women (Figure 3) (45). By comparison, breast cancer in U.S. men of all ages was more than twice as common: The annual age-adjusted incidence rate was 1.2 cases per 100 000 men (45). Although the incidence of CIN3 or worse may be similar among women younger than 20 years and those older than 65 years, younger women have few incident cases of cancer (that is, more cases of CIN3 and less invasive disease) than do older women. According to U.S. cancer statistics, only 0.2% of incident cervical cancer cases occur in women younger than 20 years, whereas 19.5% occur in women aged 65 years or older (1).

While incident cases of cervical cancer in the United States seem to peak among women in their 40s (Figure 3), with approximately one half of incident cancer cases occurring in women 35 to 55 years of age (1), CIN3 peaks among women in their late 20s. In a cohort study conducted among 150 052 women aged 15 years or older, the highest incidence of CIN3 (6 cases per 1000 routine smears) occurred among those aged 25 to 29 years—a rate 3 times that of women aged 15 to 19 years and 6 times that

of those aged 60 to 79 years (46). The study showed a sharp decrease in the yield of CIN2 and CIN3 with screening in women older than 30 years, with only 2 cases of high-grade CIN identified in 5488 routine smears in women aged 60 years or older (46). Whereas the likelihood of detecting CIN3 was lower in women younger than 25 years, the risk for a false-positive smear was higher than in women aged 25 to 29 years (ranging from 3.1% to 3.5% of smears among women aged 15 to 24 years vs. 2.1% among women aged 25 to 29 years).

EFFECT OF NATIONAL SCREENING PROGRAMS ON THE INCIDENCE OF CERVICAL CANCER

A population-based, case-control study of 4012 women with ICC and 7889 control participants done in the United Kingdom's National Health Service found that cervical cancer screening among women younger than 25 years was not associated with a decreased incidence of cervical cancer diagnosed before 30 years of age (47). The investigators could not rule out the possibility that screening women aged 20 and 24 years would be effective in reducing stage IB or worse cervical cancer in women aged 25 to 27 years because the group was small (65 women) and CIs were wide (odds ratio, 0.52 [CI, 0.23 to 1.2]). A statistically significant protective effect of screening was not demonstrated until age 32 years, when screening was associated with a 45% reduction (odds ratio, 0.55 [CI, 0.44 to 0.69]) in the incidence of ICC diagnosed between 35 and 39 years of age (47).

In 1969, Iceland began a national program to screen women aged 25 to 69 years of age for cervical cancer at 2- to 3-year intervals. After 1987, women aged 20 years or older were also invited to screening at 2-year intervals. In the years after the introduction of cervical cancer screening for women aged 20 to 24 years, the rate of ICC did not change among women aged 20 to 34 years (48). The rate decreased significantly among women aged 35 to 39 years, with a stage shift toward earlier disease detection. In contrast, the detection rate of CIN2 and CIN3 increased among women aged 20 to 29 years, whereas detection of CIN2 increased among women aged 30 to 34 years but detection of CIN3 decreased (48).

SUMMARY CONSIDERATIONS ON THE AGE AT WHICH TO START SCREENING

In 2003, the USPSTF recommended that cervical cancer screening begin at 21 years of age. In its 2009 update, the American College of Obstetricians and Gynecologists made the same age recommendation, citing the very low incidence of disease in women younger than 20 years, the high likelihood of HPV and CIN regression, and the potential for adverse effects related to follow-up for women identified as having abnormal cytology (49). Findings from our review support this recommendation. Invasive cervical

cancer is exceedingly rare in women younger than 20 years. Screening before 21 years of age is complicated by lower detection rates; higher rates of false-positive results than in older women; and relatively high rates of transient HPV and regressive cervical abnormalities, for which treatment may yield long-term harm to future reproduction. The goal of cervical cancer screening is to detect and treat pre-invasive lesions, and the incidence of CIN2 and CIN3 does not begin to peak until women reach their late 20s. Thus, the decision of when to screen women must carefully balance numerous potential harms associated with diagnosis and treatment with any potential benefit.

Colposcopy with biopsy is performed when evaluation of an abnormal Papanicolaou (Pap) smear is needed (50). Recent data suggest that the risk for adverse effects from this procedure is not trivial (51). In TOMBOLA (Trial of Management of Borderline and Other Low-Grade Abnormal Smears) (51), lower proportions of women in the surveillance group than the immediate colposcopy group reported pain (15.0% vs. 38.9%; $P < 0.001$), bleeding (17.2% vs. 46.9%; $P < 0.001$), or discharge (8.6% vs. 34.2%; $P < 0.001$).

Once CIN is identified, current U.S. practice is to treat lesions that are CIN2 or worse (50). Potential harms of treating CIN include immediate, short-term, and long-term risks. An observational study in the TOMBOLA cohort found that 67% of women who had a loop electrosurgical excision procedure reported pain, 87% reported bleeding, and 63% reported discharge (52). Two systematic reviews of obstetric outcomes after cold-knife conization and loop electrosurgical excision procedure found that cold-knife conization was associated with increased risk for preterm delivery (53, 54). Loop electrosurgical excision procedure was associated with a 1.7 times increased risk for birth before 37 weeks in one review (53), but was not associated with birth before 34 weeks in another review (54).

