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Point-Counterpoint

Point: Cervical Cancer Screening Guidelines Should Consider Observational Data on Screening Efficacy in Older Women

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Recent guidelines from the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology recommend cessation of cervical cancer screening at age 65 years for women with an "adequate" history of negative Papanicolaou smears. In our view, those who formulated these guidelines did not consider a growing body of evidence from nonrandomized studies that provides insight into the efficacy of cervical cancer screening among older women. First, older women are not at indefinitely low risk following negative screening results. Second, recent data from the United States, the United Kingdom, and Sweden suggest that screening of older women is associated with substantial reductions in cervical cancer incidence and mortality, even among previously screened women. It may be that after consideration of the reduced incidence of (and reduced mortality from) cervical cancer that may result from screening older women, the harms and economic costs of screening will be judged to outweigh its benefits. However, it is essential to consider the now-documented benefits of cervical screening when formulating screening guidelines for older women, and recommendations that do not do so will lack an evidence base.

cervical cancer; health policy; Papanicolaou smear; screening; women's health

Abbreviations: CIN3, cervical intraepithelial neoplasia, grade 3; HPV, human papillomavirus; ICC, invasive cervical cancer.

Editor's note: *A counterpoint to this article appears on page 1023, and a response appears on page 1027.*

In "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," Saslow et al. (1) recommend discontinuing cervical cancer screening at age 65 years for "adequately screened" women. This recommendation was based, in part, on the authors' perception of a limited efficacy of cervical screening in older women, a perception based in turn primarily on the authors' expert opinion and the results of 1 modeling study (2). The authors appear to have ignored the growing body of evidence from nonrandomized studies that has provided insight into the efficacy of cervical cancer screening among older women—evidence that we believe needs to be considered when formulating screening policy recommendations.

Saslow et al. correctly assert that no randomized trial documenting the efficacy of cervical screening in older (or younger) women has been conducted (1). However, using data on 1,305 cases with invasive cervical cancer (ICC) and 2,532 controls in the United Kingdom, Sasieni et al. (3) observed that the relative risks associated with receipt of cytological screening were similar among women aged 55–69 years and women aged 40–54 years. In a subsequent analysis from the United Kingdom with 4,012 cases and 7,889 controls, Sasieni et al. (4) found that the reduction in cervical cancer incidence associated with cytological screening increased from age 40 years to age 64 years, from 60% to 80%. In Sweden, screening of women aged ≥66 years was associated with a 64% reduction in ICC incidence (95% confidence interval: 47, 76) in an audit of that country's cervical screening program (5). More recently, the results of a case-control study conducted among

members of 2 health plans in the United States suggested that screening is associated with a 77% reduction in ICC incidence among women aged 55–79 years (95% confidence interval: 56, 89) (6). Together, these studies suggest that cervical cancer screening may be highly efficacious in reducing the incidence of cervical cancer among older women.

Most recently, the results of a follow-up analysis from Sweden suggested that cervical cancer screening is efficacious among older women with respect to reduction of ICC mortality. Andrae et al. (5) compared the "cure proportions" among women with screen-detected ICC versus symptomatically detected ICC. The "cure proportion" is the relative survival at a point in time when diseased persons no longer experience excess mortality compared with nondiseased persons of the same age and gender; a plot of relative survival will plateau at the cure proportion. In the absence of overdetection (or "pseudodisease"), it is probably a valid measure of efficacy. Andrae et al. observed that women aged ≥66 years at diagnosis with screen-detected ICC experienced an absolute 36% increase in cure proportion over that of symptomatically diagnosed women (5). Importantly, there was no appreciable difference in this percentage between women with guideline-adherent screening histories and those with nonadherent screening histories (7). This implies that even women with adequate, negative screening histories can be expected to experience reduced mortality from cervical cancer.

Furthermore, the analyses from the United Kingdom (3) and the United States (6) found that the period of low ICC incidence among older women after 1 or 2 negative cytological screening tests lasts no longer than 5–7 years, which is consistent with the International Agency for Research on Cancer's earlier estimate for women aged 35–64 years from its worldwide meta-analysis (8). In other words, a woman with consecutive negative screening tests—whom current recommendations release from screening at age 65 years—is at the same risk of cervical cancer as an unscreened woman beginning 5–7 years after her last negative test result. These findings, combined with the growing evidence for the efficacy of cervical cancer screening among older women with respect to incidence and mortality, even among guideline-adherent women, suggest that older women are not at indefinitely low risk of cervical cancer following a history of negative screening results and may benefit from continued screening.