Given the potential short- and long-term risks associated with treatment and the high likelihood of HPV, CIN1, and CIN2 regression among young women, available data suggest that screening women younger than 21 years would probably result in more harm than benefit. Whether this balance of risks and benefits is similar for women in their early 20s is unclear. Recommendations for when cervical cancer screening should begin range from age 18 to 30 years in various countries (Table). In England and Northern Ireland, the National Health Service Cervical Screening Programme does not begin screening until 25 years of age (55, 56); in Scotland and Wales, screening begins at age 20 years (57, 58). The large case-control study discussed earlier (47) was designed to determine whether screening should begin before 25 years of age in the United Kingdom. The investigators concluded that screening women aged 20 to 24 years would have little or no effect on rates of ICC up to age 30 years; however, there was still uncertainty about its effect on advanced-stage tu-

mors in women younger than 30 years (47). In June 2009, the United Kingdom Advisory Committee on Cervical Screening reviewed the practice of initiating screening at 25 years of age and unanimously agreed not to change the policy (55).

Whether the United States should adopt a later age for initiating cervical cancer screening is uncertain because it has no unifying national health care system. We found no similar analyses to those that used U.S. data and do not know whether findings from other countries are generalizable or would be representative of U.S. health outcomes. In addition, the ecologic study from Iceland suggested some potential benefit at a population level of screening women in their early 20s. In the end, further data are needed to clarify whether starting cervical cancer screening at an age older than 21 years in the United States would or would not provide a better risk-benefit tradeoff.

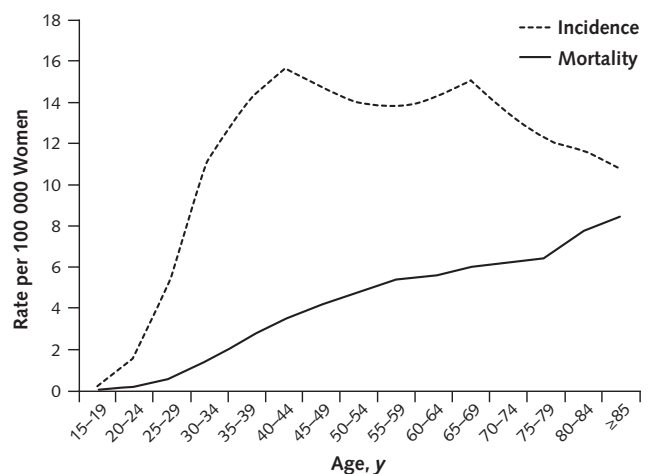
SUMMARY CONSIDERATIONS ON THE AGE AT WHICH TO STOP SCREENING

There is no national or international consensus on the age at which to discontinue cervical cancer screening (Table) (69, 70). In the United States, recommendations range from 65 to 70 years (49, 65, 68). Internationally, they range from age 59 to 60 years in Sweden and Finland, respectively, and to age 69 to 70 years in Japan, Australia, and New Zealand (Table) (55, 59, 64, 69).

A 2003 review of 12 cohort studies for the USPSTF (71) reported the following conclusions:

The incidence and prevalence of high-grade cervical lesions and cancer decreased with age and, in general, those over the age of 65 years had the lowest burden of disease. The age-related decrease in cervical disease was

Figure 3. Age-adjusted incidence of and deaths from invasive cervical cancer in the United States, 2000–2008.



Mortality rates are from 2000–2007 data. Data are from reference 45.

Table. National and International Recommendations for Cervical Cancer Screening

Country	Date of Recommendation or Initiation of National Screening Program	Age to Start Screening	Age to Stop Screening	Screening Interval
Australia (59)	1991	18*	69	2 y
Canada (60)	1994	18†	69	Once yearly for 2 y, then every 3 y
European Union (61)‡	2008	20–30	60	3–5 y
Finland (62)‡	1970	30	60	5 y
France (7)	1990	25§	65	3 y
Germany (7)	1971	20	70	Annually
Japan (63)	1983	20	70	2 y
Italy (7)	1996	25	64	3 y
The Netherlands (7)	1996	30	60	5 y
New Zealand (64)	2008	20†	70	At least 2 initial screening tests 1 y apart, then 3 y
Norway (7)	1995	25	69	3 y
Sweden (7)	1973	20	59	3 y
United States				
ACS (65)	2010	21§	70	Every year with Pap smear; every 2 y with LBC until normal results, then every 2–3 y
ACOG (49)	2009	21	65–70	2–3 y; varies by age and screening history
AAFP (66)	2008	18†	None¶	Every year until 3 normal results, then every 3 y
ACPM (67)	1996	18†	65**	Every year for 2 y, then every 3 y
USPSTF (68)	2003	21†	65	3 y
United Kingdom (55)††	1991	25	64‡‡	3–5 y; varies by age

AAFP = American Academy of Family Physicians; ACOG = American College of Obstetrics and Gynecology; ACPM = American College of Preventive Medicine; ACS = American Cancer Society; LBC = liquid-based cytology; Pap = Papanicolaou; USPSTF = U.S. Preventive Services Task Force.