Within the low-incidence period following a negative cytological test, recent data from the United States, France, and Scotland suggest that the absolute rate of dysplasia among older women is not negligible, even among women with negative, guideline-adherent screening histories. An analysis of data from 128,805 women in the National Breast and Cervical Cancer Early Detection Program, which provides breast and cervical cancer screening to low-income women in the United States, found that within 3 years of a negative Papanicolaou smear, the incidence of high-grade cytological changes (high-grade squamous intraepithelial lesion or findings suggestive of squamous-cell cancer) was 150 per 100,000 among women aged 50–64 years and 103 per 100,000 among women aged ≥65 years (9). Among 36,512 Scottish women with 2 or more negative cytology results (one of which occurred within the 5 years prior to age 50) and at least 1 cytological screening test after age 50 years, 1.8% were found to have high-grade cervical abnormalities after age 50 years (10). This percentage is probably an underestimate, because women without detected abnormalities had a substantially shorter follow-up period (median, 33.2 months) than those with detected lesions (median, 62 months). Had the follow-up period been longer for women who were apparently free of cervical abnormalities, a higher percentage would probably have been found to subsequently develop cervical lesions. Most recently, Meyer et al. (11) analyzed data from 53,644 French women aged 65–100 years at 3 cervical cancer screening laboratories in the French Alps. Among 5,696 women with guideline-adherent screening histories (≥2 consecutive negative smears, one of which took place between 2004 and 2008), 14.2% had an abnormal smear after age 65 years and 1.2% had abnormalities suggestive of cancer. The median age at diagnosis of cancer among guideline-adherent women was 72.5 years (11).

In relative terms, the rates of cervical abnormalities do decline with age (12). However, the lower percentage of positive smears in older women relative to younger women cannot be used as a direct surrogate for the relative number of invasive cancers potentially averted by screening: The likelihood that a given cervical abnormality may progress to cervical intraepithelial neoplasia, grade 3 (CIN3), or frankly invasive cancer may be higher among older women than among younger women (12–15). Rebolj et al. (12) analyzed data from the Dutch national registry of cytopathology and histopathology and observed a significantly higher rate of preinvasive lesions among younger women but no differences in ICC incidence following 3 consecutive negative cytology results between women aged 30–44 years and women aged 45–54 years at the time of the third negative smear. Using data from the British Columbia, Canada, screening program, van Oortmarssen and Habbema (13) estimated that 84% of precancerous cervical lesions regress among women younger than age 34 years, whereas only 40% of new lesions regress after age 34 years. These estimates are nearly identical to those obtained by Morrison et al. (15) in a similar study based on over 40 years of screening among 2 birth cohorts of British Columbia women born in 1914–1918 and 1929–1933. In a unique natural history study in which women were not offered surgical removal of CIN3 upon diagnosis, McCredie et al. (14) observed a 2.5-fold increase in risk of progression to frankly invasive cancer among women aged ≥50 years at the time of CIN3 diagnosis, relative to women under age 30 years at the time of CIN3 diagnosis. These results emphasize that the frequency of detection of preinvasive lesions alone cannot be used to infer that cytological screening benefits younger women more than it does older women.

Through midlife, women who are negative for human papillomavirus (HPV) are expected to be at low risk of cervical cancer for 10–15 years (16). However, relevant data for longer follow-up times and for older women are sparse. In their cohort of Kaiser Permanente Northwest enrollees, Schiffman et al. (16) did not report percentages of women by age group; however, based on the reported mean age (35.8 years) and standard deviation (12.7 years) in the cohort aged ≥30 years, at baseline fewer than 2.5% of women were older than age 61.2 years (2 standard deviations from the mean). Further, there is evidence that postmenopausal women experience a second peak in HPV prevalence, similar to that seen among

adolescent women after the onset of sexual activity (17, 18). This is hypothesized to be due to a combination of sexual behavior and immune senescence (19). Whether new and/or reactivated HPV infections among older women are correlated with cervical cancer risk to the same degree as those infections among young women is unknown. Declining immune function may facilitate viral persistence and/or an accelerated progression from cervical intraepithelial neoplasia to frankly invasive cancer, or the natural history may mirror that of younger women. Given the lack of available data on the natural history of HPV infection among older women, we cannot necessarily assume that the experiences of HPV-negative women are identical regardless of age.

In summary, recent research indicates that 1) the period of low ICC incidence after 1 or 2 negative cytological screening tests does not extend indefinitely—risk returns to the level seen in unscreened women after 5–7 years (3, 6, 8); 2) the absolute incidence of cervical lesions during this period is not trivial (9–11); 3) a relative decline in cervical abnormalities with age cannot be equated with a lower risk of ICC among older women (12–15); and 4) older women may be at increased risk of HPV infection (17–19).

At a comparable level of screening efficacy, the potential life-years gained via cervical screening will be fewer than in younger women. Therefore, even after considering the likely reduced incidence of (and probably reduced mortality from) cervical cancer that results from cervical screening in older women, the negative consequences of screening may outweigh its benefits. However, in their analysis, Saslow et al. (1) did not adequately consider the breadth of available evidence on the benefits of screening in older women, and we fear this may have slanted their recommendations.

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