- * Or within 2 y of first sexual intercourse, whichever is later.
- † Among women who have had sexual intercourse or are currently sexually active.
- ‡ Some municipalities initiate screening in women at age 25 y and end at age 65 y.
- § 3 y after beginning to have vaginal intercourse, but no later than 21 y of age.
- || Among women with normal cytology results on 3 consecutive tests.
- ¶ Women should discuss screening with a physician if they are aged >65 y.
- ** If no abnormal smears.

†† Cervical cancer screening program varies by country: 25–64 y in England (55) and Northern Ireland (56), 20–64 y in Wales (57), and 20–60 y in Scotland (58).
 ‡‡ Only screen those who have not been screened since age 50 y or have had recent abnormal results.

similar in previously unscreened women. There was no difference in the aggressiveness of invasive cancers in older women. Repeat screening after negative smears was associated with a reduced risk of high-grade cytologic abnormalities.

On the basis of that fair-quality evidence, the USPSTF recommended against routinely screening women older than 65 years for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer (68).

Improving the burden of cervical cancer in older women may best be achieved by focusing on screening those who are at higher risk for cervical cancer or who have not been adequately screened. Defining an adequate screening history, however, is clear-cut only for women who have never been screened. Although available evidence does not clearly indicate what “adequate” should be, it is commonly interpreted as 3 previous negative screenings (49, 69). The relationship between “adequate” screening history and future disease risk may vary by age. A recent observational study in Italy found a nearly 8-fold lower cumulative risk for CIN2 or worse after 3 previous negative screenings in women aged 50 to 64 years than in those aged 25 to 49 years (72). A separate study found the inci-

dence of cervical cancer after 3 consecutive negative screening tests to be the same after 10 years of follow-up in women aged 30 to 44 years and those aged 45 to 54 years (73). According to the Centers for Disease Control and Prevention, the proportion of U.S. women aged 65 or older who have had a Pap smear in the past 3 years has decreased from 64.5% in 2000 to 50% in 2008 (74). Although lower proportions of older women have received cervical cancer screening in the past decade, age-adjusted rates of cervical cancer mortality among women aged 65 and older in the United States have decreased from 7.6 cases per 100 000 women in 2000 to 6.2 cases per 100 000 women in 2007 (2).

Likewise, a recent review on screening intervals and age limits (75) determined that screening women older than 65 years who had an adequate screening history would be inefficient (69). Screening women who have not been adequately screened triennially, however, would reduce mortality by 74% (69). The inefficiency is primarily because more smears are required, less CIN is detected as women age, and there are other competing causes of death.

Race, ethnicity, and education are important predictors of recent screening. Data from 2008 show that only

about 65% of women aged 25 years or older with less than a high school education had completed a Pap test during the previous 3 years, compared with about 85% of women with some college or higher-level education (74). Data from the Centers for Disease Control and Prevention for women aged 18 years or older show that Asian women are less likely to have had a Pap smear during the previous 3 years than are women of other racial or ethnic groups (74).

Incidence and mortality rates for cervical cancer also vary by race and ethnicity (76). Among non-Hispanic white women, the incidence rate of cervical cancer increases with age and peaks among those aged 60 to 69 years and then declines (76). In contrast, the incidence rate of cervical cancer among black women does not decline with advancing age, even though this group has slightly higher-than-average rates of adherence with recommended cervical screening (77–79). In 2007, the mortality rate from cervical cancer was almost twice as high for black women as white women (4.3 vs. 2.2 cases per 100 000 women) (80). Compared with rates in white women, rates of ICC in Hispanic women peak earlier and black women have a higher absolute rate that is prolonged (to age >85 years). It is unclear whether these differences are related to variation in prevalence of risk factors for associated cervical cancer, in obtaining adequate cervical cancer screening, or other disease-related factors.

Potential concerns about recommendations to discontinue screening among older women are the need for greater vigilance on the part of health care providers for symptomatic presentation of cervical cancer and patient acceptance of discontinuation of screening. The American College of Obstetricians and Gynecologists states that if screening is discontinued, risk factors should be assessed at subsequent gynecologic examinations to determine whether screening should be reinitiated (49). A survey of U.S. adults on cessation of colon, breast, and prostate cancer screening found that plans to stop screening were uncommon among participants who had recently faced a screening decision (81). Another survey on beliefs about cervical cancer screening among 199 women aged 65 years or older found that most women believed that lifelong cervical cancer screening was important (82). Of those whose physicians had recommended ending screening, 87% reported that they had ended screening.

In conclusion, the available evidence suggests that cervical cancer screening should not begin before 21 years of age because cervical cancer is rare in this age group and the potential for harm due to treatment of regressive HPV infections and CIN is not trivial. Whether the age of screening initiation in the United States could be raised to, for example, 25 years is unclear. Studies on U.S. screening and treatment practices in relation to CIN and cervical cancer outcomes across age groups could help inform this question. Finally, available evidence also suggests that discontinuation of screening can be considered for women aged 65 years or older without a history of CIN or cervical

cancer who have had recent negative cervical cancer screening.

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